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Is acute recurrent pancreatitis in children a precursor of chronic pancreatitis? A long-term follow-up study of 93 cases

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ABSTRACT

Background/aims: In view of paucity of literature we analyzed our experience of acute recurrent pancreatitis (ARP) to study clinical profile and long-term outcome.
Methods: Over 13 years, 93 consecutive children (≤18 years) diagnosed to have ARP were included in this study. Magnetic resonance cholangiopancreatography was done at baseline and on follow-up. Common mutations for serine-protease-inhibitor (SPINK1 N34S), protease inhibitor (PRSS1 R122S) and cystic fibrosis transmembrane conductance regulator (CFTR deltaF508, 5T) were studied in 22 idiopathic cases.
Results: The median age of the children with ARP was 13 (10–14.5) years, 53 were males. Etiology included biliary in 14 (15%), pancreas divisum in 6 (7%), others in 3 (3.5%) and idiopathic in the remaining 70 (75%). SPINK1 mutation was found in 10/22 (45%) cases. Over a median follow-up of 25.5 (8.25–48) months, 37 (42%) of 88 (5 lost to follow-up) developed chronic pancreatitis (CP). On multivariate analysis idiopathic etiology ($p < 0.03$), presence of SPINK1 mutation ($p = 0.01$), longer follow-up ($p < 0.001$) were associated with progression to CP.
Conclusions: Biliopancreatic structural/obstructive causes should always be looked for. It seems ARP is a precursor of CP and progression is associated with idiopathic etiology and presence of genetic mutations. Hence, patients with ARP should be kept on regular follow-up to detect CP.

1. Introduction

Pancreatitis used to be uncommon in children but in recent times there are reports to suggest an increasing incidence of acute pancreatitis in children, as in adults [1–5]. Acute pancreatitis (AP) is an event and is expected to resolve completely after the first attack. However, a proportion (10%–30%) of AP goes on to have a second or further attacks of pancreatitis (acute recurrent pancreatitis [ARP]) [6]. Factors that predict the progression of AP to ARP are not known. The etiological spectrum of AP and ARP are different. In ARP, biliopancreatic structural/obstructive lesions are important as they are correctable causes of ARP, on the other hand drugs, trauma, infection, systemic diseases are common in AP [7–11]. There is a scarcity of published information about ARP in children. So far there are only three single center studies comprising of 19, 25 and 78 cases [6–8] and a recent multicenter study on 155 children [9]. Focus of all these studies was on clinical spectrum of ARP. The natural history of ARP has not been studied in children.

Studies in adults have shown that idiopathic ARP and ARP with genetic predisposition often progress to chronic pancreatitis (CP) in the long run [12–14]. In a study of 75 adults with ARP, Garg et al. [12] have shown that 47% had progressed to CP on follow-up. Similarly, Whitcomb [13] and Keim [14] described idiopathic ARP as a transition phase between acute and chronic pancreatitis as they have shown that genetically predisposed cases of AP over many years develop CP after going through a phase of ARP. However, we do not have any information in children to say ARP is a transition phase between AP and CP as there is no long-term follow-up study in children. We therefore analyzed our experience of ARP in children with the aims to study their clinical and demographic profile. We also analyzed our long-term follow-up data to find how often they develop chronic pancreatitis and what are the factors that predict their progression from ARP to CP.

2. Materials and methods

From January 2003 to December 2015, 93 consecutive children (≤18 years of age) diagnosed to have ARP were included in this study. AP was diagnosed when at least two of three criteria were fulfilled; [15] (1) abdominal pain suggestive of AP, (2) serum amylase and/or lipase activity at least 3 times greater than the upper

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Table 1
Etiology of acute recurrent pancreatitis (n = 93).

Etiology		Number of cases	Percentage (%)
Biliopancreatic structural causes [n = 21(22.6%)]	Choledochal cyst	11	12%
	Gallstones	3	3%
	Pancreas divisum	6	6%
	Duodenal diverticulum	1	1%
Drug[a]		1	1%
Hereditary		1	1%
Idiopathic		70	75%

[a] Drug: corticosteroids plus non-steroidal anti-inflammatory in a case of SLE.

limit of normal and (3) imaging findings characteristic of, or compatible with AP. ARP was defined as two or more distinct episodes of acute pancreatitis (AP) along with complete resolution of pain (≥1-month pain free interval between the diagnosis of AP) or complete normalization of serum pancreatic enzyme levels along with complete resolution of pain irrespective of specific time interval between AP episodes [15]. In addition to the International Study Group of Pediatric Pancreatitis: in search for a Cure (INSPPIRE) definition of ARP [15] we did a baseline cross-sectional imaging i.e. magnetic resonance cholangiopancreatography (MRCP) in all cases to detect structural causes of ARP and also to rule out the presence of chronic pancreatitis (CP). Serum calcium, lipid profile, blood sugar and stool fat (Sudan stain) were done in all cases. Genetic markers (PRSS1, SPINK1, and CFTR) were studied in a group of 22 idiopathic ARP cases (part of 68 cases of pancreatitis published previously) [16]. Common mutations like R122H for serine protease or cationic trypsin gene or PRSS1, N34S of serine protease inhibitor, Kajal type 1 or SPINK1 and Del F508 and 5T variation of cystic fibrosis transmembrane conductance regulator gene or CFTR were studied by standard PCR-RFLP method (only PCR for CFTR) in DNA of patients isolated from peripheral blood leucocytes by standard technique described before [17–19].

All patients were managed according to their etiology. Episodes of pancreatitis were managed as per standard protocol. During each episode of pancreatitis, serum amylase, lipase and transabdominal ultrasound examination were done in each case. Biliopancreatic structural anomalies and obstructive causes like choledochal cyst, duodenal diverticulum, cholelithiasis were treated surgically. Endoscopic management was done for choledocholithiasis and pancreas divisum (minor papilla sphincterotomy with stenting).

Patients were followed up every 3–6 monthly. If symptoms persisted (episodes of pancreatitis) a repeat MRCP was done after 1–2 years to look for the changes of chronic pancreatitis. A patient was labeled as having CP on follow-up if he/she had any one of the following; (1) consistent abdominal pain with imaging findings suggestive of CP (as per modified MRCP Cambridge criteria) [20], (2) evidence of exocrine pancreatic insufficiency and suggestive pancreatic imaging findings, (3) evidence of endocrine pancreatic insufficiency and suggestive pancreatic imaging finding [15]. The duration between the first episode of AP and the date of diagnosis of CP was taken as the time to develop CP.

Informed consent was obtained from either parent of each patient included in the study before any intervention and also for genetic mutation testing. The study protocol conforms to the ethical guidance of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institute's human research committee (institute's ethical committee).

2.1. Statistical analysis

Data was analyzed using SPSS-15 (SPSS Inc. Chicago, USA) statistical package. Continuous variables were expressed as median with inter-quartile range (IQR) and categorical data as number and percentages. Continuous variables were compared with Mann–Whitney U test and categorical variables with Chi-square or Fisher's exact test. For multivariate analysis binary logistic regression (backward stepwise) was used and p-value of <0.05 was taken as significant.

3. Results

During the study period of 13 years a total of 373 cases of pancreatitis were managed in our department; 169 (45%) of them were AP, 111 (30%) CP and the remaining 93 (25%) were ARP. The median age of 93 ARP cases was 13 (IQR, 10–14.5) years with male to female ratio of 53: 40. The median number of episodes prior to presentation was 3 (IQR, 2–4) and the duration of symptoms was 12 (IQR, 6–24) months. All of them presented with episodes of pain with raised pancreatic enzymes. The etiology of ARP is shown in Table 1. A known cause was found in 23 (25%) cases and the remaining 70 (75%) were idiopathic. Of the known causes, biliopancreatic structural or obstructive causes were seen in the majority (21 of 23; 91%). Choledochal cysts, pancreas divisum and gallstones were the major causes. None had metabolic causes like hypercalcemia or hyperlipidemia. Of the 70 so-called "idiopathic" cases we could do genetic mutations study in 22 cases due to resource constraint and heterozygous SPINK1 mutation was found in 10 of 22 (45%) cases and none were found to have PRSS1 or CFTR mutations.

Of the 11 cases of choledochal cysts, 7 had type I and 4 had type IVa cysts. Surgical resection of cyst and choledocho-jejunostomy was done in 9 and 2 were lost to follow-up. On a median follow-up of 18 (IQR, 5–67) months following surgery, there was no recurrence of pancreatitis in any of them. There were 3 cases of gallstones; one of them had associated choledocholithiasis during presentation. Endoscopic common bile duct clearance was done in the child with choledocholithiasis. Cholecystectomy was done in all three and on a median follow-up of 24 (IQR, 15–27) months there was no recurrence of symptoms. Pancreas divisum was diagnosed in 6 cases, minor papilla sphincterotomy and stenting was done in 4. One patient was lost to follow-up after endotherapy. On a median follow-up of 48 (IQR, 18–96) months, two of the three showed improvement (no further attacks of pain) and two cases

Table 2
Differences between idiopathic (n = 23) and known causes of ARP (n = 70).

	Idiopathic (n = 70)	Known causes (n = 23)	p Value (univariate)	p Value (multivariate)
Median (IQR) age (years)	**13.00 (10.75–15.00)**	**11.00 (8.00–14.00)**	**0.04**	**0.013**
Male: female	42:28	11:12	0.31	0.89
Median (IQR) number of episodes at presentation	3.00 (2.00–4.00)	3.00 (2.25–5.00)	0.56	0.13
Duration of symptoms	12.00 (6.00–24.00)	22.50 (9.75–36.00)	**0.04**	0.12
Median (IQR) weight z score at presentation	−0.48(−1.39 −0.30)	−0.79 (−2.04 −0.24)	0.28	0.56
Median (IQR) height z score at presentation	−0.49 (−1.10 −0.18)	−0.56 (−1.73–0.88)	0.85	0.08
Median (IQR) duration of follow-up (months)	25.50 (7.75–48.00)	18.00 (4.00–48.00)	0.39	0.91
Progression to chronic pancreatitis	**34**	**3**	**0.003**	**0.01**

*Figures in bold are statistically significant. IQR: inter quartile range.