Arch Argent Pediatr. 2025;e202410437

Recurrent acute pancreatitis in pediatrics: characteristics and risk factors

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ABSTRACT

Recurrent acute pancreatitis (RAP) affects 15-36% of children with acute pancreatitis (AP) and may progress to chronicity. To determine the etiology and evolution of RAP, a descriptive retrospective cohort study was conducted in patients aged 1-18 years. Twelve patients with RAP were included out of 79 with AP, and demographic, etiological, clinical, analytical, and imaging data were collected. The results showed that the median age was 11 years for RAP and 13 years for AP. There were no significant differences between sexes or initial severity. Significant associations were found in the weight percentile, ultrasound findings, and genetic studies. These factors may influence the progression of RAP. Biliary lithiasis was the most common etiology in both groups. The multidisciplinary approach allows for avoiding its progression to chronicity.

Keywords: *pancreatitis; recurrence; pediatrics; lithiasis.*

doi: http://dx.doi.org/10.5546/aap.2024-10437.eng

To cite: Perdomo Muñoz JM, Morise S, Pallito MB, Patiño O, Ortiz G, Silvestri G, et al. Recurrent acute pancreatitis in pediatrics: characteristics and risk factors. *Arch Argent Pediatr.* 2025;e202410437. Online ahead of print 23-JAN-2025.

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Funding*: None.*

Conflict of interest*: None.*

Received*: 5-14-2024*
Accepted*: 11-15-2024*

INTRODUCTION

Recurrent acute pancreatitis (RAP) is defined according to INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) as two or more episodes of acute pancreatitis (AP) with complete resolution of pain or complete normalization of pancreatic enzymes before the diagnosis of the next episode, regardless of the time between episodes of AP.[1] RAP occurs in 15-36% of children with AP.[2] Genetic and molecular studies are currently playing an essential role in RAP's etiological search. Knowledge of diagnostic methods and treatments is crucial to avoid recurrent pain and irreversible pancreatic insufficiency.

OBJECTIVE

To describe the characteristics of RAP in pediatrics and identify risk factors.

POPULATION AND METHOD

A descriptive retrospective cohort study was performed with patients aged 1-18 years who were seen in the Pediatric Gastroenterology Service of our institution and diagnosed with AP and RAP between 2016 and 2023. We collected demographic (sex, age), clinical (weight, height), etiological (lithiasis, idiopathic, metabolic, genetic, autoimmune, toxic-drug), parenteral hydration requirement (volume greater than 1500 ml/m^2), biochemical data (amylasemia >600 IU and white blood cell count >15 000/mm^3), imaging, with initial pathological ultrasound (focal or diffuse edema) and tomography 72 hours after the first episode of AP (focal or diffuse pancreatic enlargement, peripancreatic inflammation and percentage of pancreatic necrosis), degrees of AP's severity (mild, moderate, severe[1]) and the requirement for pediatric intensive care. Patients were followed up from the first episode of AP weekly for 2 months, then biweekly for 2 months, monthly for 3 months, and then quarterly according to clinical and laboratory control. The variables were compared between AP and RAP; using Fisher's exact test, p <0.05 was considered statistically significant. Statistical analysis was performed with STATA 14 statistical software.

The study was approved by the Research Ethics Committee of the Hospital Nacional Profesor Alejandro Posadas (Registration Code 716) and developed in accordance with the Helsinki Declaration and Ministerial Resolution 1480/11.

RESULTS

We selected all patients diagnosed with AP from 2016-2023 (79); 63.3% (n = 50) were female, and 9.4% (n = 6) developed RAP (p = 0.23). The median age of the AP group was 13 years (IQR $_{25\text{-}75}$ 10-14).

The patients were followed for one year, with a median of 3.5 months (minimum 1 and maximum 12). Fifteen percent (n = 12) developed RAP during this period (2016-2023), with a median age of 11. Sixty-seven percent of RAPs (8/12) presented before 6 months after the first episode of AP; median progression was 5.3 months.

Most patients had a weight percentile >90 and amylasemia >600 IU/ml; white blood cell count <15 000/mm^3 was the most frequent in both groups (*Table 1*).

In both groups, most patients required parenteral hydration greater than 1500 ml/m^2. Thirteen patients with AP required admission to the intensive care unit; of these, only one presented RAP.

Of the patients with a single AP episode, two had a toxic-drug etiology (1 due to azathioprine and 1 due to 6-mercaptopurine); both normalized amylase levels after the medication was discontinued.

In three patients, AP was found at the onset of autoimmune diseases (systemic lupus erythematosus, inflammatory bowel disease, and type 1 diabetes)—all three normalized amylase levels when the underlying disease was controlled.

Twelve patients presented RAP; lithiasis was the most frequent etiology (n = 6). One patient presented metabolic origin with familial hyperchylomicronemia. Another patient presented non-lithiasis obstruction by gastrojejunal anastomosis with double pyloric exclusion. The etiology was not detected in only four patients; the genetic study was performed with a pancreatitis panel, cystic fibrosis transmembrane conductance regulator (*CFTR*), serine protease inhibitor Kazal-type 1 (*SPINK1*), protease serine 1 (*PRSS1*) and cationic trypsinogen by chymotrypsin C (*CTRC*).

In two patients was found a *CFTR* mutation, in one, *SPINK1* mutation, and one was negative and assumed to be idiopathic (*Table 2*). Ultrasonography was pathological in 35 of 79 patients with PA and 10 of 36 with RAP. Abdominal CT was performed only in 27 patients 72 hours after the first episode of PA to rule out severe pancreatic involvement (*Table 3*).

No patients with RAP had moderate or severe degrees (*Table 4*).

Table 1. Comparison between acute pancreatitis and recurrent acute pancreatitis

Factors	AP (n = 67) (100%)	RAP (n = 12) (100%)	*p*
Median age in years (range)	13 (1-18)	11 (5-17)	
Female sex	44 (65%)	6 (50%)	0.23
Ultrasound (pathologic)	25 (37%)	10 (83%)	0.02
CT (necrosis)	8 (12%)	1 (8%)	0.58
PICU	12 (18%)	1 (8%)	0.36
Weight (percentile >90)	30 (45%)	11 (92%)	0.002
Initial hydration plan >1500 ml/m^2	51 (76%)	11 (92%)	0.21
Amylase >600 IU	39 (58%)	10 (83%)	0.08
Leukocytosis >15 000/mm^3	28 (42%)	3 (25%)	0.22

AP, acute pancreatitis; RAP, recurrent acute pancreatitis; CT, computed axial tomography; PICU, pediatric intensive care unit.

There were no statistically significant differences concerning sex, initial severity, biochemical findings, pancreatic necrosis on CT, and initial intravenous hydration. Progression from AP to RAP was found to be statistically significant in patients with weight percentile >90% (p = 0.002), in those with ultrasound with pathological findings in the first episode (p = 0.02), and in those with an etiology of genetic cause (p = 0.014).

DISCUSSION

Pediatric AP has increased in recent years, with a reported incidence of 13/100 000 children.[2] As a multifactorial disease, it has several clinical presentations and different triggers for developing AP. About 15% to 36% of APs develop a RAP.[3] In our population, the female sex predominated (63%) in the first episode of AP, in contrast to that described by Sweeny KF et al.[2]

Table 2. Etiology

Etiology	AP (N = 67)	RAP (n = 12)
Lithiasis	58 (74.6%)	6 (50%)
Genetics	-	3 (25%)
Metabolic	2 (3%)	1 (8.3%)
Toxic/medicinal	2 (3%)	0 (0%)
Idiopathic	7 (10.4%)	1 (8.3%)
Autoimmune	3 (4.4%)	0 (0%)
Obstructive, non-lithiasis	3 (4.4%)	1 (8.3%)

AP, acute pancreatitis; RAP, recurrent acute pancreatitis.

Table 3. Abdominal CT scan results at 72 hours

CT 72 h	AP (n = 21)	RAP (n = 6)
Normal	3	2
Focal or diffuse pancreatic enlargement	3	1
Peripancreatic inflammation	6	2
Presence of a cyst	1	-
Pancreatic necrosis	8	1

CT, computed axial tomography; AP, acute pancreatitis; RAP, recurrent acute pancreatitis.

Table 4. Classification by severity

Classification	AP (n = 67)	RAP (n = 12)
Mild	56	12
Moderate	8	0
Severe	3	0

AP, acute pancreatitis; RAP, recurrent acute pancreatitis.

The etiology of AP varies according to age. Biliary disease, abdominal trauma, and drug intake are the most frequent causes in adults in Latin America.[4] In the pediatric population, the highest incidence is biliary and idiopathic disease,[5] as in our case reports.

The mean progression from AP to RAP was 5.3 months, which is different from that reported by other studies (3 months).[2]

Half of our patients with RAP had a history of AP secondary to biliary lithiasis, in whom surgery had been deferred for more than four weeks. The latter was a predisposing factor for the second episode of AP, as described by Vázquez-Frias R et al.[5] This observation motivated the change in the surgical timing of cholecystectomy, which was performed before discharge of the following patients in their first episode of AP at our institution.

Investigating the cause of RAP prevents chronicity and pancreatic insufficiency, as Liu QY et al. described in the INSPPIRE report. Pathogenic genetic variants (*PRSS1*), older age at first episode of AP, and absence of toxic/metabolic risk factors were associated with faster progression to pancreatic insufficiency.[6]

In our study, body mass index in obesity was identified as a risk factor for recurrent form, as described by Sweeny K.F et al.[2]

Autoimmune pancreatitis has a low incidence of 0.71 to 0.82/100 000 children.[7,8]

We did not find any cases in our series, although three patients presented AP at the onset of autoimmune diseases.

The literature reports that the most frequent genetic cause factors are the *PRSS1* gene that encodes for trypsin 1 and increases the autocatalytic conversion of trypsinogen into active trypsin, causing a premature activation of intrapancreatic trypsinogen that alters the balance of proteases and their inhibitors. Mutation of other genes presents alteration in inhibitory function, which are *SPINK1*;5q32, *CFTR*;7q31.2 and *CTRC*;1p36.21.[9,10]

In addition, it is described that patients with alteration in *SPINK1* are at increased risk of developing chronic pancreatitis.[6]

Lipid metabolism disorders, such as familial hyperchylomicronemia, should be investigated as probable etiologies related to RAP.[6] In our investigation, we found only one patient with this diagnosis.

According to the Atlanta classification, pancreatitis can be:

- Mild: No local or regional systemic complications; resolve in the first week.
- Moderate to severe: Presence of transient organ failure (less than 48 hours), local complications (liquid collections or necrosis), or systemic (exacerbation of previously diagnosed diseases).
- Severe: Presence of single or multiple organ failure persisting more than 48 hours.[1,11]

In our experience, the severity of the first AP episode did not influence the evolution of RAP, and none of our patients developed chronic pancreatic insufficiency.

Mirza et al.[12] found that the most common ultrasound alterations were enlarged and edematous pancreas, which were present in up to 70% of patients with AP. In our series, 41% of the patients presented focal lesions or diffuse edema on ultrasound, with a higher incidence of RAP. This finding was statistically significant.

CONCLUSION

Although RAP is uncommon, its incidence has recently increased in the pediatric population. Obesity is one of the main risk factors. Implementing follow-ups with these patients is necessary to facilitate the diagnosis of other factors that may be involved, such as lithiasis and genetic alterations. It is essential to establish timely surgical treatment to avoid progression to chronicity and pancreatic insufficiency.

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