ASPECTS IN ACUTE PANCREATITIS ETIOPATHOGENY

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Abstract: *Acute pancreatitis is characterized by the occurrence of necroinflammatory changes in the pancreas. Three types of necrosis may be distinguished: (1) interstitial tissue necrosis, which subsequently may also involve acinar and ductal cells, (2) ductal necrosis, and (3) acinar necrosis. The first type of necrosis is autodigestive in nature and is typical of the most common forms of acute pancreatitis, which are associated with alcohol, bile duct disease, metabolic conditions, and other rare factors. Clinically, these types of pancreatitis may be either mild or severe (Atlanta classification). The mild form is also known as edematous pancreatitis, because there is edematous swelling of the pancreas combined with tiny foci of interstitial (fat) necrosis. Severe or necrotizing pancreatitis shows large areas of often hemorrhagic necrosis of the pancreatic and particularly the peripancreatic tissue. Complications of acute pancreatitis, such as pseudocyst, bleeding, and infection, determine the course of the disease.*

Cuvinte cheie: *pancreatita acută, etiologie, patogenie*

Rezumat: *Pancreatita acută este caracterizată prin apariția modificărilor necroinflamatorii în pancreas. Trei tipuri de necroză pot fi diferențiate: (1) necroză de țesut interstițial, care ulterior afectează celulele acinare şi ductale, (2) necroză ductală şi necroză acinară. Primul tip este autodigestia şi este tipică pentru majoritatea pancreatitelor, care sunt asociate cu alcool, afecțiuni ale căilor biliare, afecțiuni metabolice şi alți factori mai rari. Clinic, aceste tipuri de pancreatită pot fi uşoare sau severe (clasificarea Atlanta). Forma uşoară este cunoscută ca pancreatită edematoasă, deoarece este o creştere în volum edematoasă a pancreasului însoțită de pete de citosteatonecroză. Pancreatita severă sau necrozantă prezintă zone de necroză pancreatică şi peripancreatică. Complicațiile pancreatitei acute ca pseudochistul, hemoragia, infecția, determină evoluția bolii.*

SCIENTIFICAL ARTICLE PREDOMINANTLY THEORETICAL

Acute pancreatitis is acute inflammation of the pancreas, which may remain localized to the gland or variable extends the peripancreatic and retroperitoneal tissues and organs located away from pancreatic tissue[1].

Such definition was adopted at the Consensus Conference in Atlanta in 1992 that proposed a systematization of acute pancreatitis morphoclinical clearer, and standardized terminology used in clinical and research to convey more clearly the progress in diagnosis and treatment of this condition. The classic design is a consequence of acute pancreatitis morphofunctional intraglandular, pancreatic and peripancreatic autodigestion by activating its own enzymes, triggered by different mechanisms and under the action of multiple etiologic factors.

From mild to multiple organ dysfunction and sepsis, acute pancreatitis is a disorder which has numerous causes, an obscure pathogenesis, few effective therapeutic remedies evolving and often unpredictable.

Epidemiology of acute pancreatitis

Studies on the epidemiology of acute pancreatitis varies considerably on the etiology of acute pancreatitis, either because of inadequate reporting, the difficulty of diagnosis, differences in population and the prevalence of alcohol sick. Several studies have noted an increased incidence of acute pancreatitis in North America and Europe. [7]

Table no. 1. Summary of published population-based studies reporting on incidence and mortality of first acute pancreatitis since the year 2000.*

First author, publication year	Period	Country	Incidence per 100,000/year	Aetiology (%)B:A:I **	Case fatality%
Eland (2000)	1985-1995	Holland	12.4 (1985) 15.9 (1995)	----	14.3(1985)
Birgisson(2002)	1998-1999	Island	32.3	42:32:2	10,7(1995)
Floyd (2002)	1981-2000	Denmark	18 (1981) 27,1 (2000)	----	6,7(2000)
Lankish (2002)	1988-1995	Germany	19,7	40:32:20	7
Gislason (2004)	1986-1995	Norway	20	49:19:12	3
Goldacre (2004)	1963-1998	Great Britain	4,9 (1963-74) 7,7 (1975-86), 9,8 (1987-98)	----	14,2; 7,6; 6,7
Linkvist (2004)	1985-1999	Sweden	22(1985) 37(1999)	42:25:33	5,7
Frey (2006)	1 994-2001	USA	33.2 (1994) 43.8(2001)	33:20:37	4,2

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* adapted from Spanier-Best Practice clinical Gasroenterology-vol.22 No1, pp 45-63,2008 ** Rounded % of causes (gallstones, alcohol, idiopathic).

Some of these increases can be explained by improved diagnostic methods, but studies after 1985 have confirmed an increase in incidence, indicating that improved diagnosis is not only one explanation. The incidence of acute pancreatitis varies between 10 and 50 cases per 100,000 per year. In a recent analysis of 1999, the number of cases of acute pancreatitis requiring hospitalization in the U.S. was between 166,000 and 252,000. U.S. incidence rate is reported at 50 cases per 100,000 per year. Gallstones was identified as the most common etiology in the first attack, accounting for 30% -50%. The combination of alcohol is between 20% -40% in patients with pancreatitis. The etiologies are all major world gallstones (41%) and alcohol (31.7%). There is a strong association between sex and age and the incidence of PA was higher in men than in women increases with age. Peak incidence for alcoholic pancreatitis in the third and fourth decade and for biliary pancreatitis, is the seventh decade [7].

Causes of acute pancreatitis

- Alcohol
- Cholelithiasis, microlithiasis, choledocholithiasis
- Post-endoscopic retrograde cholangiopancreatography
- Hypertriglyceridaemia, Hypercalcaemia
- Autoimmune pancreatitis
- Pancreatic ductal obstruction: pancreatic cancer, sphincter of Oddi dysfunction, pancreas divisum, periampullary tumours, ascariasis
- Genetic: hereditary pancreatitis, cystic fibrosis
- Viral infection: coxsackie, mumps, HIV, adenovirus
- Ischaemia: intra-abdominal surgery, coronary artery bypass surgery, embolism, vasculitis
- Venom: spider, scorpion
- Idiopathic (<10%)
- Drugs
  - Common: Azathioprine, 6-Mercaptopurine, Didanosine, Valproic acid, Oestrogens, Furosemide, Pentamidine, Sulphonamides, Tetracycline, Tamoxifen;
  - Rare: Corticosteroids, Aminosalicylates, Metronidazole, L-asparaginase, ACE* inhibitors.

New elements in the pathogenesis of acute pancreatitis

Triggered by various pathogens, acute pancreatitis results from intraparenchimatous enzymatic activation with tissue destruction and necrosis disease.

Pancreatitis induced by gallstone is due mainly by biliary stones passage, and forms idiopathic labeled, the detection of the biliary sludge and microstones, is more common than previously believed. Reducing the recurrence rate of acute pancreatitis after gallbladder removal, supports the view that microstones are actually the cause of acute pancreatitis in these patients. While passage of gallstones is now accepted as a critical event in the onset of acute pancreatitis, pathophysiological mechanism is not yet well understood nor universally accepted. [2]

Acute pancreatitis in alcoholics is explained by chronic gastroduodenitis , duodenal dyskinesias, oddian spasm that stimulates releasing of secretin and pancreatic secretion in closed duct.Hyperviscosity of pancreatic secretion by protein precipitated enable canalar obstruction. In addition to this, direct toxic effect on pancreatic parenchyma, hypertriglyceridemia, and hypercalcemia, late duodenopancreatic reflux [2] Therefore, in the end and in these forms of pancreatitis is criminalized duodeno-pancreatic reflux.

In acute postoperative and posttraumatic pancreatitis, in those installed after extracorporeal circulation and organ transplants, vascular factor intervenes. It is responsible for the initiation and evolution of severe acute pancreatitis, the extension of necrosis by massive microthrombosis and release powerful vasoactive amines [2].

From the pathophysiological point of view, this condition was compared by Lucien Leger with an explosion in a factory of arms, wanting to emphasize that every moment of its causes and worsens performance following moments. Cascade of events begins with the intraglandular proteolic and lipolytic enzymes activation. Their release has the effect of edema, hemorrhage and tissue necrosis gland and its adjacent. So, in addition to autodigestion, responsible for the emergency citosteanecrosis spots, vascular factors intervene, leading to worsening initial phenomena [5]

This fluid is rich in enzymes may disseminate in the retroperitoneal space, usually at the root of mesentery and to the celiac plexus, leading to hydrocele, a sign which prove a severe form. Sometimes the fluid around the pancreatic gland remains stuck inside it, making pancreatic pseudocysts secondary to pancreatic necrosis. If there is a breach in parietal peritoneum , the pancreatic liquid floods peritoneal cavity, term phenomenon described as ascites pancreatitis. [4

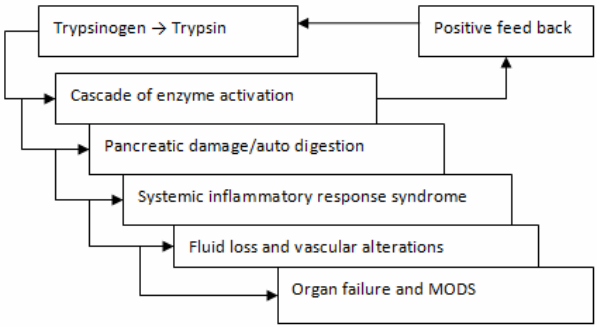
In addition to these changes we are witnessing the passage into the systemic circulation via portal and lymphatic and activated pancreatic enzymes. When so-called toxic enzimatic septicemia is installed-this lead to MSOF. Heavy losses in the liquid phase of pancreatitis by restraint in the Randall III space and release of hypotensive substances lead to installation of hypovolemia, an aggravating factor of organ failure, pancreatic encephalopathy and CID [4].

Next, I will briefly describe some of the elements that lead to installation deficiencies. Heart failure occurs as a result of and release of pancreatic cardiac depressant factor which lead to hypotension, hypovolemia and peripheral vasoconstriction.

At a high proportion of patients with severe acute pancreatitis, liver failure occurs with a marked decrease in the rates of phosphorylation and 40% reduction in mitochondrial ATP synthesis [3].

Hypoxia is also frequently present in these patients. Its appearance is early, whereas chest radiographs and respiratory rate are normal yet. Changes in O2 saturation but are detectable by pulse oximetry. [3] It is therefore recommended daily assessment of blood gases to detect hypoxemic patients and therefore treat them accordingly.

Figure no. 1. Pathogenesis of acute pancreatitis



Another complication in the evolution of acute pancreatitis is acute renal failure. Initially it was thought that would be due to hypovolemia. Werner and his colleagues have demonstrated the existence of a factor but produces alterations in the cortical blood flow with the consequence of decreased glomerular filtration rate. [4] So hypovolaemia correction is not sufficient, and requiring the administration of diuretics.

A small percentage of the total number of patients with acute pancreratitis can develop toxic psychosis with confusion (not due to excessive alcohol consumption), with complete reversibility for improving pathology.

More rarely meets encephalopathy pancreatitis. The most common diagnosis is confirmed by necropsy in unconscious patients before death, where there is a central nervous system demyelination. It is possible that these changes occur due to increased levels of lipases and proteases.

Early intracellular events in acute pancreatitis

In the sequence of events leading to pancreatic necrosis, the initial trigger mechanism is controversial and debated. It is universally accepted that the phenomenon is the autodigestion of the gland by its own enzymes. Some postmortem studies suggest that the primary premises would be periductal inflammation or periglobular fat necrosis. Many experimental studies contradict these assertions, showing that the primary lesions are acinar cell injury [9]. Acinar tissue changes not only procede those affecting the ducts pancreatic and adipose tissue, but continuous progress towards what we describe as a variety of bleeding and necrotizing pancreatitis. Moreover, an early desobstruction of the obliterated duct allows regression of the tissue necrosis. It also concluded that the critical intracellular events that precede any changes in acute pancreatits involves the acinar cells . Acinar cells possess a remarkable variety of defense mechanisms to protect them from proteolytic and lipolytic action, of their own digestive products.

First, since the synthesis of digestive enzymes, these proteins remain stored in secretory vesicles bounded by membranes, which prevents their contact with the cytosolic vital structures. [9]

Secondly, proteases are synthesized with an activation peptide in their C-terminal end, which prevents enzymatic activity until their split by enterokinase in the intestine. [9]

Thirdly, digestive enzymes are packaged and shipped together with large amounts of protease inhibitors that will prevent the activation of proteases in their compartment, thereby preventing cell necrosis. Then, even if you could get rid of digestive enzymes authoring fragile digestive enzymes could even get rid of fragile intracellular transport vesicles, strong buffering of cytosolic proteins made by its action will protect cells from potentially active proteases. [9]

Despite these protective mechanisms developed, there was direct evidence that intraglandular activation of proteases appear indeed during the initial phase of experimental pathology. By blocking the pancreatic enzymes,acinar cells are not able to unload their zymogens to digestive enzymes .

Two intracellular components of the cytoskeleton seem to be particularly important for regular exocytosis zymogens regular digestive enzyme and therefore involved in blocking their secretion: microfilaments network terminal, which is mainly composed of actin and microtubules. During the initial phase of experimental pancreatitis has been shown that both microtubules and microfilaments undergoes rapid disassembly [2]. In addition to the gradual disintegration of the cytoskeleton a rapid deterioration of its structural proteins,actine and betabulin has been seen. Prophylaxis exocytosis might not be sufficient to explain the premature intracellular activation of zymogens digestive enzymatic.

They proposed two hypotheses for the interpretation of early intracellular proteolysis. Some authors believe that the trypsinogen autoactivation is the responsible mechanism. Once there is a small amount of active protease, it catalyzes the conversion of remained trypsinogen and activation of other proenzymes such as chymotrypsinogen, procarboxypeptidase and proelastase [2].

The second hypothesis that attempts to explain autodigestion considers that trypsinogen is transformed into active trypsin by the action of lysosomal enzymes. In physiological conditions these two classes of pancreatic hydrolases (digestive and lysosomal) are separated from one another through a complex sorting mechanism by Golgi apparatus.

Potent inhibitors of lysosomal enzymes does not prevent pancreatitis or intracellular activation of proteases, while a serum protease inhibitor do so. The conclusion is that the subcelular redistribution or co-localisation of the lysosomal and digestive hydrolases taken separately, are not sufficient to induce activation of intracellular proteases and thus pancreas autodigestion in acute pancreatitis [9].

Swivel pancreatic enzyme trypsin, is because she is working on other proenzime. The trypsinogen trigger specific activation, resulting ultimately in autodigestion and pancreatitis is unknown, but several mechanisms have been proposed

•Cytoskeleton rupture

•Reduce pH

• Activation of apical hydrolases and enzymes

Molecular initial steps, the induction of biliary and alcoholic pancreatitis are likely different. Typically, acinar cell injury is followed by sequestration of inflammatory cells within the gland in the acute phase. This second phase is a balance between pro and anti-inflammatory cytokines. Nitric oxide and other meditation are produced and released into circulation, causing systemic inflammatory response syndrome (SIRS) [9]. MODS is likely to start several hours after onset of acute pancreatitis. Later stimulation may result from the activation of systemic inflammatory cells by extracellular matrix components released from necrotic tissue. They stimulate monocytes to secrete TNF-alpha factor, the resulting cascade of proinflammatory cytokines. Extension of pancreatic necrosis correlates with the development of organ failure and subsequently infection and appearance, but SIRS may occur without signs of infection and necrosis. [8]

Progression of acute pancreatitis

At the tissue level, the biochemical changes resulting from premature digestive enzyme activation damage the acinar cells, pancreatic interstitium,and vascular endothelium . In experimental models of acute pancreatitis,microcirculatory changes following acute pancreatic injury include vasoconstriction,capillary stasis, decreased oxygen saturation, and progressive ischemia. These microcirculatory changes lead to increased vascular permeability and edema of the gland (interstitial pancreatitis). Vascular injury could lead to amplification of the pancreatic injury by means of local microcirculatory failure, and through selective pancreatic ischemia , or ischemia–reperfusion injury.

The activation of granulocyte and macrophage leads to the release of proteolytic and lipolytic enzymes, reactive oxygen metabolites, proinflammatory cytokines as interleukins (IL) 1, 6, and 8, tumor necrosis factor (TNF),and arachidonic acid metabolites as prostaglandins, platelet-activating factor,and leukotrienes. Interestingly, cytokine activation is not limited to the intra or peri-pancreatic tissue, but can be systemic in nature.

CONCLUSIONS

Acute pancreatits is a disease that has many causes. Each cause seems to affect the acimar cell in some way that results in the premature activation and retention of potent proteolytic enzymes.These activated enzymes then injure the acinar cell andcause the immediate release of cytokines ans activate the complimate system. Together, these molecules attract and sequester inflammatory cells, in particular

neutrophils, which causesfurther secretion of cytokines, free radicals, and other vasoactive molecules, such as nitric oxide. We propose that the released inflammatory molecules induce local effects, such as pancreatic edemaand necrosis, and systemis complications, such hypotension, tachycardia, fever, capillary leak syndrome, and hypoxia. The cytokine relaeased in the pancreas also stimulates apoptosis, further enhancing the cell death response in pancreatitis. Much of the current research is aimed at understanding the links between these seriesof eventsand fiding agents that can modulate the cascade of events involved in pancreatitis. What is promising in this endeavour is that the response produced with pancreatitis is nearly identical with all etiologies, suggesting that therapy may not have tobe specific to a particular cause.

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