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Original Investigation

Risk Factors Associated With Pediatric Acute Recurrent and Chronic Pancreatitis
Lessons From INSPPIRE

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IMPORTANCE Pediatric acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) are poorly understood.

OBJECTIVE To characterize and identify risk factors associated with ARP and CP in childhood.

DESIGN, SETTING, AND PARTICIPANTS A multinational cross-sectional study of children with ARP or CP at the time of enrollment to the INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) study at participant institutions of the INSPPIRE Consortium. From August 22, 2012, to February 8, 2015, 155 children with ARP and 146 with CP (aged ≤19 years) were enrolled. Their demographic and clinical information was entered into the REDCap (Research Electronic Data Capture) database at the 15 centers. Differences were analyzed using 2-sample *t* test or Wilcoxon rank sum test for continuous variables and Pearson χ^2 test or Fisher exact test for categorical variables. Disease burden variables (pain variables, hospital/emergency department visits, missed school days) were compared using Wilcoxon rank sum test.

MAIN OUTCOMES AND MEASURES Demographic characteristics, risk factors, abdominal pain, and disease burden.

RESULTS A total of 301 children were enrolled (mean [SD] age, 11.9 [4.5] years; 172 [57%] female); 155 had ARP and 146 had CP. The majority of children with CP (123 of 146 [84%]) reported prior recurrent episodes of acute pancreatitis. Sex distribution was similar between the groups (57% female in both). Hispanic children were less likely to have CP than ARP (17% vs 28%, respectively; odds ratio [OR] = 0.51; 95% CI, 0.29-0.92; *P* = .02). At least 1 gene mutation in pancreatitis-related genes was found in 48% of patients with ARP vs 73% of patients with CP (*P* < .001). Children with *PRSS1* or *SPINK1* mutations were more likely to present with CP compared with ARP (*PRSS1*: OR = 4.20; 95% CI, 2.14-8.22; *P* < .001; and *SPINK1*: OR = 2.30; 95% CI, 1.03-5.13; *P* = .04). Obstructive risk factors did not differ between children with ARP or CP (33% in both the ARP and CP groups), but toxic/metabolic risk factors were more common in children with ARP (21% overall; 26% in the ARP group and 15% in the CP group; OR = 0.55; 95% CI, 0.31-0.99; *P* = .046). Pancreatitis-related abdominal pain was a major symptom in 81% of children with ARP or CP within the last year. The disease burden was greater in the CP group compared with the ARP group (more emergency department visits, hospitalizations, and medical, endoscopic, and surgical interventions).

CONCLUSIONS AND RELEVANCE Genetic mutations are common in both ARP and CP. Ethnicity and mutations in *PRSS1* or *SPINK1* may influence the development of CP. The high disease burden in pediatric CP underscores the importance of identifying predisposing factors for progression of ARP to CP in children.

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Acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) are poorly understood conditions of childhood.[1] Single-center studies estimate that 9% to 35% of children with acute pancreatitis (AP) have recurrent episodes,[2-5] and the incidence of CP is approximately 0.5 per 100 000 persons per year in young adults.[6,7]

Factors that predispose children to recurrent episodes of AP and progression from ARP to CP are unknown. Although alcohol use and smoking have long been recognized as major risk factors for ARP and CP in adults,[8] they are uncommon in the pediatric age group. Recent single-center studies have identified several genetic risk factors in children with ARP or CP,[4,5,9-14] including mutations in the following genes: cystic fibrosis transmembrane conductance regulator (*CFTR*), cationic trypsinogen (*PRSS1*), pancreatic secretory trypsin inhibitor (*SPINK1*), chymotrypsin C (*CTRC*), and carboxypeptidase 1 (*CPA1*). Other risk factors include obstructive, traumatic, infectious, and metabolic causes.[15,16]

Most of our current knowledge on ARP and CP comes from studies in adults. Because the etiologies of these diseases differ greatly between children and adults, applying the knowledge on the natural history and management of these diseases from adults to children may be inappropriate. The international, multicenter INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) Consortium was created to address this issue by collecting data on the largest group of pediatric patients with ARP or CP to date.[10,17] We have recently reported that genetic and obstructive factors are common in children with CP and that the associated disease burden is substantial.[10]

In this study, we analyzed the demographic and clinical characteristics of children with ARP and CP with the goal of identifying the risk factors and disease burden.

Key Points

Question What are the risk factors and disease burden of acute recurrent pancreatitis and chronic pancreatitis in children?

Findings In this cross-sectional study of children with acute recurrent pancreatitis and chronic pancreatitis, pancreatitis-associated gene mutations were the most common risk factor. Children with chronic pancreatitis were mostly of non-Hispanic ethnicity, had *PRSS1* or *SPINK1* mutations, and had higher disease burden than those with acute recurrent pancreatitis.

Meaning The high disease burden in pediatric chronic pancreatitis underscores the importance of identifying predisposing factors for development of chronic pancreatitis in children.

Methods

Study Design and Participants

In this cross-sectional study from 15 institutions, demographic and clinical data were collected in patient/parent and physician questionnaires on children who fulfilled the criteria for ARP or CP and were aged 19 years or younger at the time of enrollment.[10,17] Acute recurrent pancreatitis was defined as 2 episodes of AP along with resolution of pain (≥1 month between episodes) or as normalization of pancreatic enzyme levels and resolution of pain between episodes irrespective of time interval.[1] Diagnosis of CP required at least 1 of the following: (1) abdominal pain plus imaging findings suggestive of chronic pancreatic damage; (2) exocrine pancreatic insufficiency and imaging findings suggestive of chronic pancreatic damage; or (3) endocrine pancreatic insufficiency and imaging findings suggestive of chronic pancreatic damage.[1] Information was entered into the REDCap (Research Electronic Data Capture) database from August 22, 2012, to February 8, 2015, and represented baseline information of the INSPPIRE cohort. All centers obtained institutional review board approval or the equivalent for their country. Written informed consent and/or assent was obtained from all parents and children. Seventy-six of the patients with CP were described in a previous study.[10] We included patients with cystic fibrosis if they were pancreatic sufficient and having recurrent episodes of AP.

Statistical Analysis

Summary statistics were presented as mean with standard deviation, median with interquartile range (IQR), or frequency count with percentage. Patient characteristics, risk factors, and clinical variables were compared between ARP and CP using 2-sample *t* test or Wilcoxon rank sum test for continuous variables and using Pearson χ^2 test or Fisher exact test for categorical variables. The results from these statistical tests were reported as difference of means or medians and as odds ratio (OR), respectively, with corresponding 95% confidence interval and *P* value. $P < .05$ was considered statistically significant. Statistical analysis was performed using SAS version 9.4 statistical software (SAS Institute, Inc).

Results

Patient Characteristics

Of the 301 patients in the INSPPIRE database (mean [SD] age, 11.9 [4.5] years; 172 [57%] female), 155 patients met the criteria for ARP and 146 for CP. Demographic characteristics of these patients are shown in **Table 1**, and their distribution across INSPPIRE centers is given in eTable 1 in the Supplement. Sex distribution was similar between the groups (57% female in both), and the majority of participants were white (81% in the ARP group and 80% in the CP group). Hispanic children were less likely to have CP than ARP (17% vs 28%, respectively; OR = 0.51; 95% CI, 0.29-0.92). Children with CP tended to be older at the time of first diagnosis of pancreatitis compared with those who had ARP, but the difference was not statistically significant (mean [SD] age, 10.2 [4.5] vs 9.1 [5.0] years, respectively; mean difference, 1.1 years; 95% CI, −0.1 to 2.3; $P = .08$). Of the 146 children with CP, 123 (84%) had documented prior episodes of ARP. The date of first AP episode and the date of CP diagnosis used to calculate time for progressing from ARP to CP were available in 76 of these 123 patients; the median time was 1 year (IQR, 1.5 months to 2.7 years; range, 0-14.3 years).

Family history of AP was similar between the groups, but patients with CP were more likely than those with ARP to have a

Table 1. Demographic Characteristics[a]

Characteristic	ARP (n = 155)	CP (n = 146)	OR or Mean Difference (95% CI)
Female, No. (%)	88 (57)	84 (57)	1.03 (0.65 to 1.63)[b]
Age, mean (SD), y			
At enrollment	11.3 (4.8)	12.6 (4.2)	1.3 (0.3 to 2.3)[c]
At diagnosis	9.1 (5.0)	10.2 (4.5)	1.1 (−0.1 to 2.3)[c]
Hispanic, No./sample size, No. (%)	41/145 (28)	22/131 (17)	0.51 (0.29 to 0.92)[b]
Race, No. (%)	(n = 138)	(n = 127)	
White	112 (81)	102 (80)	
Multiracial	12 (9)	8 (6)	
African American	5 (4)	5 (4)	0.94 (0.51 to 1.74)[d]
Asian	7 (5)	7 (6)	
Other	2 (1)	5 (4)	
BMI percentile, mean (SD)	65.1 (33.6)	60.3 (30.6)	−4.8 (−12.2 to 2.5)[c]

Abbreviations: ARP, acute recurrent pancreatitis; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CP, chronic pancreatitis; OR, odds ratio.

[a] The differences in sample sizes between rows reflect available data for these parameters.

[b] Value is expressed as OR (95% CI) of CP.

[c] Value is expressed as mean difference (95% CI) for CP minus ARP.

[d] Value is expressed as OR (95% CI) of CP for white.

Table 2. Risk Factors for ARP vs CP in Children[a]

Risk Factor	No./Sample Size, No. (%)		OR (95% CI) of CP
	ARP (n = 155)	CP (n = 146)	
Genetic	49/102 (48)	86/118 (73)	2.91 (1.66-5.10)
CFTR	30/89 (34)	24/104 (23)	0.59 (0.31-1.11)
PRSS1	15/88 (17)	50/108 (46)	4.20 (2.14-8.22)
SPINK1	10/78 (13)	25/99 (25)	2.30 (1.03-5.13)
CTRC	5/48 (10)	4/73 (5)	0.50 (0.09-2.47)
Obstructive	50/152 (33)	47/144 (33)	0.99 (0.61-1.61)
Pancreas divisum	13/146 (9)	22/140 (16)	1.91 (0.92-3.95)
Gallstones	9/147 (6)	6/139 (4)	0.69 (0.24-2.00)
Pancreaticobiliary malunion	7/146 (5)	6/139 (4)	0.90 (0.29-2.73)
Biliary cyst	5/148 (3)	2/141 (1)	0.41 (0.04-2.57)
Sphincter of Oddi dysfunction	5/144 (3)	2/139 (1)	0.41 (0.04-2.54)
Annular pancreas	3/148 (2)	1/141 (1)	0.35 (0.01-4.37)
Autoimmune	16/112 (14)	14/108 (13)	0.89 (0.41-1.93)
Toxic/metabolic	39/152 (26)	22/137 (16)	0.55 (0.31-0.99)
Medications	19/108 (18)	4/87 (5)	0.23 (0.07-0.69)
Passive smoking exposure	12/140 (9)	12/129 (9)	1.09 (0.47-2.53)
Hypertriglyceridemia	9/104 (9)	2/78 (3)	0.28 (0.03-1.41)
Chronic kidney disease	3/111 (3)	1/91 (1)	0.40 (0.01-5.10)
Alcohol use	2/150 (1)	5/137 (4)	2.80 (0.45-29.80)
Active smoking	1/150 (1)	3/137 (2)	3.34 (0.26-176.27)

Abbreviations: ARP, acute recurrent pancreatitis; CP, chronic pancreatitis; OR, odds ratio.

[a] The differences in sample sizes between rows reflect available data for these parameters.

family history of CP (36% vs 16%, respectively; OR = 3.12; 95% CI, 1.70-5.73; $P < .001$). Chronic pancreatitis was less common in Hispanic patients than in non-Hispanic patients (OR = 0.51; 95% CI, 0.29-0.92; $P = .02$) (eTable 2 in the Supplement).

Risk Factors

Risk factors were divided into 4 categories: genetic (*CFTR*, *SPINK1*, *PRSS1*, *CTRC*), obstructive, toxic/metabolic, and autoimmune. At least 1 risk factor was identified in 111 patients with ARP (72%) and 125 patients with CP (86%). The most common risk factors for development of ARP or CP were genetic and obstructive (**Table 2**).

At least 1 gene mutation in pancreatitis-related genes was found in 49 of 102 patients with ARP (48%) and 86 of 118 patients with CP (73%) ($P < .001$). Of the 53 patients with ARP in whom no mutations were identified, 18 were screened for 2 or fewer gene mutations. Of the 32 patients with CP who had no identified mutations, 6 were tested for fewer than 3 gene mutations.

The most common mutation identified in ARP was in *CFTR* (30 of 89 patients [34%]), and the most common mutation identified in CP was in *PRSS1* (50 of 108 patients [46%]). Six children in the ARP group and 2 in the CP group had cystic fibrosis as determined by 2 *CFTR* disease-causing mutations and/or abnormal sweat chloride level. Children with *PRSS1* or *SPINK1* mutations were more likely to present with CP compared with ARP (*PRSS1*: OR = 4.20; 95% CI, 2.14-8.22; $P < .001$; and *SPINK1*: OR = 2.30; 95% CI, 1.03-5.13; $P = .04$).

Some children had more than 1 genetic risk factor. In children who had 3 or more genes tested, 8 of 84 patients with ARP

Table 3. Disease Burden of ARP or CP in Children[a]

Factor	ARP (n = 155)	CP (n = 146)	OR or Median Difference (95% CI)
Pattern of abdominal pain, No. (%)	(n = 142)	(n = 127)	
No abdominal pain	18 (13)	17 (13)	
Usually pain free; episodes of mild to moderate pain	21 (15)	19 (15)	
Constant mild to moderate pain	7 (5)	4 (3)	
Usually pain free; episodes of severe pain	57 (40)	39 (31)	1.50 (0.89 to 2.51)[b]
Constant mild to moderate pain plus episodes of severe pain	31 (22)	40 (32)	
Constant severe pain	8 (6)	6 (6)	
Constant pain score	(n = 134)	(n = 116)	
Median (IQR) [range]	0 (0-0) [0-100]	0 (0-15) [0-99]	
With any level of constant pain, No. (%)	27 (20)	30 (26)	1.38 (0.76 to 2.50)[c]
Episodic pain score	n = 128	n = 113	
Median (IQR) [range]	61 (0-82.5) [0-100]	70 (37-89) [0-100]	9.0 (−0.5 to 18.5)[d]
With any level of episodic pain, No. (%)	92 (72)	89 (79)	
ED visits, No.			
Lifelong	(n = 129)	(n = 114)	
Median (IQR) [range]	2 (1-4) [0-30]	4.5 (1-10) [0-300]	2.5 (1.4 to 3.6)[d]
Past year	(n = 130)	(n = 108)	
Median (IQR) [range]	1.5 (1-2) [0-12]	2 (0-3) [0-20]	0.5 (−0.2 to 1.2)[d]
Hospitalizations, No.			
Lifelong	(n = 133)	(n = 117)	
Median (IQR) [range]	2 (1-4) [0-30]	4 (1-8) [0-300]	2.0 (1.0 to 3.0)[d]
Past year	(n = 132)	(n = 111)	
Median (IQR) [range]	1 (1-2) [0-9]	1 (0-3) [0-23]	0 (−0.7 to 0.7)[d]
Missed school in past mo, d	(n = 117)	(n = 103)	
Median (IQR) [range]	0 (0-5) [0-31]	2 (0-6) [0-40]	2 (0.2 to 3.8)[d]

Abbreviations: ARP, acute recurrent pancreatitis; CP, chronic pancreatitis; ED, emergency department; IQR, interquartile range; OR, odds ratio.

[a] The differences in sample sizes between rows reflect available data for these parameters.

[b] Value is expressed as OR (95% CI) for constant severe pain.

[c] Value is expressed as OR (95% CI) for any constant pain.

[d] Value is expressed as median difference (95% CI) for CP minus ARP.

(10%) and 17 of 112 patients with CP (15%) had more than 1 genetic risk factor. A combination of *CFTR* and *SPINK1* mutations was most common (found in 5 children with ARP and 9 with CP).

Obstructive risk factors were found in 33% of patients and toxic/metabolic factors were found in 21% (Table 2). Pancreas divisum (PD) was present in 13 of 146 children with ARP (9%) and 22 of 140 children with CP (16%). It was less frequent with *PRSS1* mutations (eTable 3 in the Supplement). Obstructive and autoimmune risk factors were not significantly different between children with ARP and those with CP. Children with CP as compared with those with ARP less commonly had toxic/metabolic factors (22 of 137 children with CP [16%] vs 39 of 152 children with ARP [26%]; OR = 0.55; 95% CI, 0.31-0.99; P = .046) and specifically medications (ie, azathioprine sodium and 6-mercaptopurine; 4 of 87 children with CP [5%] vs 19 of 108 children with ARP [18%]; OR = 0.23; 95% CI, 0.07-0.69; P = .005). Alcohol use (1%) and cigarette smoking (4%) were uncommon in pediatric ARP or CP. Sixteen of 112 children with ARP (14%) and 14 of 108 children with CP (13%) were diagnosed as having autoimmune pancreatitis (AIP). Only 1 child with CP had an elevated IgG4 level, consistent with type 1 AIP.

Children with ARP or CP often had multiple risk factors. At least 1 risk factor was identified in 111 of 155 patients with ARP (72%), and 47 of 155 (30%) had multiple risk factors from different categories present. In the remaining 44 patients with ARP, only 8 were evaluated for all 4 genes and other risk factors. Of the 146 patients with CP, at least 1 risk factor was identified in 125 (86%), and 40 (27%) had multiple risk factors present. In the remaining 21 patients with CP, only 4 tested negative for all 4 genetic risk factors as well as other risk factors.

Burden of Disease

Pancreatitis-related abdominal pain was a major symptom in 81% of children with ARP or CP within the last year. The pain was mostly episodic in both groups (**Table 3**). Although constant and episodic pain scores were slightly higher in CP, the differences were not significant. The numbers of emergency department (ED) visits and hospitalizations were higher in patients with CP compared with ARP (lifelong ED visits: median [IQR], 4.5 [1-10] vs 2 [1-4], respectively; median difference, 2.5 visits; 95% CI, 1.4-3.6; P < .001; lifelong hospitalizations: median [IQR], 4 [1-8] vs 2 [1-4], respectively; median difference, 2.0; 95% CI, 1.0-3.0; P < .001), but no differences were found

Table 4. Imaging Findings in ARP and CP in Children[a]

Imaging	No./Sample Size, No. (%) ARP (n = 155)	CP (n = 146)	OR (95% CI) of CP
Imaging studies, No. (%)			
ERCP	25 (16)	97 (66)	10.29 (5.95-17.82)
Times performed, No.[b]			
1	20	66	
2	3	18	
3	0	6	
≥4	2	7	
CT	65 (42)	88 (60)	2.10 (1.33-3.33)
MRI only	40 (26)	52 (36)	1.59 (0.97-2.61)
MRCP	90 (58)	111 (76)	2.29 (1.39-3.76)
EUS	4 (3)	27 (18)	8.56 (2.92-25.15)
Findings on CT and MRI			
Focal acute pancreatitis	19/96 (20)	18/123 (15)	0.65 (0.34-1.41)
Inflammatory changes	41/98 (42)	48/124 (39)	0.88 (0.51-1.51)
Gland enlargement	35/98 (36)	19/124 (15)	0.33 (0.17-0.62)
Pancreatic atrophy	6/101 (6)	47/123 (38)	9.79 (3.97-24.12)
Calcifications	0/99	17/123 (14)	32.70 (1.94-551.00)[c]
Duct irregularities	11/102 (11)	67/122 (55)	10.08 (4.90-20.71)
Pancreatic duct dilatation	9/101 (9)	74/122 (61)	15.76 (7.26-34.20)
Lesions in the pancreas	1/103 (1)	7/127 (6)	5.95 (0.74-270.74)
Gallstones or sludge	5/100 (5)	9/124 (7)	1.49 (0.48-4.59)
Intrahepatic biliary dilatation	8/98 (8)	15/124 (12)	1.58 (0.63-3.82)
Evidence for liver disease	7/101 (7)	8/122 (7)	0.94 (0.33-2.69)
Findings on CT, MRI, MRCP, and ERCP			
Pancreatic duct obstruction or stricture	3/110 (3)	39/135 (29)	14.49 (4.34-48.41)
CBD stricture in intrapancreatic portion	4/125 (3)	7/142 (5)	1.57 (0.45-5.49)
Dilated CBD	13/126 (10)	35/143 (24)	2.82 (1.41-5.61)
CBD stone	7/126 (6)	11/143 (8)	1.42 (0.53-3.77)
Findings on CT, MRI, and EUS			
Peripancreatic inflammation or fat stranding	31/97 (32)	47/121 (39)	1.35 (0.77-2.37)
Findings on CT, MRI, MRCP, ERCP, and EUS			
Cysts or pseudocysts	9/129 (7)	28/142 (20)	3.27 (1.48-7.24)
Findings on MRCP and ERCP			
Abnormal main pancreatic duct	16/92 (17)	97/130 (75)	13.96 (7.16-27.24)
Abnormal side branches	4/92 (4)	56/123 (46)	18.39 (6.35-53.23)
Intraductal filling defects or calculi	1/92 (1)	36/126 (29)	36.40 (4.89-271.19)
Pancreas divisum	11/92 (12)	19/126 (15)	1.31 (0.59-2.90)

Abbreviations: ARP, acute recurrent pancreatitis; CBD, common bile duct; CP, chronic pancreatitis; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; MRCP, magnetic retrograde cholangiopancreatography; MRI, magnetic resonance imaging; OR, odds ratio.

[a] Imaging findings include results from all studies combined. The differences in sample sizes between rows reflect available data for these parameters.

[b] The range of number of times ERCP was performed for a patient was 1 to 7 for children in the ARP group and 1 to 9 for those in the CP group.

[c] The OR was computed based on the logit estimate that used a correction of 0.5 in every cell.

between groups for ED visits and hospitalizations within the past year (Table 3). Children with CP missed a median of 2 days (IQR, 0-6 days) of school in the past month, whereas the median was 0 days (IQR, 0-5 days) for children with ARP; however, the difference was not statistically significant (median difference, 2 days; 95% CI, 0.2-3.8).

Table 4 summarizes all imaging studies performed on children with ARP or CP. Overall, imaging studies were more frequently ordered for CP compared with ARP. Magnetic retrograde cholangiopancreatography was the most commonly used imaging modality; some children with CP had endoscopic retrograde cholangiopancreatography performed up to 9 times since their diagnosis. As expected, children with ARP had findings consistent with AP (pancreas enlargement, focal AP, inflammatory changes) compared with children with CP, who had evidence of persistent pancreatic injury (atrophy; calcifications; ductal irregularities, obstruction, dilatation, or stones; abnormal side branches).

Children with CP were more likely to receive medical, endoscopic, and surgical therapies compared with those who had ARP (**Table 5**). Medical therapy primarily consisted of pain medications and pancreatic enzymes. Acetaminophen and ibuprofen were the leading pain medications for ARP, while patients with CP used acetaminophen and hydrocodone bitartrate for pain. Therapeutic endoscopic retrograde cholangiopancreatography was performed in only 14% of children with ARP compared with 68% of those with CP. The most common type of surgery for pediatric ARP was cholecystectomy:

Table 5. Treatments for ARP and CP in Children[a]

Treatment	No./Sample Size, No. (%)		OR (95% CI) of CP
	ARP (n = 155)	CP (n = 146)	
Medications			
Pain medications	41/115 (36)	62/109 (57)	2.38 (1.39-4.08)
Medical therapies	44/149 (30)	101/140 (72)	6.18 (3.71-10.29)
Pancreatic enzymes	32/149 (21)	82/139 (59)	5.26 (3.14-8.82)
Vitamins or antioxidants	12/145 (8)	20/134 (15)	1.94 (0.91-4.15)
Steroids	0/143	8/135 (6)	19.13 (1.09-334.81)[b]
Octreotide	2/147 (1)	5/135 (4)	2.79 (0.45-29.65)
Endoscopic procedures			
Any ERCP	21/152 (14)	96/142 (68)	13.02 (7.29-23.34)
Biliary sphincterotomy	11/151 (7)	36/136 (26)	4.58 (2.23-9.44)
Pancreatic duct stent	6/151 (4)	60/137 (44)	18.83 (7.78-45.56)
Biliary stent	2/151 (1)	11/138 (8)	6.45 (1.40-29.65)
Pancreatic duct stone removal	1/151 (1)	30/137 (22)	42.06 (5.65-313.17)
Surgical procedures			
Surgical therapies	18/149 (12)	53/143 (37)	4.29 (2.36-7.80)
Cholecystectomy	15/148 (10)	28/143 (20)	2.16 (1.10-4.24)
Celiac plexus block	0/149	4/142 (3)	9.71 (0.52-182.09)[b]
Cyst or pseudocyst operation	3/149 (2)	5/142 (4)	1.78 (0.42-7.57)
Lateral pancreaticojejunostomy	0/149	13/142 (9)	31.17 (1.83-529.49)[b]
Partial pancreatectomy	0/149	2/142 (1)	5.32 (0.25-111.79)[b]
Total pancreatectomy or islet cell autotransplantation	0/148	29/143 (20)	76.52 (4.63-1265.67)[b]

Abbreviations: ARP, acute recurrent pancreatitis; CP, chronic pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography; OR, odds ratio.

[a] The differences in sample sizes between rows reflect available data for these parameters.

[b] The OR was computed based on the logit estimate that used a correction of 0.5 in every cell.

8 were performed for pain, 3 for recurrent episodes of AP, and 1 for both pain and recurrent episodes of AP. Pain did not resolve after cholecystectomy (0 of 9 patients); recurrent pancreatitis resolved in 2 of 4 patients. Lateral pancreaticojejunostomy, partial pancreatectomy, total pancreatectomy or islet cell autotransplantation, and celiac plexus block were exclusively performed in CP.

Discussion

This international, multicenter study is the largest characterized cohort of children with ARP and CP and, to our knowledge, it is the first observational study comparing a large number of children with ARP vs children with CP. Most children with CP described a history of ARP and tended to be older at the time of diagnosis compared with children with ARP, suggesting that ARP and CP are a disease continuum. A large proportion of children with ARP or CP had multiple risk factors, suggesting the multifactorial nature of these conditions. The clustering of *PRSS1* or *SPINK1* mutations in children with CP raises the possibility that these gene mutations are important risk factors for progression from ARP to CP in the pediatric population. The disease burden was higher in CP compared with ARP, suggesting the importance of identifying early interventions to prevent or delay progression from ARP to CP.

Among the risk factors analyzed, an underlying genetic predisposition was most commonly found in our patients, almost 50% in ARP and approaching 75% in CP. Our findings agree with previous reports showing genetic mutations as common risk factors in children with ARP or CP.[9,12,14,18,19] We may be underestimating the impact of gene mutations as risk factors for ARP or CP because we do not have analysis of the most commonly tested genes (*PRSS1*, *CFTR*, *SPINK1*, *CTRC*) for every patient in the database, as gene testing for INSPPIRE patients was at the physician's discretion. Some of the newly discovered pancreatitis susceptibility genes also were not tested, as tests for them were not commercially available (*CPA1*, *CLDN2*, *CEL*, *CEL-HYB*).[11,20-22]

To our knowledge, the natural history of pediatric pancreatitis has not been systematically investigated in children. Most of the data in adults that support progression of ARP to CP come from hereditary pancreatitis populations.[23,24] Indeed, pancreatitis follows a severe course in patients with *PRSS1* mutations (particularly R122H and N29I) with first episodes by approximately 10 years of age and progression to CP within the subsequent decade. Our findings support the hypothesis that *PRSS1* is involved in progression from ARP to CP in children as well.

The role of *SPINK1* mutations as a cause of pancreatitis is debated because these mutations can be found in 1% to 3% of the general population. We report a higher percentage of *SPINK1* mutations in the INSPPIRE cohort (13% of those with ARP; 25% of those with CP). Similarly, *SPINK1* N34S mutations have been found in approximately 25% of children with ARP or CP, a higher percentage compared with the general population.[12,19,25] In addition, people with *SPINK1* mutations are more prone to ARP or CP if mutations in other pancreatitis-relevant genes are also present (ie, *PRSS1*, *CFTR*, *CTRC*), with up to 900-fold increased risk by having both *CFTR* and *SPINK1*

mutations.[26-28] In our cohort, *CFTR* and *SPINK1* mutations were commonly associated. Taken together, *SPINK1* mutations (alone or in combination with other risk factors) may be playing a role in pediatric ARP and CP development.

We found PD in 9% to 16% of children with ARP and CP, similar to the frequency found in autopsy studies (5%-10%).[29] It was associated with decreased frequency in children with *PRSS1* mutations. Most studies reporting association of PD with ARP or CP, similar to this study, are based on symptomatic patients who had imaging studies done for the evaluation of pancreatitis. The involvement of PD in the pathogenesis of ARP or CP needs to be further studied.

We found that a large subset of children with ARP or CP had more than 1 identifiable risk factor, including patients with more than 1 risk factor in a single category (genetic factors) and patients with a combination of factors across categories. Our observations are consistent with previous studies suggesting that the pathogenesis of ARP or CP is multifactorial.

We observed that most of the children with ARP and CP were white and CP was less common in patients with Hispanic ethnicity. This is likely due to genetic mutations found in white individuals and not referral bias in our study. In a recent analysis of 2 large national databases that included more than 1.5 million hospitalized US children, CP was also found more commonly in white patients.[30] The possible reduced risk noted in our pediatric Hispanic population may be explained by the lower prevalence of *PRSS1* and *SPINK1* mutations in this group.

Most of the children in our study reported pancreatitis-related pain within the previous year; the pain was chronic in one-third of the patients. The disease burden was higher in the CP group compared with the ARP group (significantly more ED visits and hospitalizations; significantly more medical, endoscopic, and surgical therapies; and more missed school days). Pancreatitis causes a serious burden on the health care system, with AP being the top gastrointestinal cause for admission in adults.[31] With increasing incidence of AP in childhood,[32,33] we expect that the disease burden in our cohort is substantial.

We were surprised by the large number of children with AIP in our cohort. The diagnosis of AIP in the medical literature is limited to few case reports.[34] As previously reported, most children with AIP in our study had type 2. Our future goal is to develop diagnostic and therapeutic criteria for pediatric AIP. These guidelines will be aimed to better phenotype children in our database as well as to bring a unifying definition to this disease.

Our study has several limitations. The prevalence of genetic predisposing factors was underestimated because not every patient underwent genetic testing and when they did, it was not always complete. Newly identified pancreatitis-associated genes could not be identified in our population, as tests are not commercially available. Moving forward, we plan to test INSPPIRE patients for all pancreatitis-relevant genes. While we acknowledge a potential referral bias from large referral centers in our study, we note that a center that performed most islet cell transplants (University of Minnesota) contributed approximately 10% to our cohort (eTable 1 in the Supplement). The analysis of children with ARP or CP was done at the time of enrollment; therefore, assessment of risk factors could not be done over time as children progressed from ARP to CP. Nevertheless, the large number of well-phenotyped patients with ARP or CP allowed us to compare the characteristics of these children. Our study is underpowered to study the role of cholecystectomy on relieving recurrent disease. Prospective data collection is more likely to shed light on this question. Through a prospective registry of longitudinal clinical data, INSPPIRE aims to determine the natural course of pediatric ARP and CP and identify risk factors for the progression to CP.

Conclusions

Pancreatitis-associated gene mutations are the most common risk factors in children with ARP or CP, and multiple risk factors are usually coexistent. The socioeconomic burden of disease is significant given the presence of pain, health care visits, and number of diagnostic tests performed. Further work will focus on analyzing the impact of genetic and other risk factors on the natural history of pediatric pancreatitis and its sequelae and developing a standardized approach to the evaluation of children with ARP or CP.

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