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ORIGINAL ARTICLE

Clinical profile and treatment outcome of chronic pancreatitis in children: a long-term follow-up study of 156 cases

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ABSTRACT

Aim: There is a paucity of literature in pediatric chronic pancreatitis (CP) and most information is derived from adult literature. We, therefore, analyzed our experience of CP to look for clinical profile and long-term outcome.

Methods: From January 2003 to December 2015, 156 consecutive children (≤18 years) diagnosed as CP were included. Their clinical profile, management, and follow-up data were retrieved. Genetic markers (PRSS1, SPINK1, and CFTR) were studied in 40 idiopathic cases.

Results: The median age of the patients was 13 [inter-quartile range (IQR): 10–14] years (93 males) and 134 (86%) were idiopathic. Genetic mutations were found in 22/40 (55%) idiopathic cases. All but two presented with pain abdomen (episodic pain in 93.6%) and symptom duration was 12 (IQR: 6–24) months. There were two subsets; calcific (CCP) 68 (43.5%) and non-calcific (NCCP) 88 (56.5%). In CCP group, significantly more children had Cambridge grade 5 magnetic resonance cholangiopancreatography changes, low weight Z-score, and had continuous pain more compared to NCCP group. Over a median follow-up of 23 (IQR: 8–45.5) months, more children in CCP group had complications. Endoscopic therapy (done for persistent pain in 40) relieved pain in 52.5% of cases while medical therapy did so in 36% of cases.

Conclusion: Pediatric CP in Asia presents with episodic pain and genetic predisposition seems to be a major cause. There are two subsets; CCP and NCCP with former showing marked imaging changes, more often associated with malnutrition and complications. Endoscopic therapy for pain relief gives modest benefit but medical therapy is not encouraging.

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Idiopathic; genetic mutations; chronic-calcific; malnutrition; endoscopic therapy

Introduction

Pancreatitis was believed to be uncommon in children but in recent times there are reports to suggest an increasing incidence of pancreatitis in children as well [1–5]. Acute pancreatitis (AP) is an event and is expected to recover completely after the first attack. On the other hand, chronic pancreatitis (CP) is a progressive inflammatory condition of the pancreas, which leads to irreversible structural and functional damage with time. Globally, there is a paucity of literature regarding CP in children [6,7]. Most of the information related to its diagnosis and management is derived from the literature on CP in adults. The literature on pediatric CP is mainly in the form of case series [8–10] with only one multicenter study of 146 cases [11]. The etiology of CP in children is different from that in adults as smoking and alcohol consumption which play a major role in the pathogenesis of CP in adults [12] do not have much role to play in children. Data from India and Asia suggest that the bulk of CP in children is due to idiopathic cause [6–8] while Western data suggests genetic risk factor in the majority of so-called 'idiopathic' CP in children [11,13,14].

Tropical calcific pancreatitis (TCP) used to be the commonest cause of CP in developing countries, but recent studies on adult population have shown that TCP is no longer a common cause of CP in India [15]. The classical presentation of TCP was in young age (children/adolescents) with pain, severe malnutrition, diabetes mellitus, and exocrine insufficiency and was invariably associated with large pancreatic calculi [16]. However, recent pediatric case series from India have shown that calcific pancreatitis is common in children but not the classical type of TCP [7–9]. The natural history of CP in children is unknown as there is not much information in the current literature. We, therefore, studied the clinical profile, etiology, complications, and long-term outcome of children with CP.

Materials and methods

From January 2003 to December 2015, 156 consecutive children (up to 18 years of age), diagnosed to have CP in Pediatric Gastroenterology services of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India,

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were included in this study. Their follow-up data was collected till June 2016. In this audit, medical records of all children during the study period were retrieved and data pertinent to their clinical features, investigations, treatment, outcome, and follow-up details were recorded in a proforma. CP was diagnosed as per the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) definition [17] with one of the following; (1) consistent abdominal pain with imaging findings suggestive of CP (as per modified magnetic resonance cholangiopancreatography (MRCP) Cambridge criteria) [18], (2) evidence of exocrine pancreatic insufficiency and suggestive pancreatic imaging findings, and (3) evidence of endocrine pancreatic insufficiency and suggestive pancreatic imaging finding [17]. Familial pancreatitis was defined as more than one affected family member, mostly within the same generation [18].

Modified MRCP Cambridge criteria for CP were used to grade MRCP changes. As per these criteria, Cambridge grade 1 is normal pancreas; Cambridge grade 2 (equivocal findings) with dilatation/obstruction of less than three side branches and normal main pancreatic duct (MPD); Cambridge grade 3 (mild disease) with dilatation of three or more side branches and normal MPD; Cambridge grade 4 (moderate disease) includes Cambridge grade 3 plus stenosis or dilatation of MPD and Cambridge grade 5 (severe disease) includes Cambridge 3 and 4 criteria plus additional obstructions, cysts, stenosis of MPD, and calculi [19].

In our department, we follow a fixed protocol for the management of pancreatitis. Besides detailed family history, metabolic work up in the form of serum calcium and lipid profile were done in all cases to find out an etiology. Cross-sectional imaging i.e., MRCP was done in all cases at baseline to diagnose CP and also to find any associated structural anomalies like pancreas divisum. Endocrine and exocrine insufficiency were tested by random blood sugar (if abnormal then glucose tolerance test) and Sudan's stain of stool for fat (>10 globules/high power field was taken as abnormal) [20] at diagnosis and then on follow-up at 6–12 monthly intervals. Random blood sugar of 79–140 mg/dl were taken as normal, > 200 mg/dl as suggestive of diabetes mellitus and glucose tolerance test was ordered if the value was >140 mg/dl [21].

Genetic markers (PRSS1, SPINK1, and CFTR) were studied in a group of 40 cases with no known etiology (part of 68 cases of pancreatitis published before) [22]. Common mutations like R122H for serine protease or cationic trypsin gene 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 [23–25].

Children with pain and pancreatic duct obstruction due to stone with or without stricture were managed endoscopically by stricture dilatation, stone extraction, and stent placement. Medical management for pain was done with on-demand analgesics along with antioxidants; Betamore-G twice daily (Osper Formulations Pvt. Ltd., New Delhi, India, each capsule contains carotenoids: 10.33 mg, vitamin E acetate 25 IU, vitamin C 100 mg, methylcobalamin 500 microgram) with or without pancreatic enzyme replacement (enteric coated @ 1000 lipase units/kg body weight per major meal) therapy (PERT). The success of endoscopic therapy and medical therapy was assessed in semi-quantitative method of asking question-related to pain severity and frequency and put them into three categories as per their response; complete response (no pain), partial response (reduction in severity, and frequency of pain by more than 50%), and no response (remained unchanged or worsen or reduction of severity and frequency by less than 50% from the pretreatment level). Children were followed-up every 3–6 months. Complications of CP like pseudocyst, biliary stricture, bleeding from pseudoaneurysm or gastric fundal varices were managed as per standard protocol.

Informed consent was taken from either parent of each patient before any intervention and also for genetic marker testing. This audit was done after taking due ethical clearance from the institute's ethical committee (IEC code: 2015-127-IP-87).

Statistical analysis

The data was analyzed using SPSS-15 (SPSS Inc., Chicago, IL) 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 the *p* value of <.05 was taken as significant. Z-score for weight for age and height for age was calculated by using Epi Info software (CDC, Atlanta, GA) and as per WHO criteria weight Z-score < -2 was taken as wasting and height Z-score < -2 as stunting [26].

Results

Over 13 years, 156 children were diagnosed as CP and managed at our tertiary care center. Their median age was

Table 1. Clinical features of chronic pancreatitis ($n = 156$).

Clinical features	Number	Percentage
Males	93	59.6
Calcific chronic pancreatitis	68	43.6
Etiology		
Idiopathic	134	85.9
Known causes	22	14.1
Pain abdomen as presenting symptoms	154	98.7
Episodic pain	146	93.6
Continuous pain	8	5.1
Weight Z-score < -2	56	36.4
Height Z-score < -2	33	22.0
MRCP*: ductal changes (modified MRCP Cambridge grading)		
Ductal changes	146	93.6
Grade 5	53	34.0
Grade 4	91	58.3
Grade 3	2	1.3
Parenchymal atrophy with/without calcification	10	6.4
Genetic mutations	22/40	55.0

*MRCP: magnetic resonance cholangiopancreatography (grade 3: mild with side branch changes only; grade 4: moderate with main pancreatic duct [MPD] dilatation, grade 5: severe with MPD stenosis, calculi, etc.) [18].

13 (IQR: 10–14) years and male to female ratio was 93:63. Their clinical presentations are given in Table 1. The pain was the main clinical presentation in all but two cases (98.7%) who were picked up incidentally on a transabdominal ultrasound done for some other indication. Episodic or type A pain was the presenting complaint in 146 (93.5%) with pain-free periods of varying duration in between. The etiology of CP was familial in 9 (5.7%), pancreas divisum in 10 (6.4%), post-traumatic in 3 (1.9%), and the remaining 134 (86%) cases of unknown etiology. There were two distinct subsets of patients; calcific CP 68 (43.5%) and non-calcific CP 88 (56.5%). The comparison between them is shown in Table 2. As expected children with calcific CP had more severe disease; significantly more children had Cambridge grade 5 changes on MRCP, had low height Z-score and had continuous pain more often compared to non-calcific CP children. However, there was no difference in age of presentation, gender distribution or duration of symptoms.

Genetic mutations were present in 22 of 40 (55%) children with unknown etiology. SPINK1 mutation was present in 18 of 22 (82%) (heterozygous in 16, homozygous in 2), CFTR (5T variant) in 3 (13.5%), and one child (4.5%) had both heterozygous SPINK1 and CFTR (5T variant) mutation. None had PRSS1 or major CFTR mutations. There was no difference in the distribution of genetic mutations between calcific and non-calcific CP (Table 2).

A total of 14 (9%) children (eight from calcific CP group and six from non-calcific CP group) were lost to follow-up; the remaining 142 (91%) had a median follow-up of 23 (IQR: 8–45.5) months. Comparison of follow-up data is given in Table 3. More children in calcific CP group had complications than in non-calcific CP group. During follow-up, 24 (17%) children had complications like pseudocyst in 17, biliary stricture in 3, upper gastrointestinal bleeding due to ruptured pseudoaneurysm in 3 and ruptured gastric varices in 1. Overall, complications were seen more often in calcific CP group. There was no difference in the distribution of individual complications except pseudocyst which was seen more often in calcific CP group (14 versus 3, $p < .0005$). Of the 17 children with pseudocyst, endoscopic cystogastrostomy was done in three, transpapillary drainage in two, percutaneous drainage in two, surgical in one and in the remaining nine cases, pseudocyst resolved spontaneously. Endoscopic balloon dilatation and plastic stent placement relieved biliary stricture in all three. Of three pseudoaneurysm bleeding, angiographic embolization was done in one, surgical ligation in one, and one child improved with conservative management. Endoscopic glue injection controlled bleeding in the child with gastric fundal varices and he underwent splenectomy with lateral pancreaticojejunostomy later. At presentation, none of the 156 children had endocrine or exocrine insufficiency. However, on follow-up 8 of 142 (5.6%) developed diabetes mellitus and 14 (9.8%) developed steatorrhea. There was no difference in the distribution of endocrine or exocrine insufficiency in calcific CP and non-calcific CP.

Endoscopic pancreatic intervention in the form of sphincterotomy with stricture dilatation and stone extraction with or without stent placement was done in 40 children, 20 in calcific CP group and 20 in non-calcific CP group, the indication being pain abdomen. Some response was seen in 21 of 40 (52.5%) (complete in 7, partial in 14) and the remaining 19 (47.5%) did not show any response in severity or frequency of pain. Medical therapy in the form of the pancreatic enzyme with or without antioxidants was used in 89 children (32 in calcific CP group and 57 in non-calcific CP group), enzyme alone in 11, antioxidants alone in 48 and combination of enzyme and antioxidants in 30 children for pain abdomen. Overall 32 (36%) showed some response (complete response in 14 and partial response in 18) and 57 (64%) did not show any response. There was an almost identical response with antioxidants alone and with antioxidants plus enzyme (some response in 37.5% versus 43.3% respectively, $p = .64$). However, enzyme therapy alone showed a poor response (some response in 9% only). Though endotherapy showed some response in half of the cases in comparison to one-third with medical therapy, the difference was not statistically significant ($p = .08$). There was no difference in response (complete, partial, or no response) with various medical therapies between calcific CP and non-calcific CP group. Surgery was performed in just four cases in this cohort; one pseudocyst drainage, one pseudoaneurysm ligation and two lateral pancreaticojejunostomies for pain. There was no death or pancreatic cancer in this cohort of patients.

Discussion

In this cohort study, we have documented that the etiology of CP in Indian children was unknown in the majority, pain was the presenting symptom in almost all and the majority had type A or episodic pain, pancreatic ductal changes were

Table 2. Differences between calcific and non-calcific pancreatitis.

	Calcific-CP ($n = 68$)	Non-calcific CP ($n = 88$)	p (Univariate)	p (Multivariate)
Median age (IQR) in years	13 (10–14)	13 (9.25–14)	.805	.599
Male: female	44:24	49:39	.258	.295
Median duration of symptoms (months)	24 (12–48)	18 (8–43.5)	.143	.659
Idiopathic etiology	61 (90%)	73 (83%)	.232	.555
Modified MRCP* Cambridge grade 5	**33 (48.5%)**	**20 (22.7%)**	**.001**	**.002**
Episodic pain	**59 (86.8%)**	**87 (99%)**	**.002**	**.001**
No. of cases with weight Z-score < −2	**32/67 (48%)**	**24/87 (27.6%)**	**.010**	.493
No. of cases with height Z-score < −2	**21/65 (32%)**	**11/86 (13%)**	**.046**	**.046**
Median weight Z-score	**−1.86 (−2.53 to −1.23)**	**−1.08 (−2.06 to −0.22)**	**.003**	.324
Median height Z-score	−1.25 (−2.53 to −0.28)	−1.07 (−1.76 to −0.18)	.189	.767
Genetic mutations	10/19 (52.6%)	12/21 (57.1%)	.807	.068

*MRCP: magnetic resonance cholangiopancreatography (grade 5: main pancreatic duct dilatation with stenosis, calculi, etc.) [18]; IQR: inter-quartile range.
Bold values are significant.

Table 3: Comparisons of follow-up data between chronic calcific and non-calcific pancreatitis.

	Calcific CP ($n = 60$)	Non-calcific CP ($n = 82$)	p (Univariate)	p (Multivariate)
Median age (IQR) in years	13 (9.25–14)	13 (10–14)	.955	.630
Male: female	38:22	48:34	.567	.538
Median duration of follow up (months)	21.5 (10–49.75)	30 (14–48.75)	.390	.113
Follow-up weight Z-score < −2	**25/65 (38.5%)**	**19/86 (22%)**	**.001**	**.001**
Follow-up height Z-score < −2	12/49 (24.5%)	16/68 (23.5%)	.905	.128
Median follow-up weight Z-score	**−1.45 (−2.53 to −1.02)**	**−1.15 (−1.89 to −0.18)**	**.002**	.450
Median follow-up height Z-score	−1.44 (−2.00 to −0.66)	−1.17 (−1.96 to −0.20)	.336	.301
Diabetes mellitus	5 (8.3%)	3 (3.6%)	.282	.146
Steatorrhea	9 (15%)	5 (6%)	.093	.095
Associated complications	**19 (31.7%)**	**5 (6%)**	**.001**	**.005**
Endoscopic therapy	20 (36.7%)	20 (23.2%)	.245	.483
Death	0	0		
Malignancy	0	0		

IQR: inter-quartile range.
Bold values are significant.

seen in most, almost half of them had calcification and a small proportion developed exocrine or endocrine insufficiency on follow-up. As far as our knowledge goes, this is the largest series on CP in children so far. Previous single center studies were in 37, 42, and 99 cases [6–8], and the recent multicenter study of INSPPIRE comprised of 146 cases [11]. The strength of this study compared to the study by Kumar et al. which was a cross-sectional study, is that we have follow-up data of >90 of cases and have meticulously looked at their nutritional status and outcome of various treatment modalities.

The etiological spectrum of our study is almost similar to other published series from Asia [6–8]. The study from China in 42 children showed unknown etiology in 74% of cases [6] and the figure from two other studies from India in 37 and 99 cases were 81% and 85% of cases, respectively [7,8]. Nevertheless, recent studies from Asia as well as from the West have shown that the vast majority of cases of unknown etiology have an underlying genetic predisposition for CP [11,13,14]. Wang et al. [14] in a study of 75 idiopathic CP cases from China showed genetic mutations in 66.6% of cases (SPINK1 in 57.3% and PRSS1 in 9.3%). Kumar et al. [11] in their multicenter study of 146 cases documented genetic mutations in 86 of 118 cases (73%) in whom these were done. Due to resource constraint, genetic mutations analysis could be done in 40 of 134 cases with unknown etiology and as in other studies in children we too documented mutations in 55% cases. Hence, it is likely that many cases of unknown etiology are not truly idiopathic and might have had a genetic predisposition. The prevalence of pancreas divisum in our study is almost the same as expected in the general population [27].

There are differences in the distribution of various pancreatitis causing genetic mutations in different population across the World. Kumar et al. [11] showed that PRSS1 mutation was present in 50 of 108 cases, CFTR in 24 of 104 cases, and SPINK1 in 25 of 99 cases. In our study, we did not find any PRSS1 mutation, and SPINK1 was the main genetic predisposing factor present in 18 of 40 (45%) cases. Though PRSS1 and CFTR mutations are common in Europe and America [11,13], it is the SPINK1 which is common in Asia especially in China, India, and Korea [14,22,28]. Studies in adults from the subcontinent [29–32] and our own study in children [22], showed that almost half of the cases of idiopathic CP were associated with SPINK1 gene mutations. SPINK1 gene is known as a disease modifier [33] and is probably not responsible for initiation of pancreatitis but mutations of SPINK1 lead to disease progression. Children with mutations in SPINK1 who had an episode of pancreatitis of unknown etiology (may be some environmental factor) had a higher risk of developing CP.

For some reason, parenchymal calcification in children with CP is seen more often in Asia than in the West. Despite having parenchymal calcification, these do not fit into the typical description of tropical chronic pancreatitis (TCP) [16]. INSPPIRE data of 144 cases of CP showed calcification in just 14% cases [11]. We found calcification in 43.6% and a similar figure (45.4%) has been reported from China [6]. Studies from the Southern part of India, where TCP used to be common, reported a much higher figure (70–82%) of calcification [7,8]. We have compared calcific with non-calcific pancreatitis and found that calcific group had more advanced disease in the form of more advanced changes in MRCP, more often had continuous pain and malnutrition. It is difficult to say whether they are in different stages of the same disease or two different subtypes of CP in children. Chowdhury et al. [7] in a study from south India have shown that 72% of 99 cases were idiopathic calcific CP and compared to non-calcific CP they had a higher prevalence of diabetes mellitus. Our follow-up data did not reveal increased prevalence of exocrine or endocrine insufficiencies in the calcific group but they continued to have more aggressive disease as they had more complications and were more often malnourished as compared to the non-calcific group. These features have not been highlighted before. The proportion of cases with malnutrition in our study is almost similar to that of other Indian studies [7,34]. In a study of 120 CP of unknown etiology in adults, Midha et al. [34] showed that the incidence of malnutrition was similar to controls before the onset of CP but increased significantly after the onset of CP (45.8% versus 22.5%, $p < .001$). The causes of malnutrition were dietary restriction, diabetes mellitus, and pseudocyst. They concluded that malnutrition was not the cause of CP but an effect of CP. In our study, malnutrition was more common in calcific CP and the factors that might have contributed were associated complications and continuous pain which these children experienced more often than children in the non-calcific group.

Pain is the main complaint in this cohort of the patient and various medical therapies were tried to control pain. The response to medical therapy in the form of antioxidants with or without enzymes was not encouraging. Pancreatic enzymes are commonly prescribed in CP to reduce pancreatic enzyme secretion by negative feedback mechanism but their role in pain control is debatable [35]. The initial study with antioxidants showed encouraging results in controlling pain in CP but subsequent studies could not establish their beneficial effect in controlling pain [36,37]. In our study, there was a limited response to enzyme therapy and there was no additive effect of the enzyme to antioxidants therapy. Hence, if at all, only antioxidants may be considered in a setting where endotherapy is not indicated. As we have used enteric-coated enzyme preparation, it may be worth trying uncoated preparation which has an edge over coated one in controlling pain. Endoscopic therapy may be useful if there is pancreatic duct obstruction by stricture or stone [38–40]. Recently published pediatric series on endoscopic therapy in 143 CP cases showed short-term (follow-up 13 ± 4.7 months) success rate of complete response in 63.6% and some improvement in 21.6% [36]. However, long-term outcome was not good [40]. In a multicenter study of 1000 adult patients with CP, it was shown that endoscopic therapy for pancreatic duct obstruction led to a successful outcome in 65% of cases on long-term [40]. Our results of endoscopic therapy were almost similar.

The limitations of our study are; those of being retrospective in nature and inability to do complete etiological work-up like autoimmune pancreatitis, sphincter of Oddi manometry and genetic mutation analysis in all cases. As the study spread over 13 years, there was a change in Magnetic Resonance Imaging (MRI) technology and that might have influenced our MRCP findings. Our estimate of steatorrhea might not be accurate as Sudan stain is not an accurate method and we could not do the 72-h fecal fat or fecal elastase. Similarly, random blood sugar estimation might not have picked up all cases of diabetes mellitus as we have not done HbA1C and glucose tolerance test in all cases. Our findings need confirmation with larger studies from other countries, to make them generalized.

In conclusion, CP in children in Asia presents with episodic pain mimicking recurrent AP and genetic predisposition seems to play a major role in so-called 'idiopathic' cases. There are two subsets of CP seen in the subcontinent; chronic calcific and non-calcific type, the former presents with more advanced disease with marked imaging changes, is more often associated with malnutrition and complications are seen more commonly on follow-up with the calcific group. However, endocrine and exocrine insufficiency are not common. Endoscopic therapy for pain relief in obstructive pancreatic duct gives modest benefit while medical therapy for pain is not encouraging. Enzyme therapy, with enteric coated preparation, either alone or in combination with antioxidants, is not much of use.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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