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Acute pancreatitis- A comprehensive review

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ABSTRACT

Acute pancreatitis (AP) is defined as an acute PATHOPHYSIOLOGY inflammatory process of the pancreas, with variable involvement of other regional tissues or remote organ systems. Global Burden of Disease study of 2015 has recorded an 8.9 million cases of Pancreatitis in the world with 132,700 deaths. It has been noted that the incidence of AP has been steadily rising during the last decade in developed and developing countries. Acute pancreatitis had an equal distribution between females and males. But, females were two times more likely to have gallstone pancreatitis, alcohol induced pancreatitis was less likely to occur in females.Patients exposed to multiple medications were more likely to develop idiopathic pancreatitis. There are many recognized causes of acute pancreatitis, but gallstones constitute the predominant etiological factor.Acute pancreatitis is less frequently related to chronic use or abuse of alcohol and rarely is secondary to abdominal surgery, diagnostic and/or interventional endoscopic procedures on the abdominal trauma, dyslipidemia, papilla of Vater, or the use of drugs with pancreatic toxicity. Th e diagnosis of AP is most often established by the presence of abdominal pain consistent with the disease, Serum amylase and / or lipase greater than the upper limit of normal and Characteristic findings from abdominal imaging. CECT or MRI imaging is recommended to assess local complications such as pancreatic necrosis. Computed tomography (CT) and MRI are comparable in the early assessment of AP. Three most important issues initially are pain relief, fluid replacement and nutrition. The standard treatment for infected pancreatic necrosis is open or laparoscopic surgical drainage. However, on occasions, percutaneous drainage may work well.

Keywords: Acute pancreatitis (AP), abdominal pain, digestive enzymes, serum amylase, serum lipase, Magnetic resonance imaging- MRI, pancreatic necrosis, gallstones, pancreatic toxicity.

INTRODUCTION

Acute pancreatitis (AP) is defined as an acute PATHOPHYSIOLOGY inflammatory process of the pancreas, with variable involvement of other regional tissues or remote organ systems [1]. AP is one of the most common diseases of the gastrointestinal tract, leading to tremendous emotional, physical, and financial human burden [2,3].The first case of Acute Pancreatitis (AP) was reported in year 1652 by Dutch anatomist Nicholas Tulp and in 1889, Reginald Fitz, a pathologist from Harvard published the diagnosis of Acute Pancreatitis with its signs and symptoms [4,5]. A nationwide hospital based study in Columbus recorded a raise of 13.3% in AP related admissions from 2002-05 to 2009-12 [6]. Global Burden of Disease study of 2015 has recorded an 8.9 million cases of Pancreatitis in the world with 132,700 deaths [7]. In the United States, AP is a leading cause of inpatient care among gastrointestinal conditions: above 275,000 patients are hospitalized for AP annually [8]. Furthermore, it has been noted that the incidence of AP has been steadily rising during the last decade in developed and developing countries [9,10]. The organ pancreas is a gland weighing 100 g and producing quite a lot of active proteolytic, lipolytic, and amylolytic enzymes which do not

accomplish their function until they reach the small intestine. A system of protective mechanisms is needed to defend the pancreas against its own enzymes. This protection is maintained intracellularly by inactive precursors, in the tissue by the mucous film on the surface of the duct epithelium, and last, but not least, by the free and immediate discharge of pancreatic juice. Should pancreatic juice enter the circulating blood, it encounters a potent system of enzyme inhibitors. The intrinsic cell metabolism is the most important protective mechanism, producing a one-way permeability and thus preventing the return of the secreted products into the glandular epithelial cells [11].Gallstones and alcohol are the most common causes of AP, gallstones being about twice as common as alcohol in our population. Other causes are hypertriglyceridemia, hypercalcemia, postendoscopic retrograde cholangiopan-creatography (ERCP) and drug-induced pancreatitis, but these are much less common. Microlithiasis is perhaps also a common especially in those who present with recurrent AP and should be looked for carefully using endoscopic ultrasound (EUS)[12]. In toxin-induced pancreatitis, smoking is being increasingly incriminated as an important causative factor [13,14].

Epidemiology

Acute pancreatitis had an equal distribution between females and males. But, females were two times more likely to have gallstone pancreatitis, alcohol induced pancreatitis was less likely to occur in females. The median age at which the disease appeared was 50. Gallstone pancreatitis increased with age whereas, alcohol induced pancreatitis was more common in those less than 56 years. Patients exposed to multiple medications were more likely to develop idiopathic pancreatitis. Patients with hypertension were more likely to have gallstone pancreatitisand less likely to have alcohol induced pancreatitis. Patients with ischemic heart disease was also significantly to have gallstone pancreatitis. Type 2 diabetes, gastro-oesophageal reflux diseaseand hypercholesterolemia, did not show any statistically significant relationships with the different etiologies[15].

Pathophysiology

There are many recognized causes of acute pancreatitis, but gallstones constitute the predominant etiological factor [16]. Acute pancreatitis is less frequently related to chronic use or abuse of alcohol and rarely is secondary to abdominal surgery, diagnostic and/or interventional endoscopic procedures on the abdominal trauma, dyslipidemia, papilla of Vater, or the use of drugs with pancreatic toxicity [17,18,19]. Under normal conditions pancreas produce digestive enzymes and lysosomal enzymes, the former segregated in lysosomal vacuoles, the latter in the vacuoles of zymogen. In acute pancreatitis this strict compartmentalization can be overridden by alteration of a complex biological process, calcium-dependent, defined as "stimulus-secretion coupling". A colocalization of lysosomes and zymogen granules in a unique vacuole is thus determined: the lysosomal enzyme cathepsin B can activate trypsinogen at this point with consequent cascade activation of other proteases and phospholipases. It follows the rupture of vacuoles, cell damage, necrosis and release of cellular activated enzymes in the interstitium. Local processes of vasoconstriction-dilatation determine infiltration of inflammatory cells and increased necrosis. In the most severe forms of acute pancreatitis it is present a complex biochemical cellular and humoral response not substantially different from what happens in other serious diseases such as septic shock, the poly-trauma and extensive burns. The magnitude and the continuation of such events, assignable to the so-called SIRS (systemic inflammatory response syndrome), affect the extent and severity of local damage and progression to systemic complications [20]. Implicated mediators are various cytokines such as interleukin-1 (IL-1), IL-6, IL-8, TNF (tumor necrosis factor), PAF (platelet activating factor). All these mediators are markedly elevated in the first 24 hours of illness, whereas the anti-inflammatory cytokines to (IL-2, IL-10) are reduced. The result is the activation of neutrophils, monocytes, lymphocytes, platelets and endothelial cells. The increased expression of cell adhesion molecules and integrins on neutrophils results in increased adhesion to the endothelium, diapedesis and invasion of distant organs (first of all the lungs) where hyperactive neutrophils call forth other polymorphonuclear leukocytes and result in extensive tissue destruction [20,21,22]. The presence of trypsin, chymotrypsin and elastase in the pancreatic interstitium, in serum and peritoneal fluid is responsible for activation of the coagulation-fibrinolysis systems, endothelial cells, PMN leukocytes and monocytes-macrophages with synthesis and release of cytokines, superoxide ions and PAF [23]. The latter is a key mediator capable of stimulating the release of other proinflammatory cytokines, increase vascular permeability, induce a negative inotropic effect, leukocyte chemotaxis, tissue edema and cellular damage. It is possible to clearly appreciate the possibility of a serious involvement of distant organs up to the development of the "fearsome" multi-organ failure syndrome[24].

Diagnosis

The diagnosis of AP is most often established by the presence of 2 of the 3 following criteria:

1. Abdominal pain consistent with the disease.
2. Serum amylase and / or lipase greater than the upper limit of normal.
3. Characteristic findings from abdominal imaging.

Contrast-enhanced computed tomography (CECT) and / or magnetic resonance imaging (MRI) of the pancreas should be reserved for patients in whom the diagnosis is unclear or who fail to improve clinically within the first 48 – 72 h after hospital admission or to evaluate complications (strong recommendation, low quality of evidence).

Patients with AP would be present with epigastric or left upper quadrant pain. The pain is usually described as constant with radiation to the back, chest,flanks. The intensity of the pain is usually severe. Do not correlate the location of the pain with severity and intensity. Pain described as dull, colicky, or located in the lower abdominal region is not consistent with AP and suggests an alternative etiology. Abdominal imaging will be helpful to determine the diagnosis of AP in patients[25].

Because of limitations in prediction of values, sensitivity, specificity, serum amylase only cannot be used for the

diagnosis of AP and serum lipase is preferred. In AP patients, Serum amylase generally rises within a few hours after the onset of symptoms and returns to normal values within 3 – 5 days[26,27]. Compared with lipase, serum amylase returns more quickly to values below the upper limit of normal. Serum amylase concentrations may be normal in alcohol-induced AP and hypertriglyceridemia. Serum amylase concentrations might be high in the absence of AP in macroamylasaemia (a syndrome characterized by the formation of large molecular complexes between amylase and abnormal immunoglobulins), in patients with decreased glomerular filtration rate, diseases of the salivary glands, and extrapancreatic abdominal diseases associated with inflammation, acute appendicitis, cholecystitis, intestinal obstruction or ischemia, peptic ulcer, and gynecological diseases. Serum lipase appears to be elevated longer than amylase after disease presentation. Despite recommendations of previous investigators and guidelines for the management of AP that emphasize the advantage of serum lipase, similar problems with the predictive value remain in certain patient populations, including the existence of macro lipasemia. Lipase is also found to be elevated in a variety of nonpancreatic diseasessuch as renal disease, appendicitis and cholecystitis. In addition, an upper limit of normal greater than 3-5 times may be needed in diabetics who appear to have higher median lipase compared with nondiabetic patients for unclear reasons [28,29,30]. Assays of many other pancreatic enzymes have been assessed during the past 15 years, but none seems to offer better diagnostic value than those of serum amylase and lipase [31].

Although most studies show a diagnostic efficacy of greater than 3 – 5 times the upper limit of normal, clinicians must consider the clinical condition of the patient when evaluating amylase and lipase elevations. When a doubt regarding the diagnosis of AP exists, abdominal imaging, such as CECT, is recommended [25].

Abdominal imaging is useful to confirm the diagnosis of AP. CECT provides over 90 % sensitivity and specificity for the diagnosis of AP [32]. Routine use of CECT in patients with AP is unwarranted, as the diagnosis is apparent in many patients and most have a mild, uncomplicated course. However, in a patient failing to improve aft er 48 – 72 (e.g., persistent pain, fever, nausea, unable to begin oral feeding), CECT or MRI imaging is recommended to assess local complications such as pancreatic necrosis [33,34,35]. Computed tomography (CT) and MRI are comparable in the early assessment of AP. MRI, by employing magnetic resonance cholangiopancreatography (MRCP), has the advantage of detecting choledocholithiasis down to 3 mm diameter and pancreatic duct disruption while providing high-quality imaging for diagnostic and / or severity purposes. MRI is helpful in patients with a contrast allergy and renal insufficiency where T2-weighted images without gadolinium contrast can diagnose pancreatic necrosis [36].

Treatment

Three most important issues initially are pain relief, fluid replacement and nutrition. Thereafter, the issue of preventing or treating infection emerges. However, careful monitoring of cardiorespiratory and renalfunctions is required all through, particularly in the initial 48 hours to assess if the patient would need treatment in intensive care unit (ICU).

Pain in AP is usually very severe, often radiating to the back and associated with abdominal distension and nausea/vomiting. Nonsteroidal inflammatory agents are tried initially but if they do not give relief, patients must be provided relief by giving opioids. A combination of pentazocine and Phenergan is very effective[37].

Adequate fluid replacement to maintain effective circulating volume and perfusion pressure is necessary to maintain pancreatic microcirculation. The fluid requirement may be quite large because of substantial loss of fluid in the retroperitoneal space. Thus, experts and various guidelines started recommending fluid replacement with crystalloids at a rate of 300–350 ml per hour, especially in those with raised hematocrit and BUN. According to the Mayo group, 33% of the first 72 hours of fluid volume requirement should be administered within 24 hours of presentation[38].It was hoped that such rapid fluid replacement would help prevent necrosis and other local complications. However, it did not happen, and in fact, it was seen that large rapid fluid replacement led to an increase in peripancreatic fluid collections, compartment syndrome and increased occurrence of respiratory failure. In a recent study, it was seen that administration of more than 4 liters of fluid during the initial 24 hours was associated with increased risk of respiratory insufficiency and a longer stay in the ICU. Conversely, those who received less than 4 liters of intravenous fluid within the first 24 hours fared better—less of respiratory failure, less necrosis and lower mortality[39].

Since AP is a hypercatabolic condition, prompt and adequate provision of nutrition is essential. This was done earlier through intravenous alimentation but over the years it has become clear that enteral nutrition (EN) is far superior to parenteral nutrition (PN)[40]. Enteral nutrition can be instituted within 24 hours of AP in the vast majority of patients[41].

There is no debate on use of aggressive antibiotic therapy for infection either within the necrosed pancreas or in the peripancreatic fluid collections (see below) but, use of antibiotics prophylactically remains uncertain. It has been proposed that in SAP patients with pancreatic necrosis greater than 30%, antibiotics with deep penetration in pancreas should be given[42].

Around one-third of necrotic AP may get infected by the second week of SAP. This complication should be suspected if a systemic inflammatory response persists for more than 2 weeks after admission, clinical course worsens or air bubbles appear at CT. After excluding other foci of infection origins, infected necrosis should be confirmed by ultrasound- or CT-guided aspiration followed by Gram smear and culture. If the initial puncture is not diagnostic, it can be repeated after a few days. While waiting for the culture report, intravenous antibiotics should be started. Carbapenem (imipenem or meropenem 1 gram/8 h) or ciprofloxacin plus metronidazoleare the preferred choice. If Gram positive bacteria are isolated, vancomycin (1 gram/12 h) should be administered[43].

The standard treatment for infected pancreatic necrosis is open or laparoscopic surgical drainage. However, on occasions, percutaneous drainage may work well. As

recommended by the International Association of Pancreatology Clinical Guideline, drainage should be effectively established when the patient is septic. A step by step treatment is proposed by which percutaneous or endoscopic drainage should be established first and then necrosectomy with drainage through a minimally invasive retroperitoneal access. When this method was compared with open surgery, it offered several advantages, including the chance to avoid surgery in some patients, less complications and lower cost[44,45,46,47].

In severe biliary pancreatitis, an urgent endoscopic sphincterotomy (ES) and common bile duct (CBD) clearance has been recommended on the basis of earlier reports of its benefit.1 However, the latest metaanalysis clearly shows no advantage of this procedure unless there is evidence of cholangitis[48].

It is extremely important that all patients with biliary AP undergo laparoscopic cholecystectomy within 2–4 weeks of resolution of AP. If not done, there is a 30% probability of recurrence of AP within the next 3 months[49].

CONCLUSION

Several surveys are going on to identify the etiologies of AP. Since, the rate of AP is increasing year by year it is very essential to identify the etiologies to control future increasing rate. Our modern methods of medicines and procedures may paw the way for the quality life of the patients with AP.

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