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Acute Pancreatitis in Children: A 5-year Single Center Experience

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Abstract

Backround: Pediatric pancreatitis has increased in recent decades. The aim of the present study was to analyze the etiology, clinical manifestations, treatment, complications and outcome of pediatric pancreatitis to help physicians better manage it. Materials and Methods. Data were retrospectively collected from 36 children with pancreatitis admitted to the Gaslini Pediatric Tertiary Center from January 2015 to December 2020. Results. Idiopathic forms were frequent (27.8%), whereas the major etiologic factors were infections (8/36, 22.2%) or litiasis (16.7%). Abdominal pain was the most frequent symptom at onset (91.7%). Patients with severe forms had statistically significant higher amylase (p=0.044) and lipase (p=0.035) values. A statistically significant association between complications and severity (p=0.001) was observed. Twenty-five patients (69.4%) had oral re-feeding and 92% of them started it within 72 hours. Conclusions. Pediatric acute pancreatitis has very different characteristics and course from the adult form. Currently available literature lacks clinical-based evidence. The study provides recommendation for clinical and therapeutic management.

Introduction

Acute Pancreatitis (AP) is an inflammatory disease characterized by the sudden onset of abdominal pain, elevation of pancreatic enzymes and radiological findings. The abdominal pain can be generalized and non-back radiated, associated with jaundice, fever, vomiting and/or irritability.

In recent decades, AP in children has been increasingly diagnosed [1,2], but the natural history is poorly understood and no good predictors have been found to determine its progression to a severe disease [3-5].

Recently, pediatric-specific recommendations have been published to provide a unified approach for the management of pediatric AP [3,6-8]. However, most of the current literature describes adult cases.

The aim of this study is to analyze demographic characteristics, etiology, clinical manifestations, treatment, complications and outcome of pediatric AP to collect more data and help physicians to better manage it.

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Materials and methods

Data were retrospectively collected from 36 children with AP admitted to Gaslini Children's Hospital, Gastroenterology and Pediatric Endoscopy Unit, Genoa, Italy, from January 2015 to December 2020. The Hospital Ethical Committee has approved the study.

Diagnostic criteria for pediatric AP were in accordance with pediatric guidelines of the International Study Group of Pediatric Pancreatitis [6]. Patients younger than 18 years old with two out of three criteria were included: 1) abdominal pain compatible with AP; 2) serum amylase and/or lipase values ≥ 3 times upper normal limits; and 3) imaging findings consistent with AP.

They were classified into mild AP (MAP), moderately-severe AP (MSAP) and Severe AP (SAP), according to criteria from European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) [3].

Patients older than 18 years old, presenting an isolated increase in pancreatic enzymes, with chronic pancreatitis (CP), and/or with asparaginase-induced AP were excluded. In addition, recurrence was considered a complication.

For each patient were collected data on gender, age, etiology, symptoms and laboratory tests within 24 hours of admission (amylase, lipase, C-reactive protein (CRP), liver enzymes, albumin, calcium, creatinine and triglycerides), with imaging findings, treatment, complications and outcome.

Statistical methods

Firstly, descriptive statistics were performed. Categorical variables were summarized in terms of absolute frequencies and percentages, whereas quantitative variables in terms of median values with first and third quartile (1st – 3rd q).

Comparison of frequencies was performed by means of Chi-square test of Fisher's Exact test in case of expected frequencies <5. Comparison of quantitative variables among three categories of patients (MAP vs MSAP vs SAP) was done by means of the non-parametric Analysis of Variance (Kruskal-Wallis test) and post-hoc tests were corrected according to Bonferroni's adjustement, reporting the P value as PB. All statistical tests were two-sided and a value of $P<0.05$ was considered statistically significant. Software "Statistica" (version 9, StatSoft Corporation, Tulsa, OK, USA) was used for all the analyses.

Results

Demographic features, clinical and classification

Sixteen of 36 patients (44.4%) were admitted to the Hospital Emergency Room (ER), 12/36 (33.3%) were transferred from peripheral hospitals, and 8/36 (22.2%) were directly admitted onto the hospital ward.

Median age at onset was 10 years old (range 5.2-13.2) with 21/36 (58.3%) being female. Most of the patients had a MAP (24/36, 66.7%); 5/36 (13.9%) and 7/36 (13,9%) were suffering from MSAP and SAP, respectively. Demographic, clinical, etiology, imaging and treatment data are summarized in **Table 1**.

Clinical and serological characteristics

Most of the etiologies were infections (8/36, 22.2%) and litiasis (6/36, 16.7%). No causes were found in a relevant proportion of patients (10/36, 27.8%), labeled as idiopathic forms. Other anedoctal causes were cystic fibrosis (5.6%), iatrogenic (5.6%), biliary tract malformations (5.6%) and trauma (2.8%). Abdominal pain was the most frequent symptom at onset in 32/36 patients (91.7%). Vomiting was present in 24/36 patients (66.7%), and diarrhea in 8/36 (22.2%). Seven patients presented fever (19.4%).

A statistically significant relationship between severity and pancreatic/liver enzymes was found. Patients with SAP had higher amylase, lipase, alanine transaminase (ALT), aspartate transaminase (AST) and gamma-glutamyl transpeptidase (GGT) values than patients with MAP and MSAP ($p=0.044$ for amylase, $p=0.035$ for lipase, $p=0.026$ for ALT, $p=0.011$ for AST and $p=0.021$ for GGT). No relationship with other indices, specifically between severity and CRP or blood count alterations was found **(Table 2)**.

Complications

Eight of 36 patients had complications (22.2%). A statistically significant association between complications and severity ($p=0.001$, Table 2) was found. In particular, 5/7 patients with SAP (71.4%) and 2/5 with MSAP (40%) had complications. SAP complications resulted from pancreatic pseudocyst, sepsis and organ dysfunction. Only 1/24 with MAP had a complication (recurrence). Two MSAP patients and four SAP patients were admitted to the Intensive Care Unit (ICU). No patients with MAP required ICU admission. No patients died.

Imaging

Abdominal ultrasound (US) was performed in 34/36 patients (94.4%). Of the other 2 patients, one underwent Magnetic Resonance Imaging (MRI) and the other, who had a relapse on CP in cystic fibrosis, did not undergo any radiological imaging.

The most frequent US finding was a normal pancreatic parenchyma (32.3%); other relevant findings were edema (14.7%), pancreatic parenchimal hyper/hypo-echogenicity (8.8% and 5.9%, respectively), biliary sludge (8.8%) or litiasis (8.8%). In 3/36 patients, the pancreas was not clearly visible at US thus MRI or Computed Tomography (CT) was performed. The 2 patients who underwent CT presented pancreatic parenchyma inflammation with peri-pancreatic effusion, whereas the patient who underwent the MRI suffered a hemorrhagic necrotizing pancreatitis.

MRI was performed in 17/36 patients (47.2%). A normal pancreatic parenchyma was observed in 2/17 patients and pancreatic edema with or without abdominal effusion was found in 6/17 patients (35.3%).

CT was performed in 6/36 patients (16.7%), with pancreatic inflammation with abdominal effusion in two patients (33.3 %), normal parenchyma in one patient (16.7%), pancreatic edema in one patient (16.7 %), necrosis in one patient (16.7 %), and gallbladder hydrop in one patient (16.7 %). All radiological findings are summarized in **Table 1**.

Table 1: Description of the study patients, signs and symptoms at onset, etiology, imaging, and treatment [N = 36].

	N. (%)
Gender: Male	15/36 (41.7 %)
Female	21/36 (58.3 %)
Age at onset (years), median (1st – 3rd q)	10 (5.2 - 13.2)
Access to:	
Gaslini's ER	16 (44.4 %)
Other Hospital's ER	12 (33.3 %)
No ER	8 (22.2 %)
Type of episode:	
Acute	31 (86.1 %)
Acute relapse on chronic	5 (13.9 %)
Comorbidity: yes	19 (52.8 %)
Chronic therapy: yes	13 (36.1 %)
Severity:	
Mild	24 (66.7 %)
Moderate-severe	5 (13.9 %)
Severe	7 (19.4 %)
Complications: yes	9 (25 %)
ICU: yes	6 (16.7 %)
Signs and symptoms at onset	
Abdominal pain: yes	32 (91.7 %)
Vomiting: yes	24 (66.7 %)
Diarrhea: yes	8 (22.2 %)
Fever: yes	7 (19.4 %)
Other: yes	15 (41.7 %)
Etiology	
Idiopathic	10/36 (27.8 %)
Infections	8/36 (22.2 %)
Litiasis	6/36 (16.7 %)
Multifactorial	4/36 (11.1 %)
Cystic fibrosis	2/36 (5.6 %)
Iatrogenic	2/36 (5.6 %)
Malformations	2/36 (5.6 %)
Trauma	1/36 (2.8 %)
Alimentary disorder	1/36 (2.8 %)
Ultrasound (n=34/36; 94.4 %)	
Normal	10/34 (29.4 %)
Edema	5/34 (14.7 %)
Not clearly visible	4/34 (11.8 %)
Hyper-echogenicity	3/34 (8.8 %)
Hypo-echogenicity	2/34 (5.9 %)
Post-traumatic pseudocyst	1/34 (2.9 %)
Edema and hypo-echogenicity	1/34 (2.9 %)
Biliary sludge	3/34 (8.8 %)
Litiasis	3/34 (8.8 %)
Choledochus cyst	1/34 (2.9 %)
Pancreatic hypo-echogenicity + litiasis)	1/34 (2.9 %)
Magnetic Resonance Imaging (n=17/36; 47.2 %)	
Normal	2/17 (11.8 %)
Edema	4/17 (23.5 %)
Edema and abdominal effusion	2/17 (11.8 %)
Malformation	2/17 (11.8 %)
Litiasis	2/17 (11.8 %)
Pancreatic inflammation and litiasis	1/17 (5.9 %)
Necrosis	1/17 (5.9 %)
Haemorragic pancreatitis and pseudocyst	1/17 (5.9 %)
Post-traumatic pseudocyst	1/17 (5.9 %)
Post-surgery pseudocyst	1/17 (5.9 %)
Computed Tomography (n=6/36; 16.7 %)	
Normal	1/6 (16.7 %)
Pancreatic inflammation and abdominal effusion	2/6 (33.3 %)
Edema	1/6 (16.7 %)
Necrosis	1/6 (16.7 %)
Gallbladder hydrop	1/6 (16.7 %)
Treatment	
Hydratation (IV): yes	34/36 (94.4 %)
Oral, refeeding time < 24 h	10/36 (27.8 %)
Oral, refeeding time ≥ 24 to < 48 h	10/36 (27.8 %)
Oral, refeeding time ≥ 48 to < 72 h	3/36 (8.3 %)
Oral, refeeding time ≥ 72 h	2/36 (5.6 %)
Parenteral Nutrition, refeeding time < 24 h	1/36 (2.8 %)
Parenteral Nutrition, refeeding time ≥ 24 to < 48 h	1/36 (2.8 %)
Parenteral Nutrition, refeeding time ≥ 48 to < 72 h	4/36 (11.1 %)
Parenteral Nutrition, refeeding time ≥ 72 h	4/36 (11.1 %)
Enteral + Parenteral Nutrition ≥ 48 to < 72 h	1/36 (2.8 %)
Oral, refeeding time < 72 h	23/25 (92.0 %)
Parenteral Nutrition, refeeding time < 72 h	7/11 (63.6 %)
Antibiotics: yes	23 (63.9 %)
Analgesics: yes	32/36 (88.9 %)
Protease inhibitors (Gabesate-mesilate): yes	9 (25 %)
Anti-oxidants (glutamin): yes	0 (0 %)
Somatostatine analogue (Octreotide): yes	9 (25 %)
Probiotics: yes	3 (8.3 %)
Protonic Pump Inhibitors: yes	21/35 (60 %)

ER: Emergency Room; **ICU:** Intensive Care Unit; **IV:** Intravenous.

Table 2: Age at onset, quantitative parameters, complications and refeeding in patients divided according to severity (N=36).

	Severity:			
	Mild [n=24]	Moderate-severe[n=5]	Severe[n=7]	P
Age at onset (years)	9.5 (5.2 - 13.1)	12.3 (11 - 14.2)	10.3 (3.4 - 13)	0.59
Systolic Blood Pressure (mmHg)	102 (99 - 112) [n=18]	111 (110 - 113)	112.5 (109 - 124) [n=6]	0.09
Diastolic Blood Pressure (mmHg)	63.5 (57 - 70) [n=18]	72 (71 - 72)	61.5 (56 - 75) [n=6]	0.07
Cardiac Rate (bpm)	98 (89 - 120) [n=23]	110 (95 - 118)	95 (80 - 106)	0.50
Body Temperature (°C)	36.4 (36.2 - 36.8) [n=23]	36 (36 - 36.8)	36 (36 - 36.3) [n=5]	0.15
Amylase (U/L)	491 (222.5 - 708)	1042 (648 - 1101)	1008 (414 - 2873)	0.044
Lipase (UL)	979 (614 - 1442.5)	1282 (663 - 1738)	2163 (1333 - 8323)	0.035
Hemoglobin (g/dl)	12.2 (11.6 - 13.5)	12.4 (12.2 - 17.1)	12.9 (11.2 - 14.7)	0.43
Leucocites (/mm3)	10755 (6650 - 12725)	14460 (11700 - 16350)	11000 (6650 - 20860)	0.46

Neutrophils (/mm3)	7010 (4315 - 10350)	11920 (7170 - 12750)	7140 (3500 - 19170)	0.60
Calcium (mg/dl)	4.7 (4.6 - 5)	4.9 (4.8 - 5.2) [n=4]	4.9 (4.6 - 5.1)	0.30
Total Colesterol (mg/dl)	128.5 (106 - 140) [n=14]	168.5 (156 - 181) [n=2]	130 (113 - 175.5) [n=4]	0.12
Triglicerides (mg/dl)	95 (62 - 110) [n=15]	70 (59 - 81) [n=2]	102.5 (59 - 165) [n=6]	0.65
Albumin (mg/dl)	3757 (3232 - 4231) [n=23]	3792 (3572.5 - 4608.5) [n=4]	4308 (3573 - 4777)	0.37
AST (U/L)	30 (15 - 38) [n=23]	30 (26 - 38)	57 (43 - 121)	0.011
ALT (U/L)	14 (11 - 32) [n=23]	12 (11 - 45)	42 (39 - 132)	0.026
GGT (U/L)	12 (10 - 63) [n=21]	13 (13 - 22)	135 (32 - 262)	0.021
Creatinin (mg/dl)	0.4 (0.3 - 0.5) [n=20]	0.5 (0.5 - 0.6)	0.5 (0.4 - 0.6) [n=6]	0.36
CRP (mg/dl)	0.7 (0.4 - 1.6)	1.5 (0.4 - 1.6)	0.5 (0.4 - 1.4)	0.73
	n/N (%)	**n/N (%)**	**n/N (%)**	P§§
Complications: yes	1/24 (4.2 %)	2/5 (40 %)	5/7 (71.4 %)	0.001
no	23/24 (95.8 %)	3/5 (60 %)	2/7 (28.6 %)	
ICU: yes	0/24 (0 %)	2/5 (40 %)	4/7 (57.1 %)	< 0.0001
no	24/24 (100 %)	3/5 (60 %)	3/7 (42.9 %)	
Oral refeeding	21/24 (87.5 %)	3/5 (60 %)	1/7 (14.3 %)	0.001
Parenteral refeeding	3/24 (12.5 %)	2/5 (40 %)	6/7 (85.7 %)	

P value refers to the Kruskall-Wallis test (non parametric Analysis of Variance); §§P value refers to the Fisher's Exact test. ALT: alanine transaminase. **AST:** aspartate transaminase. **GGT:** Gamma-Glutamyl Transpeptidase; **CRP:** C-Reactive Protein; **ICU:** Intensive Care Unit

Management

Intravenous (IV) fluid resuscitation was administered to 34/36 patients (94.4%). Type of IV fluid was a normal saline solution (NS) with 5% dextrose, 1-1.5 times maintenance.

Overall, 25/36 patients (69.4%) had oral re-feeding. More specifically, 23/25 patients (92%) started an Early Oral Re-feeding (EOR) within 72 hours of presenting symptoms; 10/23 patients had EOR within 24 hours and 10/23 had EOR between 24 and 48 hours. Twenty-one out of 24 (87.5%) MAP patients, 3/5 (60%) MSAP and only 1/7 (14.3%) SAP had EOR (p=0.001).

A total of 11/36 (30.5%) patients received parenteral nutrition (PN); three were MAP, two were MSAP and six were SAP (p = 0.001). The association between severity and type and timing of re-feeding are summarized in **Table 2**.

Thirty-two of 36 patients (88.9%) needed analgesic therapies. Antibiotic prophylaxis was administered to 23/36 patients (63.9%); there were seven SAP (7/7, 100%), four MSAP (4/5, 80%), and twelve MAP (12/24, 50%).

Nine patients received protease inhibitors, and nine received octreotide. Sixty percent of the patients received Protonic Pump Inhibitors. One patient required surgery for biliary peritonitis due to gallbladder empyema and another patient needed surgical drainage of pancreatic pseudocysts.

Discussion

In this study, one of the few studies within Pediatrics, we focused on the clinical characteristics and the management of children with AP who had been admitted to the Gaslini Children Hospital.

Up to few years ago, the management of pediatric AP was mainly based on adult guidelines and/or personal experiences. In the past ten years, the epidemiology and etiology of pediatric pancreatitis has been greatly developed [9,10] and evidence shows that AP in children has very different characteristics and course compared to adult PA. Therefore, new guidelines have been recommended specifically for pediatric age, drawing upon adult literature, limited pediatric studies and expert opinions, in order to provide recommendations for optimal and standardized management. This is relevant because the reported incidence of AP in children has been increasing, estimated to be currently 1 in 10,000 per year [8,11-13]. The incidence rate found in the present study is slightly higher than that reported in literature, with 1.8 cases per 10,000 per year; this higher incidence is probably due to the 8 patients transferred from other Italian hospitals directly onto the ward without previously admission to the ER.

When AP is suspected, laboratory tests and imaging are recommended. It is important to perform a complete baseline investigation (blood count, serum electrolytes, creatinine, triglycerides, and hepatic/pancreatic enzymes) in order to monitor the fluid/hydration status and to assess organ involvement [7]. Current consensus recommendations favor transabdominal US as the initial imaging examination due to its advantages over other forms of imaging. A negative US, known or suspected complications, or the need for surgery [8,9,14] are all indications to perform CT and/or MRI.

In previous studies, Park et al. [15] found biliary tract diseases (36.2%) and medications (25.6%) as the leading causes of pediatric AP in the United States. More recently, Poddar et al. [16] studied 320 children with AP from India in which trauma (21%) and biliary tract diseases (10%) were the most common causes whereas Sweeny et al.[17] in analyzing 115 children with AP in the United States found idiopathic (31%) and medications (23%) as the main causes. Moreover, Zhong et al.[10] found that major etiological factors in China were biliary (31.5%) and idiopathic (28.5%), and finally, in our study, most of the AP cases were idiopathic (27.8%), followed by infective causes (22.2%) and biliar litiasis (16.7%). Hypertriglyceridemia and alcohol-induced PA are significantly rarer than in adults.

More than half of patients considered in our study had MAP, which is consistent with literature. An interesting point emerged is that MAP patients always have a benign course without developing complications. Major complications and need for ICU are reserved only for SAP with organ involvement at diagnosis. Our results confirm that overall outcomes are favorable and mortality is very low, even including SAP and ICU admissions [18]; thus we can conclude that pediatric AP, that appears mild at diagnosis and in following days remains mild over time, can be managed in local hospitals without being transferred to a Tertiary Care center.

Although guidelines specify that the degree of severity of AP is not dependent on the absolute value of pancreatic enzymes if these are greater than 3 times the normal values, our data shows that there is a correlation between severity and amylases/lipases values at diagnosis. Patients with SAP had higher amylase and lipase range values than patients with MAP and MSAP, and the association is also present for liver enzymes. This data may be important because it can estimate the severity of pancreatitis at onset.

The two cornerstones of treatment of AP are fluids and nutrition as summarized in a recently published review[19] and crystalloid has been the most recommended type of fluid in adult guidelines. Recommendations from ESPGHAN/NASPGHAN indicate 1.5 to 2 times maintenance IV fluids for pediatric AP, but clinical evidence is lacking. Our patients received early NS with 5% dextrose, up to 1.5 times maintenance. The addition of 5% dextrose does not alter the tonicity and it is a useful carbohydrate support for the increased risk of malnutrition [20]. From our experience, an early administration of NS with 5% dextrose is a safe and well-tolerated option. The timing of intervention may be the key rather than the aggressiveness of fluid resuscitation.

According to the latest indications, all AP pediatric patients can start oral or enteral feeding early, compatible with their general conditions[20]. In the clinical practice, patients with SAP are often admitted to the ICU and complications do not allow for EOR. However, they have benefit from an early PN. In the present study, 69.4% of patients had oral nutrition and 92% started it early; no patient had any complications in terms of relapse or worsening of the AP course.

Conclusions

AP is uncommon in children. Prompt diagnosis and stratification of severity influences its correct handling, but fluid management, nutrition and treatment of complications are the most important aspects of the care required.

Despite current available literature being somewhat limited and the lack of clinical-based evidence, our work provides suggestions on the clinical and therapeutic management of pediatric AP. In addition, due to the increase in incidence in recent years, other multi-center studies aimed at evaluating the incidence, etiology, natural history and risk factors of Pediatric AP are recommended.

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