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Early Onset Acute Recurrent and Chronic Pancreatitis is Associated with *PRSS1* or *CTRC* Gene Mutations

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Abstract

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Objectives—To assess whether the age of onset was associated with unique features or disease course in pediatric acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP).

Study design—Demographic and clinical information on children with ARP or CP was collected at INSPPIRE (INternational Study Group of Pediatric Pancreatitis: In Search for a CuRE) centers. The Cochran-Armitage trend test and Jonckheere-Terpstra test were used to examine for differences between pediatric age groups (<6, 6–11 and ≥12 years).

Results—Between September 2012 and March 2016, 342 children with ARP or CP were enrolled; 129 (38%) were <6 y/o at the time of first diagnosis of acute pancreatitis (AP), 111 (32%) were 6–11 y/o and 102 (30%) were ≥12 y/o. Early onset disease was associated with mutations in cationic trypsinogen (*PRSS1*) (p<0.01), chymotrypsin C (*CTRC*) (p=0.01), family history of AP (p=0.02), family history of CP (p<0.01), biliary cysts (p=0.04) or chronic renal failure (p=0.02). Later onset disease was more commonly present with hypertriglyceridemia (p=0.04), ulcerative colitis (p=0.02), autoimmune diseases (p<0.0001) or medication use (p<0.01). Children with later onset disease were also more likely to visit emergency room (p<0.05) or have diabetes (p<0.01).

Conclusions—Early onset pancreatitis is strongly associated with *PRSS1* or *CTRC* mutations and family history of pancreatitis. Children with later onset disease are more likely to have non-genetic risk factors. Future studies are needed to investigate whether the disease course, response to therapy or clinical outcomes differ relative to the timing of disease onset.

Keywords

Pediatric; Children; Young; Risk; Genetic

The etiopathogenesis, clinical features and disease course of acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) are poorly understood. ARP and CP in children have been previously defined.[1] Most children who experience an episode of acute pancreatitis (AP) have no additional episodes and do not develop ARP or CP. However, single-center studies estimate that 9–35% of children with AP ultimately suffer from ARP/CP.[2–7] The incidence of CP has been found to be ~0.5 per 100,000 persons per year in young adults.[8–9]

Although alcohol and smoking have long been recognized as major risk factors for ARP and CP in adults[10], these risk factors are uncommon in the pediatric age group. Recent studies have shown that pediatric patients with ARP and CP are likely to have underlying genetic predispositions including mutations in *cystic fibrosis transmembrane conductance regulator (CFTR), cationic trypsinogen (PRSS1), serine protease inhibitor Kazal-type 1 (SPINK1), chymotrypsin C (CTRC)* and *carboxypeptidase 1 (CPA1)*.[4,6,11–15] Obstructive factors, trauma, infection and metabolic abnormalities are other known causes of pediatric ARP and CP.[12,16–18]

Unique genetic risk factors have been identified in the pathogenesis of chronic inflammatory conditions presenting at a young age including early onset inflammatory bowel disease.[19, 20] We hypothesized that children presenting prior to age 6 with early onset pancreatitis (EOP) would have a high incidence of genetic risk factors and a more severe disease burden compared with children who develop pancreatitis at a later age.

Methods

Demographic and clinical information were collected on children who fulfilled the criteria for ARP and CP from 16 institutions at the time of enrollment. INSPPIRE study design and enrollment criteria have been previously described.[21] Three age cohorts (<6, 6–11 and ≥12 years) were created based on published recommendations for age grouping in pediatric trials.[22] The youngest cohort (those presenting prior to age 6) was defined as EOP. All patients were <19 years at the time of enrollment. Clinical and demographic data were entered into the REDCap™ (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA) database at 16 centers from September 2012 to March 2016, through standardized patient and physician questionnaires and represented baseline information of the INSPPIRE cohort. All centers obtained Institutional Review Board approval or the equivalent for their country for this study. A total of 301 patients included in this study have been previously reported.[12,18]Patients with established cystic fibrosis were not excluded from this study as long as they fulfilled enrollment criteria and had a clinically documented episode of AP prior to being diagnosed with ARP/CP.

Statistical analyses

Summary statistics use mean with standard deviation (SD) or median with interquartile range (IQR) according to the normality of distribution. Subject characteristics, risk and clinical variables were compared between age groups of disease onset (<6, 6–11 and ≥12 years) using Cochran-Armitage trend test for categorical variables, and Jonckheere-Terpstra test for ordinal/continuous variables. A p-value <0.05 was considered statistically significant.

Results

Among the 342 children with ARP or CP who were enrolled; 129 (38%) were <6 years old at the time of their first acute pancreatitis (AP) diagnosis, 111 (32%) were 6–11 years and 102 (30%) were ≥12 years. Demographics of the cohorts are shown in Table I. Sex, ethnicity and race were similar between the groups. Over 80% of subjects were white. The incidence of CP was not different between the age groups (46% age <6, 50% age 6–11, 41% age ≥12 years; p=0.54). Duration of disease at the time of enrollment was longer for those with EOP (p<0.0001).

Genetic abnormalities were the most common risk factor for ARP or CP in all age groups (Table II). A family history of AP (38%) or CP (34%) was more common among children with EOP (p=0.02 and <0.01 respectively).

At least one pancreatitis-associated genetic mutation (*PRSS1, CFTR, SPINK1, CTRC*) was found in 72/102 patients (71%) with EOP, which was significantly greater than the frequency in patients with later onset disease (58% age 6–11 yr, 54% age ≥12 yr, p=0.02). The frequency of genetic testing was similar among age groups. Screening for any genetic abnormality was performed in 102/129 (79%) among those presenting <6 yr, 90/111 (81%) in the 6–11 yr group and 72/102 (71%) in the ≥12 yr group.

PRSS1 mutations were found in 43% of patients with EOP compared with 21–25% in the later onset cohorts ($p<0.01$). The most common *PRSS1* mutation in all cohorts was p.R122H (Table III). *CTRC* mutations were also more common among those with EOP (14%) than in the later onset cohorts ($p=0.01$). Seven different *CTRC* mutations were found and the p.R254W mutation was identified in three patients, all of whom had EOP. Only 2 patients with onset of disease at age 6 years or older were found to have a *CTRC* mutation. There were no differences detected in the frequency of *SPINK1* or *CFTR* mutations among the cohorts.

Some patients carried more than one pancreatitis-associated mutation. Among patients with EOP, 14 (11%) were found to have mutations in more than one gene (12 with two genes, 1 with three genes and 1 with four genes). In those with disease onset 6–11 yr, 14 (13%) had mutations in 2 genes. Five patients (5%) had 2 mutations in the ≥12 yr group. Most of the multiple mutations observed in the later onset groups were combined mutations to *CFTR* and *SPINK1* (12 patients).

Obstructive disease was the second most common risk factor among the three cohorts. Biliary cysts were more common in children with EOP and onset 6–11 yr (both 5%) than in the later onset cohort (1%, $p=0.04$). There were no differences in the frequency of other obstructive causes among the groups.

Toxic/metabolic factors including hypertriglyceridemia ($p=0.04$), autoimmune diseases ($p<0.0001$) and medication use ($p<0.01$) were more common among those with later onset disease. Chronic renal failure was more common in the EOP cohort ($p=0.02$). Of 14 children with autoimmune pancreatitis, the date of first AP attack was only available in 6 patients; no significant difference was found among the age groups.

There were no differences in pancreatitis-related pain among the cohorts (Table IV). Patients with later onset disease had a higher number of average emergency room visits per year ($p=0.02$). There were no differences in pancreatic exocrine insufficiency among the cohorts but diabetes was more common among those with later onset disease ($p<0.01$). We also tracked treatment options including medications, procedures and surgeries and found no difference in the utilization of these treatments among the cohorts. There was also no difference in the effectiveness of these treatments based on patient/family or provider perception.

Discussion

This international, multicenter study from INSPPIRE represents a large cohort of well-defined and characterized children with ARP and CP. From this study, we have identified that EOP is predominantly associated with genetic susceptibility as illustrated by the observation that 71% of patients tested were found to possess at least one pancreatitis-associated gene mutation (*PRSS1, CFTR, SPINK1* or *CTRC*). Some of the newly discovered pancreatitis susceptibility genes (*carboxypeptidase 1 (CPA1), claudin 2 (CLDN2) carboxylesterlipase (CEL)* and *CEL-HYB* allele) were not evaluated because they are not yet commercially available.[13,23–25]

This study demonstrates that *PRSS1* or *CTRC* mutations are particularly important risk factors in children with EOP. Pathogenic *PRSS1* gene mutations have been shown to have a high penetrance at over 90% and a more severe disease phenotype has been associated with R122H and N29I mutations, which were the two most common mutations observed in our study.[26] The frequency of *PRSS1* mutations found in patients with EOP was 43%, which is significantly higher than the frequency in previously published series.[11, 12, 14, 27] We have previously shown that children with *PRSS1* mutations are more likely to present with CP than ARP at the time of enrollment to INSPPIRE.[18] Taken together, our data suggest that *PRSS1* mutations predict an aggressive disease course in children with early onset of symptoms and rapid progression to CP.

CTRC mutations have been shown to occur in 0.7% of healthy controls and 2.9–3.3% of adults with CP.[28] We have found that *CTRC* mutations were significantly more likely to occur in children with EOP (14%), suggesting that abnormalities to this trypsin-degrading pathway may be particularly important to disease pathogenesis among this cohort. Determining the true pathogenic potential of a specific variant can be challenging. However, the mutations reported here are likely disease causing given that all but one are projected to lead to amino acid substitutions or frame shift mutations.[28].

At the current time, approximately 2000 *CFTR* variants have been described and, although they have variable effects on pancreatic function, a strong correlation has been shown between *CFTR* mutations and ARP/CP.[29] Although we identified *CFTR* mutations in a large subset of patients, we did not find that EOP was associated with a higher incidence of *CFTR* mutation.

The role of *SPINK1* mutations as a cause of ARP or CP continues to be debated because such mutations are found relatively frequently among the general population (1–3%).[30] In adults, *SPINK1* mutations are considered significant if they coexist with obstructive factors or mutations in other pancreatitis susceptibility genes (i.e. *CFTR, PRSS1* or *CTRC*).[27,31,32] Among children with later onset disease, we observed 12 cases of coexistent *CFTR* and *SPINK1* mutations. In the EOP cohort, coexistent *CFTR* and *SPINK1* mutations were observed in four children while one of these patients also had a mutation in *CTRC* and another had additional mutations to *CTRC* and *PRSS1*. These data suggest that *SPINK1* may be an important modifier gene for pancreatic disease presenting later in childhood and that there may be compounding effects when other pancreatitis susceptibility genes are involved. Additional studies are necessary to evaluate the synergistic effects of mutations to multiple susceptibility genes in the development of ARP and CP.

Obstructive causes have long been recognized as an etiology in children with ARP and CP[2,4–6,17]. A large subset of patients were identified as having an obstructive etiology, however, the only obstructive factor found to be related to age of onset was biliary cyst (or choledochal cyst) (p=0.040). This finding is not surprising because most biliary cysts present clinically in infancy and early childhood.

We expected that EOP would be associated with a more aggressive clinical course. However, disease burden was similar among the groups except for the number of annual emergency

room visits which was higher among those with later onset disease. Our data offer no clear explanation for this, but it has been shown previously that young children may be less apt to report or verbalize pancreatitis pain compared with older children and it is possible that the initial episodes of pancreatitis in these patients were not clinically diagnosed.[33] More detailed quality of life studies for EOP patients are still needed.

There is still much to be learned about EOP as genetic risk factors may vary significantly based on geographic distribution and the prevalence of specific mutations in a target population. It has not yet been shown how the frequency of pancreatitis related gene mutations may vary by race and ethnicity. The high percentage of white patients observed in this study may be attributable to an increased incidence of predisposing mutations in this population or could be an artifact of referral bias. A recently published, smaller, single-center cohort from Poland did not demonstrate an increased incidence for specific mutations involving *PRSS1, CFTR* and *SPINK1* genes in 51 CP patients with disease onset under age 5, compared with children ≥5 y/o.[34] One third of the early onset patients were classified as idiopathic, however, *CTRC* gene analysis was not reported. Our study highlights that *CTRC* may be a particularly important genetic risk factor in EOP.

In conclusion, EOP is highly associated with pancreatitis-related gene mutations, particularly *PRSS1* or *CTRC*. In the future, we plan to investigate whether the disease course, response to therapy and/or outcomes are dependent on the age of first pancreatitis attack in children. A thorough analysis of genetic and environmental factors may better identify the natural history, disease burden and sequelae of pediatric pancreatitis.

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Table 1

Demographic Characteristics Stratified by Age of Recurrent/Chronic Pancreatitis Onset. Gender, ethnicity and race reported as number patients (%). Disease duration reported as median years (25^{th}–75^{th} percentile). Bolded p-value represents statistical significance ($p<0.05$).

Characteristic	Onset <6 yr	Onset 6–11 yr	Onset ≥12 yr	p-value
Gender	n=129	n=111	n=102	
Female	71 (55)	64 (58)	61 (60)	0.46
Ethnicity	n=116	n=105	n=93	
Hispanic	22 (19)	29 (28)	25 (27)	0.16
Race	n=113	n=102	n=86	
White	91 (81)	85 (83)	70 (81)	0.12
Multi-racial	9 (8)	7 (7)	6 (7)	
Asian	6 (5)	2(2)	6 (7)	
Black/African American	7 (6)	5 (5)	0 (0)	
Other	0 (0)	3 (3)	4 (5)	
Disease duration	3.32 (1.37–6.55)	2.09 (0.79–4.67)	1.38 (0.58–2.59)	**<0.0001**

Table 2

Genetic, Obstructive and Toxic/Metabolic Risk Factors for Recurrent/Chronic Pancreatitis Stratified by Patient Age. Data reported as number of patients/number screened (%). Bolded p-value represents statistical significance ($p<0.05$).

Genetic Risk Factor	Onset <6 yr	Onset 6–11 yr	Onset ≥12 yr	p-value
Genetic mutation (any)	72/102 (71)	52/90 (58)	39/72 (54)	**0.02**
PRSS1	42/98 (43)	20/79 (25)	13/63 (21)	**<0.01**
CFTR	27/89 (30)	23/83 (27)	24/64 (38)	0.39
SPINK1	12/86 (14)	22/74 (30)	6/58 (10)	0.84
CTRC	8/56 (14)	1/51 (2)	1/43 (2)	**0.01**
Family History -Acute Pancreatitis	39/104 (38)	27/95 (28)	18/82 (22)	**0.02**
Family History -Chronic Pancreatitis	36/105 (34)	20/92 (22)	14/85 (16)	**<0.01**
Obstructive Risk Factor				
Any	45/128 (38)	36/110 (33)	27/102 (26)	0.16
Pancreas Divisum	18/125 (14)	12/107 (11)	8/99 (8)	0.14
Sphincter of Oddi dysfunction	4/122 (3)	2/104 (2)	3/98 (3)	0.99
Gallstones	7/125 (6)	3/106 (3)	7/101 (7)	0.70
Pancreaticobiliary malunion	7/124 (6)	4/107 (4)	1/100 (1)	0.06
Biliary cyst	5/127 (5)	5/101 (5)	1/102 (1)	**0.04**
Traumatic pancreatic stricture	1/126 (1)	1/105 (1)	0/101 (0)	0.46
Duodenal diverticulum	1/126 (1)	0/107 (0)	0/101 (0)	0.26
Annular pancreas	1/127 (1)	1/107 (1)	1/107 (1)	0.87
Other pancreatic duct obstruction	3/127 (2)	2/107 (2)	0/102 (0)	0.15
Toxic/Metabolic Risk Factor				
Alcoholic	1/129 (1)	1/110 (1)	3/101 (3)	0.18
Active smoker	1/128 (1)	0/111 (0)	1/101 (1)	0.89
Passive smoking exposure	9/126 (7)	8/107 (7)	9/95 (9)	0.54
Hypertriglyceridemia	2/106 (2)	7/96 (7)	7/82 (9)	**0.04**
Hepatitis	1/123 (1)	0/101 (0)	2/93 (2)	0.41
Chronic renal failure	4/117 (3)	0/101 (0)	0/86 (0)	**0.02**
IBD – Crohn's disease	0/123 (0)	0/101 (0)	1/94 (1)	0.18
IBD – Ulcerative colitis	0/123 (0)	0/101 (0)	3/94 (3)	0.02
IBD – Indeterminate colitis	0/123 (0)	0/101 (0)	2/94 (2)	0.06
Autoimmune pancreatitis	1/90 (1)	2/89 (2)	3/76 (4)	0.23
Other autoimmune diseases	4/123 (3)	5/102 (5)	18/96 (19)	**<0.0001**
Medication use	5/110 (5)	9/99 (9)	15/88 (17)	**<0.01**
Azathioprine/6-mercaptopurine	0/123 (0)	0/102 (0)	3/94 (3)	**0.02**
Mesalamine	0/123 (0)	0/102 (0)	3/94 (3)	**0.02**

Table 3

PRSS1, CTRC, SPINK1 and CFTR Mutations Stratified by Age of Recurrent/Chronic Pancreatitis Onset. Reported as number of patients with each mutation or combination of mutations.

PRSS1 Mutations	Onset <6 yr n screened=98	Onset 6–11yr n screened=79	Onset ≥12yr n screened=63
p.R122H	24	11	5
p.N29I	8	3	3
p.K23R	2	0	0
p.R122C	1	1	0
p.A16V	0	0	1
p.A16V, p.R122C	0	0	1
c.592-8C>T, c.592-11C>T	1	0	0
p.D21A	1	0	0
p.C135S	1	0	0
p.R116C	1	0	0
c.592-24C>T	0	1	0
c.293A>G	0	0	1
Unknown/Incomplete	3	4	2
CTRC Mutations	**Onset <6 yrn screened=56**	**Onset 6–11yr n screened=51**	**Onset ≥12yrn screened=43**
p.R254W	3	0	0
p.R254W, p.I64LfsX69	1	0	0
p.V235I	1	0	0
p.G103VfsX31	1	0	0
c.640-12G>A	1	0	0
p.Q178R	0	1	0
p.K247_R254del	0	0	1
Unknown/Incomplete	1	0	0
SPINK1 Mutations	**Onset <6 yrn screened=86**	**Onset 6–11yr n screened=74**	**Onset ≥12yrn screened=58**
p.N34S	3	14	5
p.N34S, p.K66N, c.195-66_65insTTT	1	0	0
c.147A>G	1	0	0
c.194+2T>C	1	0	0
p.R67H	1	1	0
c.194+184T>A	1	0	0
p.I42M	1	0	0
p.N37S	0	2	0
p.L9R	0	1	0
c.53C>T	0	1	0
c.194+184T>A	0	0	1
Unknown/Incomplete	3	3	0
CFTR Mutations a1/a2	**Onset <6 yrn screened=89**	**Onset 6–11yr n screened=83**	**Onset ≥12yrn screened=64**

p.F508del		4	1	4
p.F508del	**p.G85E**	1	1	
p.F508del	**p.I807M**	1		
p.F508del	**p.R237P**	1		
p.F508del	**p.R117H**	1		1
p.F508del	**p.L997F**	1	1	1
p.F508del	**p.R347P**		1	
p.F508del	**c.3717G>A**		1	
p.F508del	**p.R1162I**		1	
p.F508del	**p.V456A**			1
p.F508del	**c.2657+5G>A**			1
p.L333F	**p.S1235R**	1		
p.S1235R		3	2	1
p.S1235R	**p.W1282X**		1	
p.W1282X			1	
p.R297Q	**c.1210−12[5]**	1		
c.1210−12[5]			1	1
p.L1139V		1		
p.L1139V	**p.L206W**	1		
p.L967S		1		
p.M470V	**p.M470V**	1		
p.M470V				1
p.G1069R		1		
c.861delT		1		
p.V11L		1		
p.L227R			1	
c.164+28A>G			1	
p.H139L	**c.1550delG**		1	
p.D1152H			2	
p.R117H			1	
p.R140H			1	
c.535C>A			1	
p.R21C	**p.R117C**		1	
p.R668C	**p.G576A**		1	
p.L88IfsX22	**c.3123G>C**			1
p.R1162L				1
p.A561T				1
p.S895N				1
p.S912X				1
p.G567A				1

Unknown	5	3	5

Table 4

Disease Burden of Recurrent/Chronic Pancreatitis Stratified by Age of Onset. Data reported as number of patients/number screened (%) or median (25,75 percentile). Bolded p-value represents statistical significance ($p<0.05$). Cochran-Armitage trend test used to calculate p-value for exocrine insufficiency and diabetes. Jonckheere-Terpstra test used to calculate all other p-values.

Disease Burden	Onset <6 yr	Onset 6–11 yr	Onset ≥12yr	p-value
Exocrine Insufficiency	21/112 (19)	21/98 (21)	10/82 (12)	0.28
Diabetes	2/121 (2)	5/104 (5)	11/92 (12)	**<0.01**
Pattern of abdominal pain				
No abdominal pain	18/108 (16)	8/106 (8)	11/92 (12)	0.09
Usually pain free; episodes of mild-moderate pain	15/108 (14)	12/106 (11)	14/92 (15)	
Constant mild-moderate pain	1/108 (1)	10/106 (9)	5/92 (5)	
Usually pain free; episodes of severe pain	45/108 (42)	44/106 (42)	23/92 (25)	
Constant mild-moderate pain+ episodes of severe pain	25/108 (23)	27/106 (25)	30/92 (33)	
Constant severe pain	4/108 (4)	5/106 (5)	9/92 (10)	
Average number of ER visits per year – lifelong	1.1 (0,2)	1.5 (0.8,2.5)	1.4 (0.6,2.6)	**0.02**
Number of ER visits - past year	1 (0,3)	2 (1,3)	2 (1,3)	0.05
Average number of hospitalizations per year – lifelong	0.9 (0,2)	1.3 (0.6,2.4)	1.4 (0.6,2.1)	0.14
Number of hospitalizations - past year	1 (0,2)	1 (1,2)	2 (1,2)	0.09