CHAPTER 85
PANCREATITIS

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Introduction

Pancreatitis is defined as inflammation of the pancreas (Figure 85.1). It is a rare, but significant, cause of disease in children. This relative rarity in childhood, compared to that in adulthood, may have previously resulted in the underestimation of its significance, and, indeed, to underestimation and underreporting of its true incidence.

The disease is divided into acute and chronic pancreatitis, conditions that show contrasting patterns of aetiology, clinical presentation, and outcome. Acute pancreatitis is defined as sudden, reversible inflammation of the pancreas. Chronic pancreatitis is the irreversible result of persistent inflammation and is associated with destruction and infiltration of normal pancreatic tissues.

Despite its relative rarity, pancreatitis continues to cause significant morbidity and mortality throughout the world. Prognosis is variable, according to the severity of the disease, but episodes of acute pancreatitis in children are usually mild and associated with a good prognosis. Research continues into the precise pathogenesis of this disease. However, it is most important that this condition be considered and excluded when appropriate.

Demographics

The incidence of both acute and chronic pancreatitis in childhood is low. Recent studies have reported the incidence of acute pancreatitis as approximately 1 in 50,000 in the United States.[1] An apparent increase in incidence over the past few decades may reflect either a true increase in disease prevalence or increased awareness and diagnosis of the disease.

Aetiology/Pathophysiology

The aetiology of pancreatitis in childhood is diverse. There is a definite contrast between the most common causes of pancreatitis in adults (namely, gallstones, alcohol, and—increasingly —hypertriglyceridaemia) and the causes of pancreatitis in children.

Acute Pancreatitis

Two of the most common causes of acute pancreatitis in children are blunt abdominal trauma and multisystem disease.[2] Other causes include drugs and toxins (including alcohol), infections, idiopathic causes, and congenital abnormalities. It has previously been reported that acute pancreatitis diagnosed in children under the age of 3 years is always associated with a concurrent systemic disease process.[3] In cases of trauma, it is important to also consider nonaccidental injury. Goh et al.[4] reported 12 cases of acute pancreatitis seen in their institution over a 4-year period. Two of the 5 cases attributable to trauma were a result of nonaccidental injury.[4]

More than 85 drugs have been reported to cause acute pancreatitis.[5] Important examples include the nucleoside analogues didanosine (up to 23% of cases[5]) and zalcitabine, used in the treatment of human immunodeficiency virus (HIV); cytotoxic drugs, such as L-asparaginase; and immunosuppressive drugs, such as azathioprine and mercaptopurine (3–5% of cases[5]). Other drugs associated with acute pancreatitis include analgesics (paracetamol, salicylates); thiazides; sodium valproate; corticosteroids; and antibiotics (tetracyclines and erythromycin).

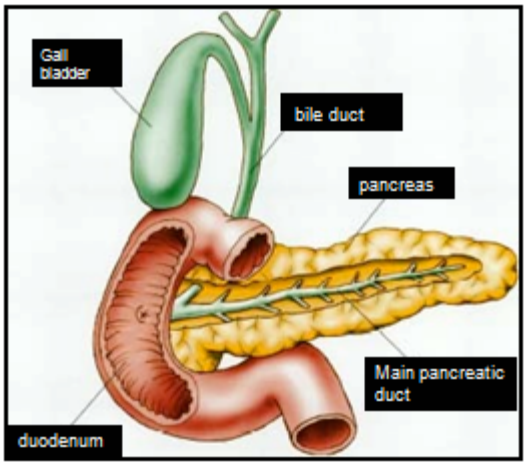

Figure 85.1: Normal anatomy of the pancreas.

A wide variety of infections (bacterial, viral, and parasitic) also have been associated with acute pancreatitis. These include mycoplasma, Epstein-Barr virus (EBV), cytomegalovirus (CMV), influenza A, mumps, measles, rubella, malaria, ascariasis, cryptosporidium, and leptospirosis. Multisystem diseases implicated with acute pancreatitis include systemic lupus erythematosus (SLE), Henoch-Schönlein purpura (HSP), Kawasaki disease, Reye's syndrome, and haemolytic-uraemic syndrome.

Congenital abnormalities of the pancreas, biliary tree, or alimentary system (including pancreas divisum, annular pancreas, pancreatic duct obstruction, choledochal cysts, and enteric duplication cysts) lead to periampullary obstruction and therefore may contribute to the development of acute pancreatitis.[6]

The process of inflammation within the pancreas involves both pancreatic acinar cell injury and premature conversion of trypsinogen to trypsin in the pancreas. This proenzyme is normally activated in the duodenum by enterokinase or trypsin. However, autodigestion and pancreatic cell damage will occur if autoactivation takes place within the pancreas. Pancreatic trypsinogen is stored in close association with other proenzymes, and its untimely activation may result in an uncontrolled production of other digestive enzymes.[2]

Chronic Pancreatitis

Chronic pancreatitis is more commonly seen in adults, particularly those with a history of alcohol misuse. However, this disease also occurs in childhood, and one of the most common causes of chronic pancreatitis in children—tropical calcific pancreatitis—occurs in the developing world. This is also known as tropical pancreatitis, juvenile tropical pancreatitis syndrome, tropical calculous pancreatopathy, or nutritional pancreatitis.[7] Other causes of chronic pancreatitis include cystic fibrosis, fibrosing pancreatitis, hereditary chronic pancreatitis, and inborn errors of metabolism.

Several hypotheses have been proposed to explain the pathophysiology of chronic pancreatitis. The necrosis-fibrosis hypothesis[8] suggests that repeated episodes of acute inflammation lead to fibrosis of pancreatic tissues. Another theory suggests that a single, severe, pathological incident is the critical factor for development of chronic pancreatitis. This event is significant enough to result in attraction of monocytes and subsequent infiltration, differentiation, and proliferation of pancreatic stellate cells.[9] Fibrosis is associated with chemokine and cytokine release, caused by recurrent cell injury.

Furthermore, work is currently under way to investigate the role of genetic mutations in the development of chronic pancreatitis. Mutations in the cationic trypsinogen gene, cystic fibrosis transmembrane conductance regulator (CFTR), and serine protease inhibitor Kazal type 1 (SPINK1) are all currently under investigation.[2]

The most common mutations in the cationic trypsinogen gene are mutations R122H and N291. These cause hereditary pancreatitis, and most patients develop chronic pancreatitis within 10 years of the onset of the initial disease. Both CFTR and SPINK1 mutations act in combination with other mutations and environmental factors to predispose individuals to development of pancreatitis. There are more than 1200 known mutations in the CFTR gene, which encodes a protein found in the apical membrane of pancreatic duct cells. This gives rise to a spectrum of disease from mild to severe, and a number of different mutation combinations predispose to development of pancreatitis. The SPINK1 mutation predisposes to idiopathic chronic pancreatitis. Ninety percent of individuals with this mutation will develop pancreatitis before the age of 20 years.[2] This mutation is thought to increase susceptibility to recurrent acute and chronic pancreatitis, especially in patients with multiple genetic mutations and exposure to environmental risk factors.[6]

Clinical Presentation

The diagnosis of pancreatitis relies upon clinical suspicion, laboratory results, and radiographic evidence. However, in the initial stages of the disease, the clinical presentation may provide important clues as to the nature of the disease. Correct interpretation of relevant features in the history and clinical findings will allow more rapid diagnosis and instigation of resuscitation and therapeutic measures.

History

There may be great variety in clinical presentation. If able, the patient with acute pancreatitis may describe increasingly severe abdominal pain (usually, but not exclusively, in the epigastrium and upper abdomen) of either sudden or gradual onset. This may radiate to the left or right upper quadrants, and is exacerbated by foods (particularly high-fat foods) and movement. Classically, in adults the pain radiates to the back; however, this is rare in children, and has not been reported in 60–90% of childhood cases.[10,11] There is often a history of nausea and vomiting. Behavioural clues may include the child who lays very still, or who positions himself on hands and knees to relieve pain.[6]

The patient with chronic pancreatitis may describe a severe, constant, epigastric pain, radiating to the back. This may be relieved by sitting forward and worsened by eating. The pain is often associated with nausea and vomiting. As the disease progresses, pain may decrease. The patient may also describe greasy, bulky stools and weight loss. With loss of pancreatic endocrine function, patients develop diabetes, which is notoriously difficult to control.

Physical Examination

At acute presentation, patients may be dehydrated, and there may be an element of systemic upset with tachycardia, hypotension, and pyrexia. Severe cases with respiratory compromise may show reduced oxygen saturations. The abdomen may be distended, and there may be abdominal tenderness (particularly in the upper abdomen) and guarding. There may also be rebound tenderness, and bowel sounds may be reduced.

Patients with chronic pancreatitis may show evidence of other multisystem or genetic diseases, such as cystic fibrosis.

Investigations

Simple laboratory investigations can help in the diagnosis of acute pancreatitis:

- Serum amylase levels increase within 12 hours of onset of inflammation, and this elevation may persist for up to 5 days.[6] Prolonged elevation may suggest the presence of a pancreatic pseudocyst or other complication.
- Elevation of serum lipase also indicates acute pancreatitis.

Serum levels may remain elevated for longer than serum amylase. It is considered diagnostic when levels of amylase or lipase are raised three times above normal; however, these markers are not specific. In addition, the destruction of pancreatic tissue in chronic pancreatitis may result in a normal amylase level despite the presence of disease. In children, serum amylase is less sensitive and specific for pancreatitis than it is in adults. In one study, 40% of children with proven pancreatitis had a normal serum amylase.[12] Indeed, many other conditions may cause a raised serum amylase, including appendicitis, intestinal obstruction, disorders of the salivary glands, and renal failure.[6] If possible, it may also be helpful to determine the specific isoenzyme of amylase that is present in order to precisely identify its source.

Patients may also develop hypocalcaemia or hyperglycaemia, occasionally severe and symptomatic.

Imaging

Imaging is important in pancreatitis for initial diagnosis, identification of complications, and subsequent follow-up.

Plain Film Radiography

Abdominal x-ray (AXR; see Figure 85.2) may show a sentinel loop (single dilated loop of bowel), dilated loops of duodenum, or loss of the psoas muscle shadow. In up to 20% of cases, chest x-ray (CXR) may show unilateral or bilateral pleural effusions.[13]

Ultrasonography

Ultrasonography (US) is an inexpensive and often readily available imaging modality that may be useful in establishing the diagnosis of pancreatitis without exposing the child to ionising radiation. It also allows evaluation of other abdominal organs in a patient who presents with acute abdominal pain of unknown aetiology. US imaging may be extremely useful in combination with clinical examination and simple laboratory tests. In the case of pancreatitis, the pancreas may be enlarged and oedematous, with altered echogenicity. There may be biliary sludge, gallstones, or dilated common bile duct or intrahepatic ducts, suggesting an obstructive cause.[2] The presence of calcification may suggest chronic pancreatitis. US may also reveal structural abnormalities, such as pancreas divisum, annular pancreas, or a choledochal cyst.

Computed Tomography

Computed tomography (CT) scans can be useful in both confirmation of the diagnosis of pancreatitis and identification of subsequent complications. In addition, it can exclude other serious intraabdominal causes of pain that may be confused with pancreatitis, including damage caused by trauma and mesenteric infarction. In acute pancreatitis (Figure 85.3), the pancreas may be enlarged, with decreased echogenicity. Chronic pancreatitis shows calcification (see Figure 85.4).

Endoscopic Retrograde Cholangiopancreatography

Although rarely used during an acute episode of pancreatitis, endoscopic retrograde cholangiopancreatography (ERCP) may identify structural causes of recurrent pancreatitis and allow for therapeutic intervention at the time of diagnosis.

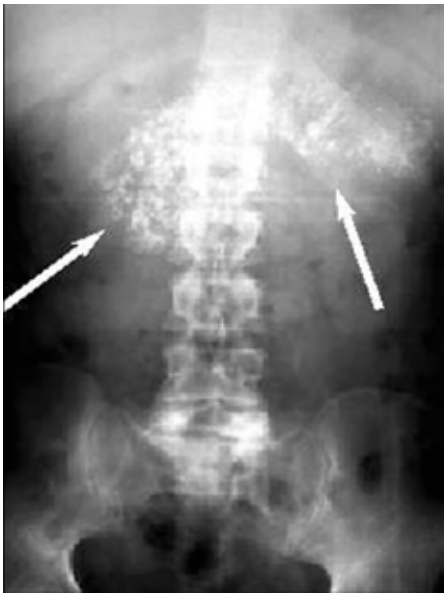

Figure 8.2: Abdominal x-ray showing pancreatic calcification.

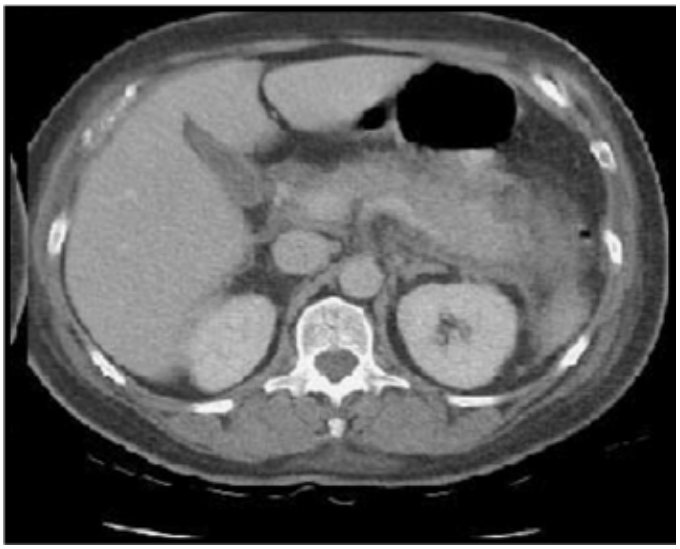

Figure 85.3: CT scan showing acute pancreatitis.

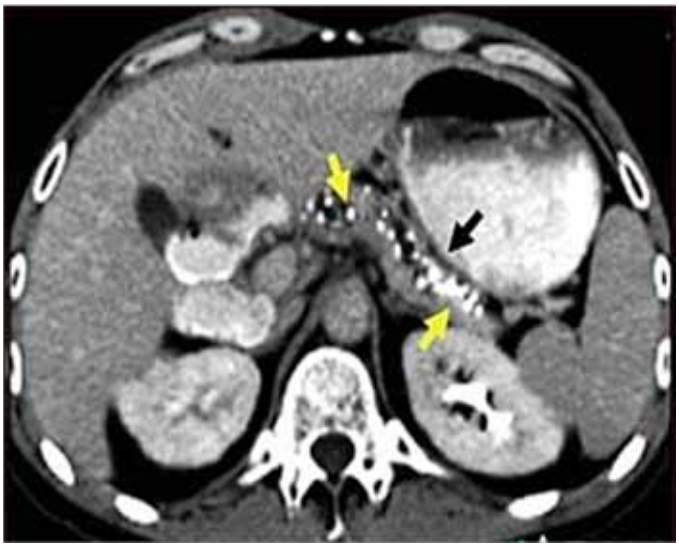

Figure 85.4: CT scan showing chronic pancreatitis with calcification (arrows).

Magnetic Resonance Cholangiopancreatography

Magnetic resonance cholangiopancreatography (MRCP) provides detailed imaging of the biliary tract without the need for an invasive procedure or exposure to ionising radiation. MRCP is frequently carried out in adults and has great potential for use in children.

Management

Acute Pancreatitis

Initially, management of acute pancreatitis must be supportive and symptomatic. This disease is commonly divided into mild and severe forms. Close monitoring is essential, as patients may deteriorate rapidly. This includes a strict fluid balance—patients may require considerable fluid resuscitation to counteract fluid losses into the "third space". Adequate analgesia is also essential. If the patient is vomiting, insertion of a nasogastric tube may increase patient comfort and significantly reduce the risk of such complications as aspiration.

In addition to these measures, resting the gut by making the patient nil by mouth for several days may promote recovery in mild cases of acute pancreatitis. These patients will require appropriate fluid management, with maintenance fluids in addition to resuscitation fluids. If recovery is prolonged, patients may require parenteral or jejunal nutrition. Unless pancreatic infection is suspected, it is not necessary to administer antibiotics.

In severe cases, patients may require much more intensive management, including high-dependency or intensive care.

Surgical intervention is required only in cases of acute pancreatitis that have become complicated by pancreatic necrosis. These cases require debridement of the necrotic tissue in an attempt to prevent secondary infection.

Chronic Pancreatitis

The management of chronic pancreatitis, once initial resuscitation and appropriate analgesia have been implemented, must focus on determining the aetiology and monitoring the disease consequences and complications. Pathological conditions, such as cystic fibrosis, other genetic mutations, and autoimmune diseases, must be excluded with genetic testing, if appropriate. Pancreatic imaging must be used to exclude structural abnormalities.

There may be functional implications of chronic pancreatitis. When pancreatic cell damage is sufficiently extensive, there will be a loss of endocrine (leading to diabetes mellitus) and exocrine (resulting in malabsorption) functions. These patients must be installed in a programme of follow-up, and they or their caregivers must receive appropriate education about their disease and its consequences.

Surgical intervention is usually indicated in chronic pancreatitis only for the relief of severe, persistent pain. These procedures aim to improve drainage of the pancreatic ducts and may also prevent disease recurrence in children.[1] This may be approached either endoscopically, with stent placement, or at open operations, such as lateral pancreaticojejunostomy.

Severity Scoring

In adults, a number of different scoring systems are used to assess the severity of acute pancreatitis. These scores are not absolutely transferable to children, but one group has compared a scoring system designed specifically to paediatric patients with these adult scoring systems.[14] This system compares eight variables to predict severe outcome and mortality during an episode of acute pancreatitis, and has been shown to have greater sensitivity and negative predictive value compared to the Ranson and Glasgow scoring systems. The factors considered were age (<7 years), weight (23 kg), admission white blood cell count (>18.5 × 10^9/L), admission LDH (>2000 IU/L), 48-hour trough albumin, 48-hour fluid sequestration, and 48-hour rise in blood urea nitrogen. Each factor is allocated a score of 1 point, and higher total scores are associated with an increased chance of severe pancreatitis and mortality. Scores of

5–7 points showed 80% severe outcome and 10% mortality; 2–4 points showed 38.5% severe outcome and 5.8% mortality; and 0–2 points showed 8.6% severe outcome and 1.4% mortality.

Complications

It is very important that patients be monitored for signs of complications of pancreatitis. Pancreatic imaging must be considered in patients whose symptoms do not improve or get worse.

Acute Pancreatitis

Most reports of acute pancreatitis suggest that the disease is mild and has a good prognosis. Goh et al.[4] reported that of a group of 12 patients, 5 had radiological evidence of pseudocyst formation (4 of which had acute pancreatitis attributed to trauma). This is in agreement with other reports that suggest that pancreatic pseudocyst development occurs most commonly in children who have trauma-induced pancreatitis.

In children, pseudocysts do not usually require surgical intervention and often resolve spontaneously. In the study by Goh et al.,[4] 2 patients developed pleural effusion, one of whom also developed pulmonary consolidation and coagulopathy, requiring administration of fresh frozen plasma. Pancreatic necrosis is rare in children; however, there have been reports of severe, haemorrhagic necrotic pancreatitis associated with very poor prognosis.

Recurrent episodes of acute pancreatitis may result in chronic pancreatitis, which has considerable implications for long-term morbidity and mortality.

Chronic Pancreatitis

Both local and systemic complications occur in chronic pancreatitis (Figure 85.5). Local complications include pseudocyst formation, splenic vein thrombosis, pseudoaneurysm, duodenal or common bile duct obstruction, pancreatic fistula, and the long-term complication of pancreatic adenocarcinoma.[6] Systemic complications, as previously mentioned, include malabsorption and development of diabetes mellitus.

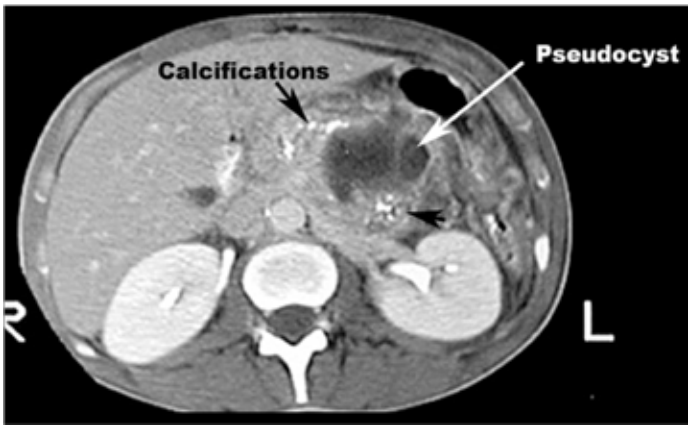

Figure 85.5: CT scan showing chronic pancreatitis with complications.

Prognosis and Outcomes

Acute Pancreatitis

In uncomplicated episodes of acute pancreatitis, prognosis is very good and symptoms may settle within days. However, the prognosis varies considerably between mild and severe forms. Mortality in mild disease is approximately 10%, compared with up to 90% in severe necrotizing or haemorrhagic disease. It has been shown that recurrent acute pancreatitis occurs in up to 10% of children after an episode of acute pancreatitis. This is more likely to occur in children with other predisposing risk factors, however.[14]

Chronic Pancreatitis

The systemic implications of chronic pancreatitis may have a significant impact upon the patient. The effects of irreversible loss of exocrine and endocrine pancreatic function may result in considerable morbidity. It has been shown that chronic pancreatitis is a risk factor for pancreatic adenocarcinoma, and a cohort study of patients with hereditary pancreatitis has reported an estimated cumulative risk of pancreatic cancer in these patients of 40% up to age 70.[15]

Prevention

As the onset of pancreatitis cannot be prevented, it is vital that this condition be considered in all children with acute abdominal pain and vomiting, especially those who may be at higher risk of the disease. These children include those who have known congenital abnormalities of the pancreas, are taking relevant medications, and have a known congenital abnormality of the pancreas or predisposing genetic condition. Early diagnosis, close monitoring, and appropriate follow-up will help to ensure a favourable outcome.

Evidence-Based Research

Table 85.1 presents a retrospective review of children with acute pancreatitis in a 4-year period.

Figure 85.1: Evidence-based research.

Title	Childhood acute pancreatitis in a children's hospital
Authors	Goh S-K, Chui C, Jacobsen A
Institution	KK Women's and Children's Hospital, Singapore
Reference	Singapore Med J 2003; 44(9):453–456
Problem	Review of all cases of acute pancreatitis, including clinical and radiological findings and outcome.
Intervention	Retrospective review of patients presenting with acute pancreatitis between 1998 and 2002.
Comparison/ control (quality of evidence)	Twelve cases were identified as having acute pancreatitis. Most presented with abdominal pain (n = 11) and vomiting (n = 7). The most common aetiological cause was trauma (n = 5).
Outcome/ effect	There was no mortality. Recurrence occurred in two patients, and one patient required surgical intervention. Mean hospital stay was 12.41 ± 4.54 days.
Historical significance/ comments	This paper describes the rarity of acute pancreatitis, but highlights its clinical significance and excellent prognosis.

Key Summary Points

1. Pancreatitis (inflammation of the pancreas) is a rare but clinically significant cause of disease in children. It must be considered in all children presenting with abdominal pain and vomiting.
2. Acute pancreatitis is sudden, reversible inflammation of the pancreas.
3. Chronic pancreatitis is the irreversible result of persistent inflammation and is associated with destruction and infiltration of normal pancreatic tissues.
4. There is a broad spectrum of aetiology of pancreatitis; the aetiology is different in children and adults.
5. Imaging is important for initial diagnosis, identification of complications, and follow-up.
6. The management of acute pancreatitis is mainly supportive and symptomatic.
7. The management of chronic pancreatitis includes identification of causative factors, including cystic fibrosis, other genetic mutations, and autoimmune disease.
8. Episodes of acute pancreatitis are usually mild and associated with good prognosis. Complications such as pancreatic necrosis, however, are associated with high mortality (up to 90%).
9. Early diagnosis, close monitoring, and appropriate follow-up all contribute to a good prognosis.

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