Chapter

Pediatric Pancreatitis: Not a Rare Entity

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Abstract

The incidence of acute pancreatitis is increasing in children and it should be considered as part of differential diagnosis in case of abdominal pain. The etiology of acute pancreatitis in this subpopulation is related to several conditions and risk factors, such as drugs, obesity, infections, trauma and anatomic abnormalities. In older children abdominal pain is the first symptom in more than 90% of cases, where as in younger children vomiting represents an early clinical manifestation. Diagnosis is based on laboratory investigation, such as serum levels of lipase, and imaging findings (ultrasonography, CT scanning or MRI) such as detecting edema, hemorrage or necrosis of pancreatic parenchyma or in peripancreatic fat. Treatments for adults and children are similar. Rapid and accurate assessment of the severity of pancreatitis is absolutely indicated for selecting the appropriate treatment and predicting the prognosis.

Keywords: pancreatitis, children, abdominal pain, severity assessment

1. Introduction

Pediatric pancreatitis has increased in incidence during last decades and 1/10,000 children per year is affected by the acute form genetic mutations and congenital abnormalities represent the major risk factors for this disease but there is no agreement about a certain pathogenetic theory. The reasons of pancreatitis' burden in pediatric population may be multifactorial and it can be explained by an improved detection instead of a real increase [1].

In children, pancreatitis is categorized as acute pancreatitis (AP), acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP). Here we summarize recent advances in the field of pediatric pancreatitis with focus on etiologies, pathogenesis, diagnosis and therapy.

2. Acute pancreatitis

Acute pancreatitis (AP), in children is increasingly recognized to be a challenge for affected patients and their families, their treating physicians and surgeons, and the health care system. The incidence of pediatric AP was estimated at 3.6–13.2 per

100,000 per children per year, which is within of the range of incidence reported for adult AP. Genetic contributions to the development of pancreatitis, especially in acute recurrent and chronic pancreatitis are now increasingly recognized. There are no evidence-based diagnostic guidelines for pancreatic disorders in children. The diagnosis criteria are based on symptoms, biochemical and imaging evidence of pancreatitis, with two of the three criteria required to diagnose AP. A multicenter effort led by INSPPIRE (INternational Study Group of Pediatric Pancreatitis: In Search for a CuRE) defined AP as requiring 2 of: (1) abdominal pain compatible with AP, (2) serum amylase and/or lipase values ≥3 times upper limits of normal, (3) imaging findings consistent with AP. Although abdominal pain is the most common clinical manifestation, it may be absent in up to one third of pediatric patients. The diagnostic yield and concordances for serum pancreatic enzymes and imaging for the diagnosis of pediatric AP will be discusses. Pediatric AP is associated with significant disease burden. There is currently no consensus on the definition for severity of AP in children. However, there are now predictors of severity for AP that has been developed and validated in children. The management of AP remains driven by adult studies and recommendations. Treatment is directed at the underlying etiologies as well as supportive measures.

2.1 Etiology

While alcohol and gallstones represent the main causes of acute pancreatitis in adult population, the etiological scenario of acute pancreatitis is mostly due to drugs, infectious diseases, congenital abnormalities or trauma (**Table 1**). Furthermore etiological factors may vary considerably according with ethnicity.

2.1.1 Infections

Pediatric acute pancreatitis is associated with paramyxovirus or mycoplasma infections. Mumps virus induces parotitis and orchitis in pediatric population and may be complicated by meningoencephalitis or pancreatitis. In the latter case clinical manifestations are represented by usually self-limiting diarrhea and abdominal pain. Mycoplasma infection-related pancreatitis can be distinguished into two types: early onset type and late-onset type following respiratory tract symptoms beginning. This different onset spectrum is due to a direct injury of mycoplasma into the acinar cells in the former type while to an autoantibodies targeting in the latter [2].

2.1.2 Congenital abnormalities

Chole-dochal cyst constitutes the most principal cause of AP. In case of abnormal junction between pancreatic and biliary ducts the sphincter of Oddi encircles

Common	Less common	Rare
Biliary disorders	Infections	Autoimmune pancreatitis
Systemic conditions	Metabolic diseases	Anatomic pancreatobiliary abnormalities
Medications	Genetic/hereditary	
Trauma		
Idiopathic		

Table 1.
Causes of acute pancreatitis in children.

a single channel leading to bile reflux into the Wirsung duct is communication between in course of sphincter contraction or bilestone impingement in the common channel [3].

2.1.3 Drugs and chemotherapeutic agents

Drug-induced acute pancreatitis accounts for 21% of all cases in pediatric population. Valproic acid, radiocontrast and corticosteroids can induce pancreatitis in the context of epilepsy or inflammatory bowel diseases [4].

L-asparaginase-associated pancreatitis (AAP) occurs in 0.7–24% of children treated for acute lymphoblastic leukemia with mortality rates of 2–5%. Older children demonstrate an high risk for developing acute pancreatitis and if it occurs they could experience cancer recurrence [5].

2.1.4 Trauma

Pediatric pancreatic injuries are uncommon and can be mostly ascribed to vehicle accidents. Anyway because of its retroperitoneal location pancreas is preserved in case of minor abdominal traumas and a pancreatic transection can occur clinically silent [6].

2.2 Pathophysiology

Acute pancreatitis is due to an organ injury with a subsequent inflammatory response that may involve both adjacent and distant structures. The first pathogenetic event may be represented by an acinar cell injury (**Figure 1**) that produces pancreatic edema with the activation of the inflammatory pathway. The release of cytokines and chemokines leads to a systemic inflammatory response (SIRS) and to complications such as pancreatic necrosis, shock and distant organ failure.

Several hypotheses have been advanced explaining the mechanism of this acinar cell damage. The autodigestion model focused on a premature calcium-mediated intracellular trypsinogen activation in trypsin (**Figure 1**). Trypsin then activates digestive enzymes that mediate acinar cell injury. On the other hand, recent studies in animal models of AP highlight the pathogenetic role of colocalized zymogens and lysosomes, intra acinar activation of zymogens, nuclear factor-κb activation and inhibition of secretion [7].

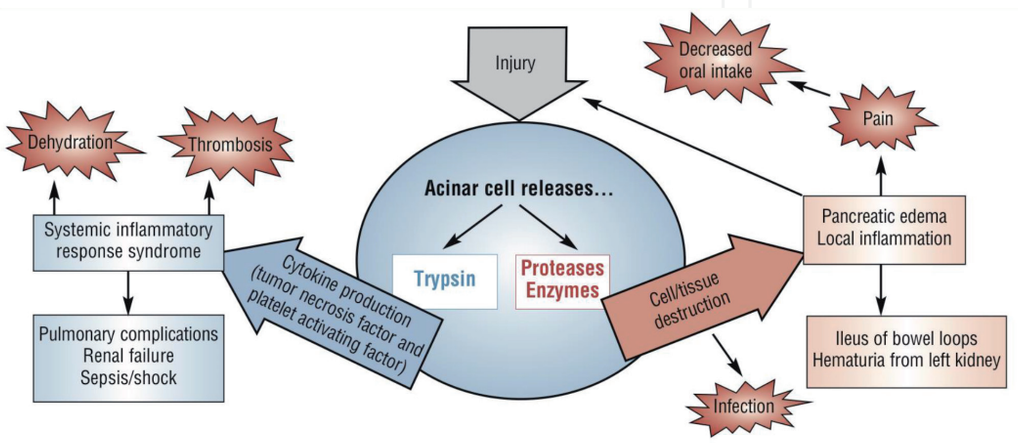

Figure 1.
Pathophysiology of acute pancreatitis.

2.3 Diagnosis

The diagnosis of AP in children depends on clinical manifestations, laboratory tests, and imaging. Moreover a careful estimation of severity is fundamental for establish the most appropriate treatment (**Figure 2**).

2.3.1 Clinical features

There are differences in clinical onset and natural course between adults and children. Acute pancreatitis symptoms are non-specific and depend on child's age and developmental level. Abdominal pain is typically epigastric but it can be localized to the right upper quadrant or left upper one. It can occur constantly or intermittently, with radiation to the back. The pain is dull, boring and deep. Pancreatitis should be suspected in all pediatric patients who experience, as isolated or combined symptoms, abdominal pain, nausea and/or vomit, the latter due to peripancreatic inflammation extended to the gastric wall [8].

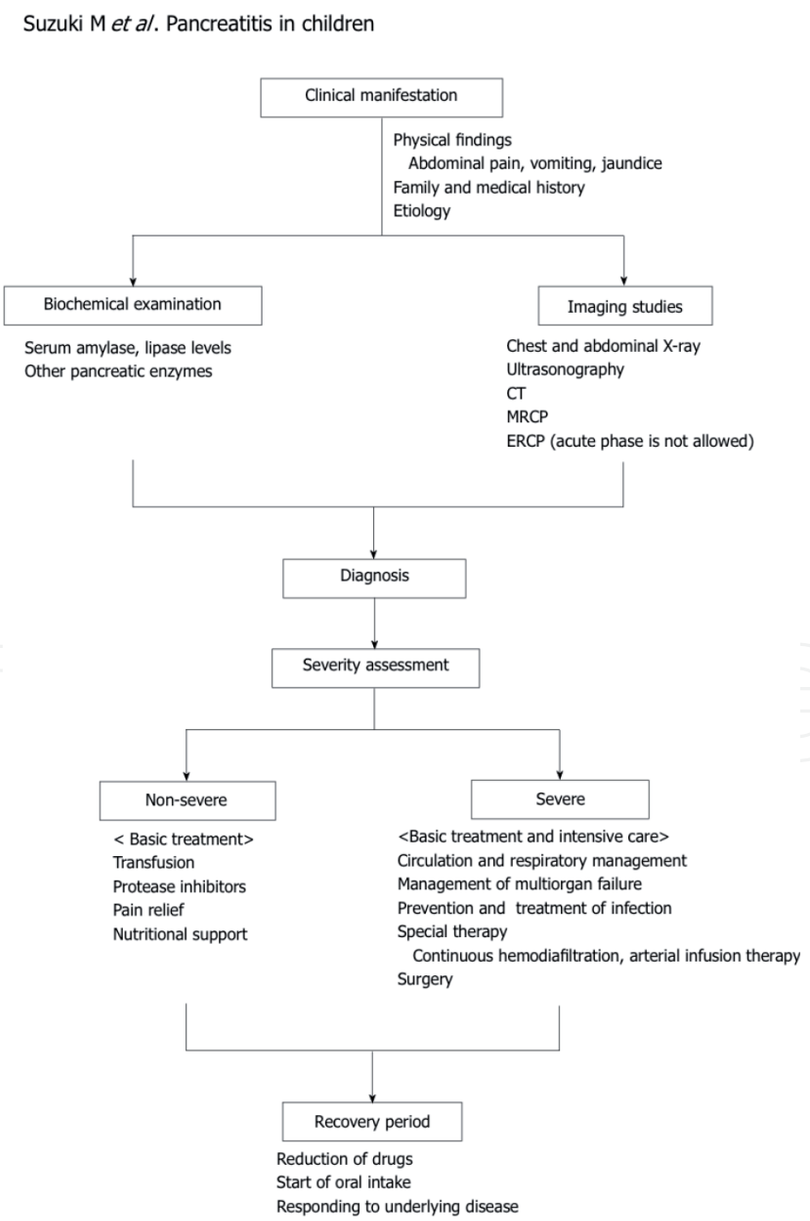

Figure 2.
Pediatric acute pancreatitis diagnostic flow chart.

2.3.2 Biochemical tests

The increased serum levels of amylase enzyme greater than three upper limits of normal are also detected in case of pancreatobiliary tract obstruction and perforative peritonitis, in addition to salivary gland pathologies and renal failure. Therefore this parameter is associated with a low specificity. On the other hand serum lipase levels have a sensitivity of 86.5–100% and specificity of 84.7–99.0%. In case of severe pancreatitis, serum lipase levels seven times higher than normal have been detected within the first 24 h. It is important to underline that in case of drug-induced acute pancreatitis serum amylase may not be elevate [9]. In addition, we may consider other chemistry panels to define a diagnosis like serum calcium, electrolytes, urea nitrogen, creatinine, transaminases, albumin, bilirubin, triglycerides and blood cell count [10].

2.3.3 Diagnostic imaging

Transabdominal ultrasound is the diagnostic study of choice to evaluate biliary tree abnormalities in children. In pediatric age pancreatic head tend to be larger than body and tail and this is a potentially confounding feature that may lead to a misdiagnosis. Diffuse or focal enlargement of the pancreatic gland may be present in AP and is attributable to edema. Echogenicity is a variable feature in case of pediatric pancreatitis, however hypoechogenicity is frequently seen.

One of the most valid radiological finding is represented by the dilatation of the pancreatic duct (1–6 years old, >1.5 mm; 7–12 years old, >1.9 mm; 13–18 years, >2.2 mm). Poorly defined borders or localized intraparenchymal fluid collection are usually detected at ultrasound imaging in the acute setting.

Parenchymal hypodensities, heterogeneity, irregularity of the glandular margins and inflammatory changes in the peripancreatic fat could be seen at CT (computed tomography) scans. The use of intravenous contrast is mandatory to evaluate different grades of glandular involvement and patency of adjacent vessels. Furthermore, CT imaging may show the extent of peripancreatic or intraparenchymal fluid collections and the presence abscessualization.

Magnetic resonance cholangiopancreatography (MRCP) is challenging o perform in pediatric patients and needs to be tailored to different body sizes. The pancreatic glands become heterogeneous and hypointense on T1-weighted images in the early stages of inflammation [11].

2.3.4 Severity assessment

Commonly used scoring systems (Ranson, modified Glasgow and pediatric acute pancreatitis severity) have demonstrated limited ability to predict disease severity in children and adolescents with acute pancreatitis. The sensitivity and negative predictive value of the above scores are insufficient to guide decision making in pediatric patients. Therefore better methods are needed for risk stratification. Anyway, in a logistic regression model [12], only white blood cell count at admission more than 18,500/mcL, trough calcium less than 8.3 mg/dL and blood urea nitrogen greater than 5 mg/dL appear to correspond independently with a poor outcome.

The lack of an accurate scoring system could cause delays in appropriate clinical management and increase the risk of progressive life-threatening complications. In recent years Suzuki [13] has investigated a modified score that reflects pediatric SIRS (systemic inflammatory response syndrome) score, age and weight (**Figure 3**) and it has proved a more adequate scoring system in children, helping to improve treatment outcome in these patients.

Parameter	Pediatric JPN scoring system[a]
1	Base excess < −3 mEq or shock
2	PaO_2 < 60 mmHg in room air or respiratory failure requiring ventilation
3	BUN > 40 mg/dl or creatinine >2 mg/dl or urine output <0.5 ml/kg/h
4	LDH > 2 times above the upper limit of normal (age adjusted values)
5	Platelet count < 1,00,000 cells/cu.mm
6	Total serum calcium <7.5 mg/dl
7	C-reactive protein > 15 mg/dl
8	Number of positive measures in pediatric SIRS score > 3 [SIRS criteria A: Core temperature > 38.53 °C or <36 °C B. Tachycardia– mean heart rate >2SD above normal for age C. Tachypnea– mean respiratory rate >2SD above normal for age D. Leucocyte count either elevated or depressed for age or >10 % immature neutrophils]
9	Age less than 7 y and/or weight below 23 kg

[a] Presence of any three of the above criteria indicates severe pancreatitis

Figure 3.
Japanese scoring system to assess severity of acute pancreatitis.

2.3.5 Complications

The most frequent complication of acute pancreatitis in pediatric age is represented by the development of pseudocysts and occurs in 13% of patients (**Figure 4**). This is a delayed complication and occurs 4 weeks after the onset of the acute inflammatory process. Pseudocysts probably arise from disruption of the main pancreatic duct, leading to an oval fluid collection with a well-defined wall in the peripancreatic tissues. The early alteration that involves pancreatic tissue in the setting of an interstitial edematous pancreatitis (IEP) is the formation of peripancreatic fluid collections that may resolve spontaneously. A necrotizing process arising in the pancreatic parenchyma or in adjacent tissues results in the development of multiple necrotic collections walled-off with an increased risk of infection.

Vascular complications may involve the arterial or venous system and are caused by extravasated pancreatic enzymes with the loss of vessel wall integrity. Thus hemorrhage secondary to the rupture of a pseudoaneurysm or erosion of a major artery may occur. Moreover, in the venous system, thrombosis is a complication that commonly affects the splenic vein. Pancreatic ascites and pancreaticopleural fistulas are two uncommon types of internal pancreatic fistulas resulting from pancreatic duct disruption with leakage of pancreatic fluid. Since complications are similar to those occurring in adults the revised Atlanta classification (**Figure 5**) is useful in children too [11].

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) are rare in children with severe acute pancreatitis but still have high mortality rates.

The increased abdominal pressure leads to alteration in microvasculature determining ischemia, congestion and edema of the organs. Thus the consequent

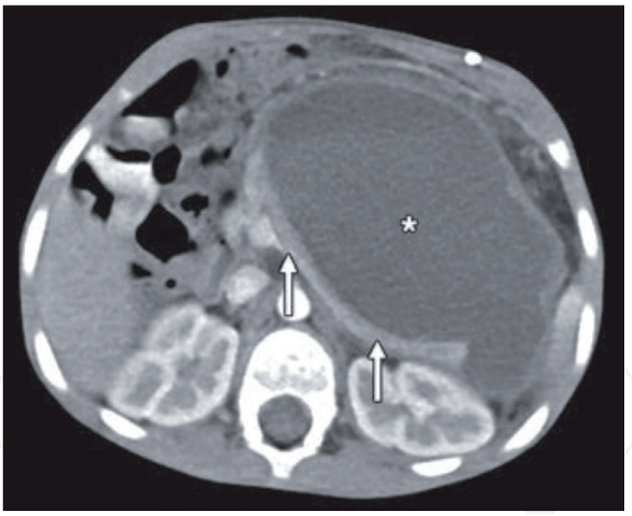

Figure 4.
Pancreatic pseudocyst at contrast-enhanced CT scan in a 6-year old patient.

Type of Pancreatitis	Fluid Collections
< 4 Weeks after Onset	
IEP	APFC
	Sterile
	Infected
Necrotizing Pancreatitis	ANC
	Parencymal necrosis alone
	Sterile
	Infected
	Peripancreatic necrosis alone
	Sterile
	Infected
	Pancreatic and peripancreatic necrosis
	Sterile
	Infected
≥ 4 Weeks after Onset	
IEP	Pancreatic pseudocyst
	Sterile
	Infected
Necrotizing Pancreatitis	WON
	Sterile
	Infected

Figure 5.
Revised Atlanta classification of complications in AP. IEP: interstitial edematous pancreatitis; APFC: acute peripancreatic fluid collection; ANC: acute necrotic collection; WON: walled-off necrosis.

bacterial shift into the bloodstream causes bacteremia, systemic inflammatory response and hemodynamic instability. The purpose of management of critical pediatric patients is to avoid ACS progression and the development of multi-organ dysfunction syndrome [14].

2.4 Treatment

2.4.1 Drug therapy

Children with AP should be resuscitated with crystalloids and be provided 1.5–2 times maintenance intravenous fluids with monitoring of urine output

over the next 24–48 h. Monitoring of patients with acute pancreatitis can provide indicators of complications arising, including SIRS and organ dysfunction/failure. Cardiac, respiratory, and renal status should be followed particularly closely within the first 48 h. Opioid analgesics in oral or parenteral forms are required for pain control in acute pancreatitis. Despite previous contentions, there is no evidence about the paradoxical contraction of the sphincter of Oddi induced by morphin and it should be used for acute pancreatitis pain not responding to acetaminophen or NSAIDs (non steroids anti-inflammatory drugs). In pediatric patients with a diagnosis of mild acute pancreatitis oral feedings or enteral nutrition (EN) can be started within 24–48 h. Parenteral nutrition (PN) should be considered in cases where EN is not possible for a prolonged period (longer than 5–7 days) such as in ileus, complex fistulae, abdominal compartment syndrome, to reduce the catabolic state of the body.

Antibiotics should not be used in the management of AP, except in the presence of documented infected necrosis, or in patients with necrotizing pancreatitis who are not improving clinically without antibiotic use. Antibiotics known to penetrate necrotic tissue (such as carbapenems, quinolones and metronidazole) should be used in management of infected pancreatic necrosis as these may delay surgical intervention and decrease morbidity and mortality. Instead antiprotease or antioxidants are not recommended in the management of acute pancreatitis in children [15].

2.4.2 Nutritional strategy

In severe pancreatitis an earlier oral re-feeding reduces the incidence of infections and contributes to a shorter hospitalization. Serum pancreatic enzymes' level tips the balance in the enteral feeding strategy. If serum amylase and lipase are decreasing liquid intake can be started, according with clinical conditions, while if they are minor than two times the upper normal values, an hypolipidic diet should be considered [13].

2.4.3 Endoscopic and surgical treatment

Undoubtedly anatomic abnormalities are an indication for surgery while ampulla of Vater anomalies or pancreatic divisum may be eligible for an endoscopic sphincterotomy. In patients with infected necrosis of the pancreatic gland a necrosectomy is mandatory in case of worsening clinical conditions and unresponsiveness to therapeutic measures. However this procedure (percutaneous, endoscopic or laparoscopic necrosectomy) has an high mortality rate and should be performed in hemodynamically stable patients.

Pancreatic pseudocysts are cysts that develop due to injury of the pancreatic duct and extravasation of fluid. These occur 4 weeks or later after the onset of pancreatitis. Treatment is indicated for pseudocysts if their size does not decrease, if they are accompanied by abdominal pain, or if there are complications of infection or hemorrhage. Whereas endoscopic ultrasound-guided transgastric drainage can safely be considered in case of growing pancreatic pseudocysts or in case of hemorrhagic complications [13].

3. Acute recurrent pancreatitis

Approximately 10–20% of pediatric patients experience recurrent episodes of acute pancreatitis beneath which it is possible to identify an idiopathic or structural

etiology. ARP may evolve in the chronic form that is clinically indistinguishable from acute pancreatitis in children [16].

3.1 Etiology

Risk factors that predispose to ARP can be categorized according the following frequency in: genetic, obstructive, metabolic and autoimmune [17]. However the etiology of ARP remains unexplained in 30% of cases and can be classified as "idiopathic" is used.

3.1.1 Genetic causes

Genetic conditions that predispose to recurrent episodes of pancreatitis are the cystic fibrosis transmembrane conductance regulator-gene (CFTR-gene), PRSS1-gene and SPINK1-gene mutations.

CFTR-gene mutations occur in about 5% of Western populations and cause an altered function of the product of this gene with a defect in the transmembrane epithelial chloride ion transfer. This dysregulation affects different organs including the pancreas and results in an abnormal production of viscous exocrine secretions that lead to ductal obstructions. Mutations in the cationic trypsinogen gene (**PRSS1-gene**) have been matched in patients with hereditary pancreatitis. The pancreas is unable to contrast an excessive trypsin activation because of the lack of protective mechanism predisposing patients to recurrent episodes of pancreatitis in childhood.

SPINK1-gene mutations predispose to the development pancreatitis and involve the serine protease inhibitor Kazal type I gene (SPINK1). This mutation results in a defect of the protective action in the pancreas mediated by SPINK1 protein that represents a feedback inhibitor of trypsin activation. Approximately 16–23% of patients with idiopathic pancreatitis have SPINK1 mutations instead [18].

3.1.2 Anatomical anomalies

Pancreas divisum is the most frequent anatomical variant and has an incidence near to 12% in general population. As a result of this incomplete fusion of the ventral and dorsal ducts pancreatic juices cause ductal hypertension. Patients may experience recurrent pain after food intake, an alteration in serum content of pancreatic enzymes, or acute recurrent pancreatitis. Annular pancreas is another anatomical variant that may be related with duodenal or biliary obstructive symptoms. Ductal abnormalities such as a common pancreatico-biliary channel may determine a bile or pancreatic juices reflux and can be diagnosed with ERCP. Sphincter of Oddi dysfunction (SOD) is another factor predisposing to ARP and is probably the most common cause of the idiopathic form. This dysfunction includes two clinical forms: SO increased basal pressure related to a structural fibrotic alteration of the sphincter and SO dyskinesia, caused by sphincter hypertone [19].

3.1.3 Metabolic disorders

Toxic and metabolic factors such as hypercalcemia, hypertriglyceridemia, diabetes, porphyria and Wilson's disease can predispose to the development of acute recurrent episodes of pancreatitis as well as medications (i.e., azathioprine and 6-mercaptopurine) [17].

3.1.4 Autoimmune disorders

Autoimmune pancreatitis is an increasingly recognized disease entity associated with hypergammaglobulinemia. High serum levels of IgG4 are suggestive of AIP in adults while just 22% of pediatric patients have immunoglobulin levels above the upper limits of normal [19]. AIP can be classified into two types: type one lymphoplasmacytic sclerosing pancreatitis and type two idiopathic duct-centric pancreatitis. The latter form seems to be more frequent in children and it is associated with inflammatory bowel syndrome. Anyway this distinctive type of pancreatitis is responsive to corticosteroid therapy.

3.2 Clinical features and diagnosis

ARP can be defined as two or more episodes of acute pancreatitis occurring with complete resolution of symptoms in between (>1 month between two episodes) or normalization of pancreatic enzymes serum levels in the time interval, with not detected radiological signs of chronic pancreatitis. ARP should be considered in the diagnostic process of children with a positive anamnesis for recurrent gastroenteritis with vomiting, epigastric pain, or irritable bowel syndrome. An early identification of the underlying etiology may lead to a complete resolution of the disease [18].

The most common risk factors in childhood are genetic mutations so gene testing is mandatory and a chloride sweat test is helpful to diagnose a CF (cystic fibrosis).

The patient's anamnesis and standard laboratory tests, trans-abdominal ultrasound, MRCP, and CT scan can easily detect the causes of recurrent pancreatitis in about 70% of cases. The remaining 30% of patients should have further investigations such as genetic testing, MRCP (magnetic resonance cholangiopancreatography), that provides the potential to delineate ductal anatomy without the risks of contrast injection, EUS (Endoscopic UltraSonography) and ERCP, that represents the most accurate imaging to define the pancreas anatomy. Genetic and autoimmune pancreatitis can be diagnosed by sequencing CFTR or SPINK1/PRSS1 gene mutations and IgG4.

3.3 Treatment

Therapeutic approach to recurrent pancreatitis associated with pancreas divisum is based on endoscopic and surgical procedures. Both strategies are effective in 70–90% so the former therapy is preferred. Surgery may include accessory duct sphincteroplasty alone or in combination with major sphincteroplasty and septoplasty. Patients with distal ductal obstruction or ductal ectasia may take advantage from pancreaticojejunostomy [20]. Annular pancreas is another congenital aletaration of the pancreatic ductal system and surgical resection represents the preferential treatment. Recurrent pancreatitis associated with the CFTR-gene mutation of hereditary pancreatitis may be prevented by endoscopic pancreatic sphincterotomy reducing intraductal hypertension.

Furthermore, in last years, many efforts have been made to identify a novel therapy for lipoprotein lipase deficiency (LPLD), a genetic disease causing chylomicronemia and an increased risk for developing acute and recurrent pancreatitis. Thus alipogene tiparvovec (Glybera) gene therapy has definitely proven to be effective in reducing frequency and severity of pancreatitis events [21].

4. Chronic pancreatitis

Pediatric chronic pancreatitis is unusual and the incidence increases with age (0.5 per 100,000 in young adults) but this condition presents a progressive behavior and is poorly responsive to therapy.

Chronic pancreatitis has been defined as a persistent inflammatory injury of the pancreas characterized by irreversible architectural changes that cause pain and/or irreversible loss of function [22].

4.1 Etiology

As mentioned above genetic mutations are the most common causative factors for pancreatitis in children despite other risk factors may be brought into play as the TIGAR-O classification system well explained and categorized according to toxic-metabolic causes, idiopathic, genetic, autoimmune and obstructive chronic pancreatitis [23]. Within the last years, multiple studies have reported rates of genetic mutations associated with pancreatitis, involving CFTR, SPINK1 and PRSS1 genes, from 36 to 73%. So future perspectives will certainly focus on a personalized medicine approach in order to define a more specific and targeted treatment. Cationic trypsinogen PRSS1 is the gene most frequently involved in the evolution to the end stage of chronic pancreatitis. Near to 80% of individuals with either the R122H or N29I gain of function mutation develop at least one episode of acute pancreatitis and half of clinically affected individuals with either the R122H or N29I mutation will evolve to chronic pancreatitis.

Moreover pancreas divisum represents an obstructive cofactor in the development of chronic involutional changes of the pancreatic gland.

4.2 Pathology

Parenchymal fibrosis, with loss of acinar cells, results in exocrine pancreatic insufficiency (EPI) as a late stage of the disease and needs to be treated with pancreatic enzyme replacement therapies. Then normal acini are replaced by fibroblasts and lymphocytic infiltration. Furthermore, progressively endocrine cells are damaged too resulting in diabetes mellitus (DM) that often occurs post chronic pancreatitis [23].

4.3 Diagnosis

According with INSPPIRE data the definition of chronic pediatric pancreatitis depends upon one of the following: (1) abdominal pain and imaging findings that can suggest a chronic pancreatic damage; (2) evidence of exocrine pancreatic insufficiency with maldigestions symptoms and diagnostic imaging suggestive for pancreatic damage; (3) evidence of pancreatic islets dysfunction and imaging findings that can suggest the presence of a pancreatic damage; or (4) a surgical or pancreatic biopsy demonstrating pathological features compatible with chronic pancreatitis [24].

4.3.1 Imaging findings

The most commonly found radiographic signs of chronic pancreatitis in children are represented by ductal anomalies and pancreatic gland atrophy. Unlike the adult form, pancreatic calcifications are not detected in childhood chronic pancreatitis.

To reduce the exposure to ionizing radiation MRI/MRCP and ultrasound (US) are preferred. ERCP, as in adults, can be considered for procedures such as stone removal or stricture dilation [23].

4.3.2 Pancreatic function tests

Altered pancreatic function tests are diagnostic of chronic pancreatitis but also are detected in case of other clinical conditions such as pancreatic agenesis or resection, intestinal atrophy, kwashiorkor and gastrinoma. We also have to consider mild or moderate forms of chronic pancreatitis in case of normal tests. Exocrine pancreatic function can be assessed by direct or indirect evaluations. Direct tests pancreatic such as the secretin-cholecystokinin test have the highest sensitivity and specificity but at the same time they are inadequate for routine clinical practice in pediatric population. On the other hand indirect tests are noninvasive and routinely used. Indirect pancreatic function test can be divided in three main groups:

1. Analysis of the hydrolyzed products of pancreatic enzymes' activity detectable in urine and serum (NBT-PABA test, pancreolauryl test);

2. Assessment of undigested and unabsorbed food components in feces (fecal fat excretion and fecal fat concentration);

3. Dosage of pancreatic enzymes in the serum (amylase, isoamylase, lipase, trypsinogen, elastase-1) or stool (chymotrypsin, lipase, elastase-1).

Fecal elastase-1 (FE1) is the most sensitive test in the evaluation of exocrine pancreatic function in chronic pancreatitis [25].

Fecal elastase-1 is a proteolytic pancreatic enzyme that is not degraded during its passage through the gastrointestinal tract. Analysis of FE1 is simple and practical to be managed but it may be compromised in case of diarrhea, with an associated risk of falsely low FE1 concentration [26].

4.3.3 Biopsy

A pancreatic EUS-guided biopsy may represent the gold standard for the diagnosis of chronic pancreatitis but it is not widely available.

And besides some etiologies of chronic pancreatitis, such as autoimmune or hereditary pancreatitis, need multiple biopsies to be diagnostic. At histological examination irregular fibrosis can be seen while intralobular fibrosis alone is not specific for chronic pancreatitis [22].

4.4 Treatment

Both the stage and etiology of CP influence its management. With disease progression, chronic pain management and treatment of pancreatic insufficiency or diabetes are required. Acetaminophen may be effective in the early stages, but therapy generally advances to narcotics. Pancreatic enzyme supplements and antioxidant therapy (selenium, ascorbic acid, b-carotene, a-tocopherol, and methionine) are prescribed frequently in this setting. Endoscopic treatment for CP should be considered only when ductal strictures or pancreatic duct calculi are present or for symptomatic pseudocysts. Surgical treatment is still indicated in selected patients when conservative treatment failed. Localized disease can be treated with partial pancreatic resection (i.e., in case of a pancreatic inflammatory head mass)

while radical pancreatectomy with islet cell autotransplant is currently offered to patients who have genetic causes of pancreatitis (as we'll describe in the next section). A longitudinal pancreaticojejunostomy (known as modified Puestow procedure) can be definitely avoided. Although many patients have pain relief, a number of patients continue to have pain. In up to 20% of adults, the pain is as intense as it was before the resection. Preadolescents are more likely to be insulin-independent than older children and adults. Thus time to surgical procedure is fundamental to avoid a progressive decrease in islet cell yield. Pancreatic insufficiency is treated with pancreatic enzyme replacement therapy. The final goal is to restore digestive function and maintain weight gain.

4.4.1 Total pancreatectomy with islet autotransplantation (TPIAT)

Children with chronic pancreatitis who suffer recurrent severe episodes of abdominal pain, chronic use of analgesics (opioids) and frequent hospitalizations may benefit from TPIAT, in order to improve their quality of life. A multidisciplinary team including gastroenterologists, endocrinologists, surgeons, anesthesiologists, psychologists, radiologists and nutritionists guides the selection of these patients.

Thus the procedure consists in a demolitive operative phase, followed by a reconstructive one that includes an hepaticojejunostomy plus gastrojejunostomy or a duodenojejunostomy and the autotransplantation of islets via the portal vein.

Osmotic, mechanical or hypoxia damage of islets should be considered, especially in the pre-engraftment phase and the risk of developing diabetes mellitus must be accepted by families.

Anyway pain resolution, independence from analgesics and significant improvement in quality of life has been reported in the majority of children with CP following TPIAT, and glycemic control is managed without difficulty [24, 27].

5. Conclusions

The incidence of acute pancreatitis is increasing in children and it should be considered as part of differential diagnosis in case of abdominal pain. The etiology of acute pancreatitis in this subpopulation is related to several conditions and risk factors, such as drugs, obesity, infections, trauma and anatomic abnormalities but genetic predisposition represents the master causative factor.

Rapid and accurate assessment of severity is useful for selecting an appropriate initial treatment and predicting the prognosis. The International Study Group for Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) focused on ARP and CP in pediatrics and we can delineate more accurately clinical presentations, risk factors and natural history of pediatric pancreatitis to define a more appropriate therapeutic strategy, often considering that a children is not a small adult.

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