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Review Article

Pancreatic disorders in children: New clues on the horizon

Claudia Della Corte[a], Simona Faraci[b], Fabio Majo[c], Vincenzina Lucidi[c], Douglas S. Fishman[d,e], Valerio Nobili[f,g,*]

[a] Hepatology Gastroenterology and Nutrition – 'Bambino Gesù' Children's Hospital IRCCS, Rome, Italy
[b] Digestive Endoscopy and Surgery Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy
[c] Cystic Fibrosis Center, 'Bambino Gesù' Children's Hospital, IRCCS, Rome, Italy
[d] Section of Pediatric Gastroenterology, Hepatology and Nutrition, Baylor College of Medicine, Houston, TX, United States
[e] Section of Pediatric Gastroenterology, Hepatology and Nutrition, Texas Children's Hospital, Houston, TX, United States
[f] Hepatology Gastroenterology and Nutrition – 'Bambino Gesù' Children's Hospital, Rome, Italy
[g] Department of Pediatric – University 'La Sapienza' Rome, Italy

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ABSTRACT

Pancreatic disorders in children represent a growing health problem in pediatric patients. In the past two decades, several advances have been made in the knowledge of pediatric pancreatic disorders, with better understanding of different etiologies and clinical manifestations of these disorders. Moreover, many efforts have been made in pancreatology, aiming to define guidelines in the management of pancreatitis in children, initially based on the available information in adults. A multidisciplinary and multicenter approach is necessary to better determine pancreatic disease pathways and treatment options in children.

1. Introduction

Pancreatic disorders in children are generally considered rare, with multiple challenges in management, due to gaps in knowledge of pancreatopathies in the pediatric setting [1]. Contrary to that however, in recent years, a marked increase in the incidence of pediatric pancreatic diseases has been reported, mainly for acute pancreatitis. These data are likely as the result of a mix of factors, such as a better knowledge of pancreatic disorders and their etiologies among pediatricians, an increased use of laboratory assays for pancreatic functions (amylase and lipase serum concentrations) and an augmented referral patterns to tertiary or quaternary care centers [2]. The burden of pancreatic disorders in children is not negligible, both in terms of health expenditure and the impact on children's health. Several studies have reported late severe complications in long-term follow up of pancreatopathies in children, such as nutritional deficits and their consequences, increased risk of diabetes mellitus and pancreatic malignancies [3]. In the last decades, several advances have been made in the clinical approaches and management of pancreatic disorders in children. Improvements in diagnosis stem from more extensive investigations for etiologies and genetic determinants of pancreatopathies and to the greater availability of imaging techniques, useful in diagnosis and treatment.

In this review, we summarize the recent evidence on pancreatic diseases in children, with an aim of providing the latest information and possible future agendas in the approaches to the diagnosis and management of pediatric pancreatic disorders.

2. Pancreatitis: acute, acute recurrent and chronic pancreatitis

2.1. Acute pancreatitis

Pancreatitis is histologically defined by the presence of inflammatory infiltration within pancreatic parenchyma. Acute pancreatitis (AP) is a reversible process, characterized by inflammatory infiltration, interstitial oedema and various degrees of necrosis. As previously stated, in the last decade, a significative increase in incidence of AP in children has been reported. Recent estimates suggest an incidence similar to that of adults (10–15/100,000), approximately 13:100,000 cases per year [4]. Some studies have tried to define the causes of this apparent surge in incidence,

* Corresponding author at: Hepatology Gastroenterology and Nutrition – 'Bambino Gesù' Children's Hospital, P.le S. Onofrio, 4-00165 Rome, Italy.
E-mail addresses: vnobili66@gmail.com, valerio.nobili@opbg.net (V. Nobili).

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Table 1
The possible causes of acute pancreatitis in children.

Biliary/obstructive causes	Choledocal cyst, gallestones, choledocolithiasis, anomalous biliopancreatic junction, pancreatic malformation (divisum or annular pancreas)
Systemic diseases	Shock, sepsis, inflammatory bowel diseases, hemolytic-uremic syndrome, reumatological disorders (lupus erythematosus, juvenile arthritis, Kawasaki syndrome, Henoch–Schonlein purpura)
Infections	Epstein Barr virus, Cytomegalovirus, Measles, Mumps, Coxsackievirus, Mycoplasma, Herpes virus simplex, Salmonella, *E. coli*
Autoimmune form	Autoimmune pancreatitis
Drug-induced pancreatitis	Valproic acid, azathioprine, prednisone, furosemide, tacrolimustetracycline, isoniazid
Trauma	Non-accidental trauma
Metabolic disorders	Diabetes mellitus, hypertriglyceridemia, hypercalcemia, cystic fibrosis, organic acidemia, glycogen storage diseases
Genetic mutations	CFTR, SPINK-1, PRSS1, CTRC
Malignancies	
Post-ERCP pancreatitis	

Abbreviations: ERCP, endoscopic retrograde cholangiopacreatography; PRSS1, cationic trypsinogen, SPINK1, pancreatic secretory trypsin inhibitor; CFTR, cystic fibrosis transmembrane conductance regulator; CTRC, chymotripsin C.

concluding that the recent advances in knowledge of pancreatitis etiologies, referral patents, and diagnosis have led to this phenomenon [2]. Recent data have also demonstrated the considerable costs of AP, with estimated inpatients cost of about $200 million per year. Obviously, neither the costs related to complicated or severe AP, that may require additional intensive care or invasive/surgical treatments, nor the indirect costs are taken into account with this estimation [2,5].

Although clear guidelines for diagnosis and treatment of pediatric acute pancreatitis are limited, recently both the INternational Study Group of Pediatric Pancreatitis: In Search for a CuRE (INSPPIRE) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) have proposed recommendations for both clinical and research for diagnosis and treatment of pediatric acute pancreatitis [6,7].

According to INSPPIRE and NASPGHAN, diagnosis of AP is based on the presence of at least 2 of the 3 criteria defined as: abdominal pain of pancreatic origin, three-fold elevation of serum amylase and/or lipase above upper limits of normal (ULN), and diagnostic imaging consistent with pancreatic involvement. In children, the diagnosis is often suspected based on clinical symptoms (characteristic abdominal pain) and confirmed by serological and/or radiological tests. However, different from adults, in which clinical presentation of AP is generally more suggestive of pancreatic involvement, in children, mainly in younger patients, the presentation may be insidious and non-specific. The presentation in children with pancreatitis may include abdominal distension, vomiting, fever and irritability [8,9]. For these reasons, in pediatrics, a high index of suspicion should be maintained, so as not to miss or delay the diagnosis of AP nor its prompt treatment.

The common causes of AP in children are different from those of adults; in the pediatric population, biliary/obstructive forms, fostered by an underlying anatomical malformation (resulting in increasing intraductal and parenchymal pressure and long-lasting pain), drug-induced forms and systemic diseases are the main etiologies, as reported in Table 1. Other causes are represented by trauma, infections, and metabolic disorders. It is also should remembered that AP in children is idiopathic in 5–30% of cases [8].

Even if a significant increase in the incidence of AP has been reported, the natural history of AP in children is still limited and tools aiming to predict disease severity are limited. None of the adult severity predictor scoring systems, such as Ranson criteria for pancreatitis mortality or Acute Physiology And Chronic Health Examination Score (APACHE II), have been validated for use in the pediatric population [10,11]. The first pediatric specific scoring system, the Pediatric Acute Pancreatitis Severity Score (PAPS), utilized eight parameters: four at admission (age, weight, white cell blood count, LDH) and four during the next 48 h (serum calcium levels, albumin concentration, fluid sequestration and blood urea nitrogen) [12]. This score however showed low sensitivity (70%) and low positive predictive value (45%) in clinical practice, not superior to other adult scoring systems [13–15]. A more simple, widely available and inexpensive method proposed to predict disease severity is serum lipase values. In the first 24 h a 7 times ULN increase in serum lipase concentration was associated with high sensitivity (85%) and negative predictive value (89%) for predicting severe AP [16]. According to the Atlanta Criteria, AP is considered *mild* in the absence of organ failure and local or systemic complications, *moderately severe* in cases of transient organ failure (<48 h) and/or local or systemic complications. AP is defined *severe* when persistent organ failure (>48 h) has been observed (single or multiple organ failure) [17,3].

Generally, AP has a benign course in children, and the vast majority of cases heal without sequelae. One of the challenges in systematically evaluating and validating scoring systems is the paucity of severe pancreatitis in children. Although rare in children, affecting fewer than 6% of pediatric cases, the most serious and feared complications of AP are multiorgan failure and pancreatic necrosis, walled-off necrosis or pseudocyst formation. The development of pseudocysts was reported in 10–20% of cases, more frequently in association to traumatic pancreatitis [18]. Generally, the management of pseudocysts is conservative. For larger or complicated and symptomatic pseudocysts, endoscopic techniques, with minimally invasive surgical approaches have emerged in the pediatric setting [19,20]. The mortality rate for pediatric AP varies from 0% to 11% in the different case series. It is important to note that the higher value of mortality range regards patients with chronic illness in which death is generally related to the underlying disease [4,8,21]. Moreover, it is important to note that patients with AP may eventually develop recurrent or chronic pancreatitis. Recurrent attacks were reported in 15–35% of patients; mainly in patients with anatomical abnormalities of the pancreaticobiliary tree and metabolic diseases (e.g. familial hypertriglyceridemia and hereditary pancreatitis). Acute recurrent pancreatitis (ARP) is characterized by two or more distinct episodes of AP, with pain-free intervals and/or with normalization of pancreatic enzymes between attacks. As detailed later, ARP may progress to chronic pancreatitis (CP) characterized by recurrent episodes of pancreatitis with possible exocrine and/or endocrine insufficiency. With repeated attacks of acute pancreatitis, evidence of typical imaging findings, such as calcifications, ductal dilatation, fibrosis and atrophic involution of pancreatic tissue may appear.

2.1.1. Management

Medical treatment

In the vast majority of pediatric cases, AP is medically treated with good outcomes. The cornerstone of treatment of AP, both in adults and children, is represented by early and adequate fluid replacement. All of the available expert consensus statements and actual recommendation in adults agree in defining the crucial role of intravenous (IV) hydration, however no clear data exists in children on the optimal fluid type and amount. There is a lack of comparative data, and recent recommendations suggest use of normal saline for initial rehydration, with normal saline and 5% dextrose as the initial choice for maintenance fluid therapy in children with AP. Following recommendations in adults with pancreatitis, there is a growing use of Lactated Ringers (LR) in children ide-

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