

ORIGINAL ARTICLES

Acute pancreatitis in children: Ten-year experience of a level II hospital

Pancreatite Aguda na Idade Pediátrica: casuística de 10 anos de um hospital nível II

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ABSTRACT

Introduction: The incidence of acute pancreatitis (AP) in children is increasing, together with the awareness of the need for pediatric-specific management recommendations. This study aimed to assess the epidemiology, etiology, management, and clinical course of pediatric AP cases followed at a secondary hospital.

Methods: Retrospective analysis of all pediatric AP cases admitted to a level II hospital in the metropolitan area of Lisbon, Portugal, between January 2009 and December 2018.

Results: Eight cases of pediatric AP were identified, with an average age of 12 years (minimum 4 years, maximum 16 years) and classified according to etiology as drug-induced (n=3), biliary (n=1), infectious (n=1), and idiopathic (n=3). Recurrent AP was identified in one patient. The median hospital stay was 6.5 days. The main symptoms at presentation were abdominal pain (100.0%) and vomiting (75.0%). All patients had increased levels of amylase activity in serum (>3 times the upper limit of normal). Pancreatic image abnormalities were observed in five patients (62.5%), four in the abdominal ultrasound and one in computed tomography scan. One patient underwent endoscopic retrograde cholangiopancreatography. Two patients received a course of antibiotics. All cases were classified as mild, according to the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition classification.

Discussion: This series showed a predominance of secondary over idiopathic AP, in agreement with recently published studies reporting a reduction in the incidence of idiopathic AP due to increased efforts to identify the underlying causes of the disease. Since the incidence of AP is increasing in pediatric age, physicians should be aware of recent recommendations for the optimal management of the condition in this age group.

Keywords: acute pancreatitis; pancreatic disease; Pediatrics

RESUMO

Introdução: A incidência de pancreatite aguda (PA) em idade pediátrica tem vindo a aumentar, havendo um reconhecimento crescente das suas particularidades neste grupo etário e da necessidade de recomendações de abordagem específicas. Este estudo teve como objetivo analisar a epidemiologia, etiologia, abordagem e evolução clínica da PA em idade pediátrica num hospital secundário.

Métodos: Análise retrospectiva de todos os casos de PA pediátrica admitidos num hospital de nível II da área metropolitana de Lisboa, Portugal, entre janeiro de 2009 e dezembro de 2018.

Resultados: Foram identificados oito casos de PA na população pediátrica, com uma idade média de 12 anos (mínimo 4 anos, máximo 16 anos) e as seguintes etiologias: medicamentosa (n=3), biliar (n=1), infecciosa (n=1) e idiopática (n=3). Foi identificado um caso de PA recorrente.

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A mediana de tempo de internamento foi de 6,5 dias. Os sintomas mais comuns na apresentação foram dor abdominal (100,0%) e vômitos (75,0%). Todos os casos apresentaram níveis elevados de amilase sérica (>3 vezes o limite superior do normal). Foram observadas alterações imagiológicas sugestivas de PA em cinco casos (62,5%), quatro na ecografia abdominal e um na tomografia computadorizada. Foi realizada colangiopancreatografia retrógrada endoscópica em um caso. Dois doentes receberam antibioticoterapia. Todos os casos foram classificados como ligeiros, de acordo com a classificação da Sociedade Norte-Americana de Gastroenterologia, Hepatologia e Nutrição Pediátricas.

Conclusões: A presente casuística revelou uma predominância de PA secundária, em conformidade com estudos recentes que demonstram uma redução da incidência de PA idiopática devido a abordagens diagnósticas cada vez mais completas. Dado o aumento da incidência de PA em idade pediátrica, é importante que os profissionais de saúde estejam alerta para esta patologia e adequem a sua prática às recomendações mais recentes.

Palavras-chave: doença pancreática; pancreatite aguda; Pediatria

INTRODUCTION

Acute pancreatitis (AP) is a reversible inflammation of the pancreas, resulting in autolysis of the organ due to the enzymatic cascade elicited by the conversion of trypsinogen to trypsin. This process is histologically characterized by pancreatic edema, acute inflammatory infiltrate, acinar cell vacuolization, and varying degrees of pancreatic necrosis or hemorrhage.^(1,2)

Pediatric pancreatitis has distinctive etiologies and broader and more variable risk factors than adult pancreatitis. Acknowledged etiologies include structural/anatomic anomalies, biliary tract disease, medication use, genetic predisposition, abdominal trauma, metabolic disorders, inborn errors of metabolism, and systemic illness. The latter is the leading cause in infants and toddlers, while biliary pancreatitis is currently the most common cause of AP in children.^(3,4)

AP diagnosis is established based on the **IN**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n Search for a **CuRE** (INSPPIRE) criteria, depicted in **Table 1**.⁽⁵⁾

In recent years, an increase in the incidence but also in the awareness of pediatric AP has been observed.⁽⁶⁾ To the author's knowledge, only two case series of the condition have been published in Portugal until now, describing the experience of single centers but making no reference to the incidence of the condition in the country.^(7,8)

The first pediatric-specific AP classification was published in 2017 and classified AP in mild, moderately severe, and severe, according to the presence of organ dysfunction and complications.⁽⁹⁾ Furthermore, pediatric-specific guidelines for the optimal management of AP have been recently published.^(10,11)

This study aimed to investigate the epidemiology, etiology, management, and clinical course of pediatric AP in a secondary hospital.

Table 1 - Definition of AP in children (INSPPIRE criteria)⁽⁴⁾

Clinical definition
Requires at least 2 out of 3 criteria: <ol style="list-style-type: none">1. Abdominal pain suggestive of or compatible with AP2. Serum amylase and/or lipase activity at least 3 times greater than the upper limit of normal3. Imaging findings characteristic of or compatible with AP

METHODS

The medical records of all patients with AP admitted to the Pediatric Department of a level II hospital in Lisbon metropolitan area over ten years (between January 2009 and December 2018) were retrospectively assessed. This center is a public hospital serving 155,628 pediatric patients, according to the Portuguese census of 2011.¹² AP diagnosis was established according to the INSPPIRE criteria. The following data were retrieved from patients' medical records: epidemiological data, AP etiology, possible risk factors, biochemical results, imaging findings, length of hospital stay, and therapeutic approach.

RESULTS

A total of eight AP cases met inclusion criteria and were included in the study. **Table 2** summarizes the most relevant characteristics of each. The average age at presentation was 12.3 years (range, 4–16 years). No differences were found in the incidence of AP according to gender.

Specific etiologies were identified in 62.5% of cases and included drug-induced (n=3), biliary (n=1), and infectious (n=1) AP (**Figure 1**). The remaining cases (n=3) were considered idiopathic.

The medications identified in these patients included valproic acid in one case (Patient five) and estrogens in two cases (Patients two and six).

Recurrent AP was identified in one patient (Patient one) with a history of two previous episodes in the past three years, all considered idiopathic. Genetic testing for the *CFTR* gene was performed, but no mutations were found. As the patient presented no additional episodes, no further genetic testing was conducted.

Abdominal pain was present in all cases. Pain intensity was an important factor guiding the differential diagnosis. Other symptoms reported included vomiting (75.0%), nausea (25.0%), and fever (12.5%). Patient three presented with jaundice, abdominal pain, and vomiting and developed fever on the third day of hospitalization. Patient seven had a history of coryza, fever, and diarrhea in the prior week, which resolved before the onset of abdominal pain.

Serum amylase levels were higher than three times the upper limit of normal in all patients, with 62.5% exceeding tenfold (mean 2226 U/L; minimum 408 U/L and maximum 4205 U/L).

Leukocytosis was present on admission in 62.5% of cases (mean 13988/mm³; minimum 10600/mm³ and maximum 25000/mm³), whereas C-reactive protein was elevated in 50.0% (mean 2.3 mg/dL; minimum 0.2 mg/dL and maximum 11.3 mg/dL).

Hyperbilirubinemia was only observed in one patient (Patient three; biliary AP). Serum triglycerides were investigated in six cases and found to be within the normal range.

Serological study for potentially involved microorganisms (*Mycoplasma pneumoniae*, cytomegalovirus, herpes virus,

enterovirus, adenovirus, and coxsackie) was performed in all cases of idiopathic AP (Patients one, four, and eight), in the case of infectious AP (Patient seven), and in one case of drug-associated AP that presented with increased inflammatory parameters (Patient five). Anti-enterovirus immunoglobulin (Ig) M was positive in Patient seven, and infectious AP was assumed. In the remaining cases, the serology for recent infections was negative. One case of chronic hepatitis B acquired by vertical transmission was identified (Patient four); however, no viral load was detected and serological markers of replication were negative, so no association with AP was assumed.

Transabdominal ultrasound (US) was performed on admission in all cases, but only four showed characteristic pancreatic parenchyma changes compatible with AP (**Figure 2**), particularly increased pancreatic volume, and peripancreatic fluid. The US also showed intrahepatic and common bile duct distension with cholelithiasis and multiple millimetric gallstones with gallbladder enlargement in Patient three, consistent with cholecystitis.

Contrast-enhanced computed tomography (CT) was performed in one case (Patient five, as the US did not allow to visualize the pancreas due to gas interposition), showing swelling of the pancreatic parenchyma, consistent with AP (**Figure 3**).

One case (Patient seven) met severity criteria according to the Midwest Multicenter Pancreatic Study Group (less than seven years old, bodyweight inferior to 23 kg, and leukocytosis over 18500/mm³ on admission),¹³ being admitted to the Pediatric Intensive Care Unit.

Nil per os was part of the management of all AP cases, with reintroduction of enteral nutrition on average 62 hours after hospital admission (minimum 48 hours; maximum 96 hours). Additionally, all patients were treated with intravenous fluid therapy and analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs] and, in one case, morphine).

Antibiotics were prescribed in two cases: cefotaxime and metronidazole were prescribed for cholecystitis in Patient three, and meropenem was prescribed for suspected bacterial infection with increased inflammatory parameters in Patient five, who had multiple comorbidities (cerebral palsy, epilepsy, and gastroesophageal reflux, for which he had been submitted to Nissen fundoplication surgery, with gastrostomy tube placement).

Patient three was submitted to therapeutic endoscopic retrograde cholangiopancreatography (ERCP), whit endoscopic papillotomy and microlithiasis extraction.

The length of hospital stay ranged from 3 to 18 days (median, 6.5 days). Patient three had biliary AP and underwent ERCP, requiring the longest hospital stay.

No AP complications or organ failure were identified in this series. Follow-up with a pediatric gastroenterologist was provided in all cases.

Table 2 - Summary of the main characteristics of the study population

Patient	Medical history/ Risk factors	Presentation	Serum amylase (U/L)	Imaging study (US and/or CT)	Length of hospital stay (days)	Etiology
1 (M, 12 y, 2009)	Recurrent acute pancreatitis	Abdominal pain, vomiting	1185	Normal	7	Idiopathic
2 (F, 15 y, 2010)	Estrogens	Abdominal pain	408	Normal	3	Medication
3 (F, 11 y, 2012)	Obesity	Abdominal pain, vomiting, jaundice	3343	Altered	18	Biliary
4 (M, 15 y, 2013)	Hepatitis B	Abdominal pain, nausea, vomiting	504	Normal	4	Idiopathic
5 (M, 13 y, 2013)	Gastrostomy tube; Valproic acid for epilepsy	Vomiting, abdominal tenderness	1000	Altered	10	Medication
6 (F, 16 y, 2015)	Estrogens	Abdominal pain, vomiting	4205	Altered	7	Medication
7 (F, 4 y, 2018)	None	Abdominal pain, vomiting	4125	Altered	5	Infection
8 (M, 12 y, 2018)	None	Abdominal pain, vomiting	2685	Altered	6	Idiopathic

CT computed tomography, F, female; M, male; US abdominal ultrasonography; y, years

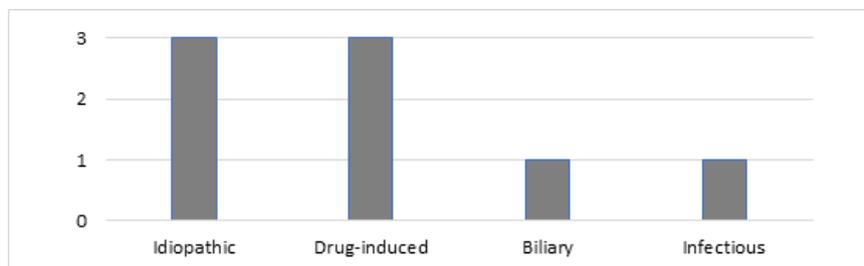


Figure 1 - Acute pancreatitis etiologies

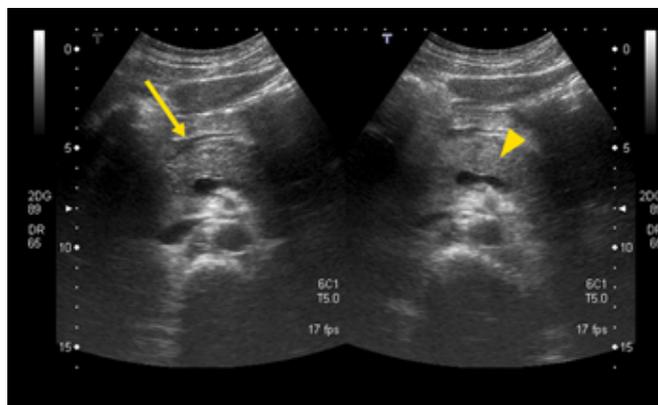


Figure 2 - Transabdominal ultrasound from Patient eight showing abundant peripancreatic fluid (arrow) and increased pancreatic volume with hypoechogenicity (arrowhead).

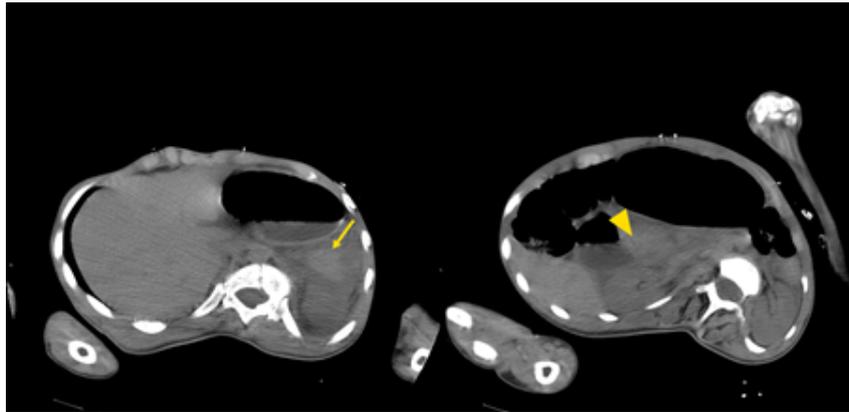


Figure 3 - Axial contrast-enhanced computed tomography from Patient five showing enlargement of the pancreatic tail with peripancreatic fluid (arrow) and heterogeneity with swelling of the pancreatic head (arrowhead).

DISCUSSION

Numerous studies have been published over the past two decades showing growing numbers of AP in children.^(6,14-18) However, it is not clear whether this is a result of increasing incidence or of a growing awareness of the disease and increased testing.^(6,19) These studies have been mainly unicentric and reported an estimated incidence of AP of 3.6-13.3 cases per 100,000 children per year.⁽¹¹⁾ There is no data regarding the incidence of pediatric AP in Portugal. Two Portuguese case series have been published so far, one from a university hospital from the northern region reporting 37 patients with AP over ten years, and the other from a private hospital in Lisbon reporting eight patients over twelve years.^(7,8) The results reported in the present study seem plausible compared to those numbers. In addition, this study did not find a consistent increase in the number of AP cases per year over the past ten years, in agreement with one of the Portuguese studies showing the absence of a statistically significant increase over an equal period.⁽⁷⁾

Drug-induced AP caused by valproic acid and estrogens was a prominent etiology in this study. Valproic acid has been shown to occasionally trigger AP in young patients as an idiosyncratic reaction weeks to years after drug initiation.⁽²⁰⁾ In this case, the patient responded well to withdrawal and conservative management. Estrogens are also a rare cause of drug-induced AP, and while the exact mechanism remains unclear, it is believed to involve estrogen-induced hypertriglyceridemia, as most cases reported have elevated serum triglyceride levels.⁽²¹⁾ There is, however, one case report describing a patient with estrogen-induced AP confirmed by a second episode after drug reintroduction and normal triglyceride levels, suggesting that other mechanisms may be implicated.⁽²²⁾ In the present series, two cases of estrogen-induced AP were assumed, but serum triglyceride levels were assessed in only one and found to be normal.

According to Uc *et al.*, biliary pancreatitis is the most common

cause of AP in children, although just one case was reported in this series in an obese patient.⁽⁴⁾ Obesity is an acknowledged risk factor for symptomatic gallstone disease, also increasing the risk of related complications, such as choledocholithiasis, pancreatitis, and cholecystitis.⁽²³⁾

Infectious AP is a challenging diagnosis that requires recognition of the characteristic prodromal phase with typical signs and symptoms of the infection or isolation of the suspected pathogen from the host.⁽⁴⁾ This study identified one case of infectious AP with positive IgM serology for enterovirus, which presented symptoms compatible with viral infection one week before the onset of abdominal pain.

The most common symptoms in this series were abdominal pain and vomiting, in agreement with the literature.⁽¹⁰⁾ One case presented with jaundice and developed fever during hospitalization due to cholelithiasis/cholecystitis, in addition to biliary AP.

Serum amylase levels were quantified in all patients and shown to be greater than three times the upper limit of normal in all. In contrast, serum lipase levels were inconsistently quantified, which may suggest a lower diagnostic yield, since lipase is more sensitive and specific, remains elevated in serum for a longer period of time, and is less altered by etiology than amylase.⁽¹⁰⁾ Recommendations state that both parameters should be assessed for optimal results.⁽¹¹⁾

In the present series, all patients underwent US, but only half had characteristic pancreatic changes compatible with AP. Although US is recommended as first-choice imaging technique in pediatric AP, access to the pancreas is sometimes hampered by interfering structures.⁽¹⁰⁾ CT scan was performed in one case, showing pancreatic findings suggestive of AP not previously identified in the US. In three other cases, the diagnosis was established despite normal imaging findings.

One case of recurrent AP was identified in this cohort. Genetic testing for the *CFTR* gene was performed, but no mutations were found. Several advances have been made over the years regarding AP putative genes, with current recommendations indicating that the

study of a second idiopathic AP episode should include full sequence analysis of *PRSS1*, *CPA1*, *SPINK1*, *CTRC*, and *CFTR* gene exons and exon-intron boundaries and testing for *CEL* gene pathogenic hybrid allele.⁽¹¹⁾

In this case series, the timing of administration of enteral nutrition was, on average, 62 hours after hospital admission. However, current recommendations advise children with mild AP should be started on a regular diet as soon as possible, ideally within 48 hours of admission.⁽¹⁰⁾ This approach differs from the previously considered advising *nil per os*, as it has been shown that it could lead to an increased risk of infectious complications due to bacterial overgrowth and translocation from the gut, resulting in higher morbidity and mortality.⁽²⁴⁾

Fluid administration and pain management were performed as per recommendations, with intravenous morphine used in one patient who failed to respond to NSAIDs. ERCP was part of the treatment in one case of biliary AP.

A course of antibiotics for suspected bacterial infection was prescribed in the case of one patient with cholecystitis and in the case of one patient with AP with multiple comorbidities and increased inflammatory parameters (leucocyte count and C-reactive protein). According to a recently published study, elevation of C-reactive protein can have a major influence on the prescription of prophylactic antibiotics in AP. However, leucocyte count and C-reactive protein should not be used as biomarkers for decision making regarding antibiotic therapy in the early phase of AP, as they have shown no association with the infection at that stage.⁽²⁵⁾ Antibiotic use is only indicated in AP in cases of documented infected necrosis.⁽¹⁰⁾

Studies document varying lengths of hospital stay, ranging from 5 to 13 days.^(1,2) In this series, the median hospital stay was 6.5 days.

All patients in this cohort were classified as having mild AP, according to the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) classification, since no complications or cases of organ failure were reported. These results support a higher prevalence of mild AP in children.

In conclusion, the analysis of the present pediatric AP series spanning ten years showed a change in the management paradigm and overall knowledge of the condition. Despite study limitations related to its retrospective nature and small sample size, it was interesting to note the predominance of secondary over idiopathic AP, emphasizing the importance of thoroughly pursuing its underlying cause. These efforts are crucial in an era where new diagnostic tools, such as genetic testing, are becoming increasingly available. Some areas of improvement in the management of these patients have been identified, specifically regarding the introduction of enteral nutrition and antibiotic prescription. Overall, results from this study should spur the development of actions to rectify the future approach for pediatric AP patients. In addition, a broader assessment, with extensive genetic testing and eventually magnetic resonance cholangiopancreatography, would have been appropriate in the case of recurrent and idiopathic AP, respectively. In-house protocols

should be revised in light of new pediatric-specific AP guidelines, and physicians should be aware of recent recommendations for the optimal management of AP in this age group. Lastly, multicentric national studies should be conducted to improve the knowledge of the incidence and epidemiology of pediatric AP in the country.

KEY MESSAGES

- Idiopathic AP should be a diagnosis of exclusion. A comprehensive anamnesis and ensuing target investigation of possible etiologies are of utmost importance to offer an adequate approach.
- This study's results suggest a higher prevalence of mild AP in children.
- Antibiotics are rarely indicated in pediatric AP, and the decision to prescribe them in early AP should not be solely based on the elevation of leucocyte count and C-reactive protein, as they are not suitable biomarkers of infection at this stage of the disease.
- As pediatric-specific guidelines emerge, Pediatric departments should revise their in-house protocols and adjust AP management in light of new recommendations for this age group.
- Multicentric national studies are warranted to improve knowledge of the incidence and epidemiology of AP in children in Portugal.

STATEMENT OF ETHICS

The study protocol was developed according to the Rules for Non-interventional Research from the Ethics Committee of the study institution and guidelines of the National Ethics Committee for Clinical Research. The study was ethically conducted following the World Medical Association Declaration of Helsinki. The authors declare that the confidential protocols of the study institution were followed, and no patient-disclosing data was included in the article.

AWARDS AND PREVIOUS PRESENTATIONS

This study was presented as an oral communication in the "ESPGHAN GI Summer School" that took place on 26-29 July in Montecatini, Italy.

AUTHORSHIP

Ana Rute Manuel – Study concept and design; Acquisition of data; Analysis and interpretation of data; Drafting of the manuscript

Rita Vieira de Carvalho – Study concept and design; Acquisition of data; Critical revision of the manuscript

Maria de Lurdes Torre – Study concept and design; Study supervision; Critical revision of the manuscript

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