Acute pancreatitis in childhood: Research of pathogenesis and clinical implications

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Although acute pancreatitis occurs less frequently in children than in adults (unpublished data), it is probably more common in childhood than has previously been considered. Recent literature analysis has demonstrated significant resulting morbidity and mortality. Clinical awareness has improved dramatically, as demonstrated by the increase in the number of recent publications and etiological considerations. This review describes novel considerations in research related to the pathogenesis of acute pancreatitis and the arising clinical implications. This relationship is discussed regarding a better understanding of pathogenesis in pediatric disorders; increasing awareness; preventing damage by drugs and toxins; using novel diagnostic markers; and introducing new therapeutic tools.

Key Words: Acute pancreatitis, Childhood, Diagnostic markers, Toxins

Pancréatite aiguë chez l’enfant : recherche sur sa pathogenèse et ses répercussions cliniques

RÉSUMÉ : La pancréatite aiguë chez les enfants est plus courante qu’on l’avait d’abord cru. Une récente analyse de la littérature a permis de démontrer qu’il en résulte une morbidité et une mortalité importantes. Les cliniciens y sont de plus en plus sensibilisés, comme en font foi l’augmentation du nombre de publications et l’attention que reçoivent les questions d’ordre étiologique. Le but de cette synthèse est de décrire les nouvelles avenues de la recherche sur la pathogenèse de la pancréatite aiguë et sur ses nouvelles implications cliniques. Ce lien sera étudié pour permettre une meilleure compréhension de la pathogenèse des maladies infantiles, pour sensibiliser les lecteurs à l’existence de la maladie, pour promouvoir la prévention au moyen de médicaments et de toxines, et le recours à de nouveaux marqueurs diagnostiques et de nouveaux outils thérapeutiques.
A great variety of etiologies of acute pancreatitis are now evident in pediatric patients. This process is the result, in part, of an increasing awareness by physicians of this condition. There are several examples to demonstrate how a high index of clinical suspicion in pediatric patients allows one to diagnose this entity more frequently.

**INCREASING AWARENESS**

A great variety of etiologies of acute pancreatitis are now evident in pediatric patients. This process is the result, in part, of an increasing awareness by physicians of this condition. There are several examples to demonstrate how a high index of clinical suspicion in pediatric patients allows one to diagnose this entity more frequently.
The first example is organophosphates and carbamates, which are used as common domestic and agricultural pesticides and insecticides. Acute pancreatitis has been described in a few adult patients after accidental ingestion of an anticholinesterase insecticide, a substance not previously known to affect the exocrine pancreas (10). The direct toxic effects of these chemicals on the pancreas have been established in a few animal studies (11). In view of these observations Weizman and Sofer (12) noticed that children with this type of intoxication very often develop vomiting and abdominal pain associated with unexplained hyperglycemia. They suspected that this clinical constellation resulted from acute pancreatitis. Subsequently they performed a prospective study in 17 consecutive intoxicated children and demonstrated the development of acute pancreatitis in five (Table 1) (12).

Another example is the acute pancreatitis caused by yellow scorpion envenomation. This association was first described in a few adult reports. An extensive study of several animal species demonstrated very clearly that these venoms are able to induce pancreatic inflammation (13). Subsequently Sofer and colleagues (14) conducted a prospective study and showed that exocrine pancreatic involvement is not rare in children with this form of envenomation, which appears to explain some of the common gastrointestinal symptoms observed in these patients. Furthermore, an in vitro study using rat pancreatic tissue demonstrated that scorpion toxin induces pancreatic hypersecretion indirectly by stimulating the release of acetylcholine from pancreatic nerves (15). These effects were blocked by atropine (Figure 2). We speculate, therefore, that atropine may be clinically effective in suppressing certain sequelae of scorpion envenomation in humans. As a result we are currently trying to establish these effects in the experimental animal and, if successful, to investigate further possible therapeutic benefits in affected humans.

**PREVENTING DAMAGE OF DRUGS AND TOXINS**

More than 85 drugs have been reported to cause acute pancreatitis (8). The drugs associated with the highest incidence are azathioprine and mercaptopurine (3% to 5%), and didanosine (up to 23%). However, little is known about the pathogenesis of drug-induced pancreatitis.

Azathioprine-induced pancreatic damage may be treatable and avoidable based upon investigation of its pathogenesis. A number of recent observations have suggested that oxidative stresses, such as hydrogen peroxide or lipid peroxide, can be a major contributor to the cellular injury found in acute pancreatitis (16). Glutathione represents one of the major intracellular defence systems against mediators of oxidative stress (Figure 3). Glutathione has been shown to be protective in experimental pancreatitis (17). Hepatic glutathione depletion occurs in rats treated with azathioprine. Azathioprine may undergo glutathione-mediated metabolism in the pancreas, leading to depletion of pancreatic glutathione (18). Alpha-tocopherol is an effective antioxidant that has been demonstrated to ameliorate the course of experimental pancreatitis (19). This observation suggests a possible beneficial role for antioxidants in azathioprine-induced pancreatitis. This mode of therapy needs to be studied in humans.

Another example is the acute pancreatitis that is a well-

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**TABLE 1**

<table>
<thead>
<tr>
<th>#</th>
<th>Age (years)</th>
<th>Sex</th>
<th>GI symp</th>
<th>Serum amylase (U/L)</th>
<th>Serum trypsin (ng/mL)</th>
<th>Serum glucose (mg/100 mL)</th>
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AP: Abdominal pain; D: Diarrhea; F Female; GI symp: Gastrointestinal symptoms; M: Male; N: Nausea; SAP: Severe abdominal pain; V: Vomiting. Data from reference 12.
known complication of open heart surgery (20). In a recent prospective study multivariate analysis was used to identify the variables most strongly associated as risk factors for the development of acute pancreatitis after cardiac surgery (21).

Interestingly, one factor was perioperative administration of calcium chloride, which displayed a dose-related increase in risk. Although this close correlation cannot firmly establish a cause and effect relationship, causality is suggested by experimental studies demonstrating that acute hypercalcemia is sufficient to induce dose-dependent morphological alterations characteristic of acute pancreatitis, acute hyperamylasemia and early ectopic trypsinogen activation (22).

### NOVEL DIAGNOSTIC MARKERS

Measurement of serum amylase levels is still the most common test used to confirm a diagnosis of acute pancreatitis. However, elevated serum total amylase is often associated with various nonpancreatic disorders. Hyperamylasemia often results from amylase of nonpancreatic origin, mainly salivary, or from decreased renal clearance (23). Better specificity has been described using urinary amylase-creatinine clearance or measuring serum isoamylase, lipase, trypsinogen, elastase or phospholipase A2 (24,25).

The search for an ideal diagnostic marker has been intensive. An optimal tool should demonstrate better specificity, longer plasma peaks and improved correlation with clinical severity.

Recently several novel diagnostic markers have been investigated in animal experimental pancreatitis and in humans with acute pancreatitis. These include trypsinogen activation peptides, phospholipase A2 activation peptides, C reactive protein and the pancreatitis-associated protein (26,27). Several inflammation markers also appear to serve as prognostic indexes, including the inflammatory cytokines interleukin (IL)-1, IL-6 (Figure 4) and tumour necrosis factor-alpha (28). Other promising markers, such as the zymogen granule membrane protein GP2, have not yet been studied in humans (29).

### FUTURE THERAPEUTIC TOOLS

Although the treatment of pancreatitis is largely supportive, several attempts – directed mainly at finding therapeutic inhibitors of proteases and phospholipase – have been made to develop specific treatment. After the protease inhibitor aprotinin failed in clinical trials, other protease inhibitors such as gabexate mesilate, camostate and nafamostat mesilate were evaluated. Despite promising results in experimental animals, clinical trials in humans have yielded conflicting results (30).

Because intravenous protease inhibitors have failed to demonstrate efficacy, investigators have suggested an alternative approach based on recent experimental evidence that digestive enzymes can be activated within the acinar cell. In this process lysosomal enzymes are being colocalized with digestive zymogens which, in turn, activate trypsin in an acidic pH optimum. The amine chloroquine is a weak base that accumulates in several acidic intracellular organelles, including lysosomes, and is capable of increasing pH. Although lysosomal acidity is a prerequisite for trypsinogen activation, and such therapy would be expected to ameliorate experimental pancreatitis, use of this drug has so far been disappointing (31). However, further research of other modes of therapy that are able to affect intracellular trypsin activation is indicated. The use of endogenous anti-inflammatory cytokines is another consideration for treating acute pancreatitis.
pancreatitis. IL-10 decreases the severity of murine experimental acute pancreatitis, mainly by inhibiting the development of acinar necrosis. Inhibition of local tumour necrosis factor-alpha might explain, at least in part, the protective effect of IL-10 (32).

The use of antioxidants and free radical scavengers in other types of experimental acute pancreatitis appear to have some potential for treatment (33). Further research using other more potent antioxidants may offer more effective therapy.

Nitrous oxide modulates pancreatic secretion and maintains pancreatic bloodflow by regulating vascular tone. Because acute pancreatitis is associated with impaired vascular function, the role of nitrous oxide and some nitric oxide

REFERENCES
