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Pediatric chronic pancreatitis without prior acute or acute recurrent pancreatitis: A report from the INSPPIRE consortium

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Declaration of competing interest

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Dear Editor,

Chronic pancreatitis (CP) is an inflammatory disease resulting in irreversible changes in the pancreas including acinar cell loss, fibrosis, ductal changes and calcifications [1]. Patients with CP suffer from abdominal pain and complications of exocrine pancreatic insufficiency (EPI) and diabetes mellitus [2]. Due to significant implications on child health and well-being, it is essential that childhood CP is recognized early, and sequalae are treated promptly [3].

Our INSPPIRE (**IN**ternational **S**tudy group of **P**ediatric **P**ancreatitis: **I**n search for a cu**RE**) study includes children with CP but did not report previous episodes of acute pancreatitis (AP) prior their enrollment. Here, we report the risk factors and clinical phenotypes of children enrolled in INSPPIRE who present “silent CP” [1,4].

Our study design included data collection utilizing patient/parent and physician questionnaires from children who fulfilled the criteria for CP at nineteen INSPPIRE centers and were ≤19 years of age at the time of enrollment [4,5]. INSPPIRE criteria were used for the diagnosis of AP, ARP and CP as previously reported [1,4]. Patients were grouped in the “traditional CP” cohort “ if they reported any history of AP prior to their CP diagnosis, and in “silent CP” cohort, if they did not.

Summary statistics were presented as mean with standard deviation (SD), median with interquartile range (IQR), or frequency count with percentage. Subject characteristics, risks and clinical variables were compared between children with CP and no prior AP or ARP (silent CP, n = 20) and children with CP and AP or ARP episodes prior (traditional CP, n = 185). A p-value <0.05 was considered statistically significant.

Among 205 children with CP, 185 had traditional CP (90%), 20 silent CP (10%). These two groups were not different in age, sex, race, ethnicity or age at diagnosis of CP (Table 1).

Subjects in both groups had genetic risk factors (*PRSS1, SPINK 1, CFTR, and CTRC*), but the differences between the groups were not statistically significant (Table 2). Likewise, the family history of AP or CP, and obstructive and environmental risk factors were also not different. Children with silent CP were more likely to have autoimmune pancreatitis (AIP) compared to traditional CP (20% vs 3%, p = 0.008) (Table 2). Other autoimmune diseases and inflammatory bowel disease (IBD) were not different between the groups.

Table 3 summarizes all imaging findings for ERCP, Computed tomography (CT), Magnetic resonance imaging (MRI/MRCP) and Endoscopic Ultrasound (EUS) during the course of their disease. Results were consistent with imaging findings typical of CP including duct irregularities, pancreatic atrophy, duct dilatation, and calcifications. Findings consistent with acute inflammatory changes in the pancreas were found in both silent and traditional CP if an imaging study was done at initial presentation or at a subsequent evaluation. Ductal

stones were significantly more common in silent CP compared to traditional CP (10/18 [56%] vs 49/161 [30%]; p = 0.032); no other differences were observed.

Medical therapy including pancreatic enzymes, pain medications, antioxidants, steroids, and diabetes medications was utilized in 13 of 20 (65%) of the silent CP patients and 126 of 185 (71%) traditional CP patients (Table 4). Corticosteroids were more commonly used in the silent CP group (3/18 [17%]) compared to the traditional CP (4/166 [2%], p = 0.022) probably reflecting the increased proportion of AIP in the silent CP group. Overall, no other significant differences were observed in the frequency of endoscopic or surgical therapies between the groups.

Our study demonstrates that CP may occur without prior AP or ARP in children. In the INSPPIRE cohort, one in ten children with CP reported no previous AP episodes. Children with this “silent” presentation are more likely to have AIP, advanced morphological changes, including pancreatic intraductal stones and tendency for chronic pain compared to the traditional presentation. Pediatricians need to be aware of this insidious presentation of CP and consider imaging patients with persistent pain or an episode suggestive of AP. Early recognition of “silent CP” is essential for the timely treatment of underlying causes and associated sequelae.

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Table 1

Demographics and clinical characteristics of patients' groups.

Variables	Silent CP (n = 20)	Traditional CP (n = 185)	p-value
Sex (Female)	13 (65%)	105/184 (57%)	0.495
Ethnicity (Hispanic)	3/18 (17%)	31/168 (18%)	1.0
Race	(n = 17)	(n = 162)	0.316
White	15(88%)	131 (81%)	
Multi-racial	0 (0%)	11 (7%)	
African American	0 (0%)	7(4%)	
Asian	2 (12%)	7 (4%)	
Other	0 (0%)	6 (4%)	
Age at first diagnosis		(n = 175)	0.162
Mean (SD)	10.0 (3.2)	8.6 (4.6)	
Range	5.3–16.3	1.0–17.4	

Table 2

Risk factors of CP.

Variables	Silent CP (n = 20)	Traditional CP (n = 185)	p-value
Family history			
Acute pancreatitis	4/16 (25%)	45/145 (31%)	0.778
Chronic pancreatitis	5/18 (28%)	49/151 (32%)	1.0
Genetic Risk Factors:			
PRSS1	9/15 (60%)	66/153 (43%)	0.210
SPINK1	2/14 (14%)	34/136 (25%)	0.520
CFTR	3/14 (21%)	48/147 (33%)	0.551
CTRC	0/7 (0%)	6/95 (6%)	1.0
Obstructive factors	6 (30%)	54/184 (29%)	0.952
Pancreas divisum	2/19 (11%)	23/181 (13%)	1.0
Risk factors			
Alcoholic	1 (5%)	4/184 (2%)	0.406
Active smoker	1 (5%)	2/184 (1%)	0.267
Passive smoking exposure	3 (15%)	12/179 (7%)	0.180
Hyperlipidemia	0/18 (0%)	5/159 (3%)	1.0
Medications	1/18 (6%)	10/173 (6%)	1.0
Autoimmune pancreatitis	4 (20%)	4/144 (3%)	0.008
Other autoimmune diseases	1/19 (5%)	12/177 (7%)	1.0
Ulcerative colitis	0/19 (0%)	2/177 (1%)	1.0
Indeterminate colitis/IBD-U	0/19 (0%)	1/176 (1%)	1.0

Cationic trypsinogen (*PRSS1), Serine Protease Inhibitor Kazal-Type1 (SPINK1), Cystic fibrosis transmembrane regulator (CFTR) and Chymotrypsin receptor C (CTRC).*

Table 3

Imaging findings.

Variables	Silent CP (n = 20)	Traditional CP (n = 185)	p-value
Imaging studies performed ERCP	14 (70%)	129 (70%)	1.0
Number ERCP (range)	(1–7)	(1–9)	
1	9	67	
2	2	31	
3	1	13	
≥4	2	18	
CT scan	11 (55%)	102 (55%)	0.991
MRI (not performed with MRCP)	3 (15%)	59 (32%)	0.118
MRCP	14 (70%)	155 (84%)	0.130
EUS	4 (20%)	32 (17%)	0.759
Findings (CT/MRI)			
Focal Acute Pancreatitis	3/15 (20%)	24/153 (16%)	0.712
Inflammatory changes in Pancreas	6/16 (38%)	57/153 (37%)	0.985
Pancreatic Gland Enlargement	2/16 (12%)	25/154 (16%)	1.0
Pancreatic Atrophy Present	10/16 (62%)	67/155 (43%)	0.140
Calcifications in Pancreas present	4/16 (25%)	24/154 (16%)	0.306
Duct Irregularities	11/15 (73%)	89/153 (58%)	0.254
Pancreatic duct dilatation present	11/16 (69%)	93/153 (61%)	0.533
Lesions present in the pancreas	2/16 (12%)	5/158 (3%)	0.127
Gallstones/Sludge	1/15 (7%)	11/156 (7%)	1.0
Intrahepatic biliary dilatation	3/16 (19%)	13/154 (8%)	0.178
Changes suggestive of cirrhosis and/or portal hypertension	1/15 (7%)	9/154 (6%)	1.0
Findings (CT/MRI/MRCP/ERCP)			
Pancreatic duct obstruction (stricture)	5/19 (26%)	67/175 (38%)	0.305
CBD stricture (Intrapancreatic portion)	3 (15%)	9/177 (5%)	0.109
Dilated CBD	3/19 (16%)	40/178 (22%)	0.770
CBD Stone	2 (10%)	10/178 (6%)	0.347

Variables	Silent CP (n = 20)	Traditional CP (n = 185)	p-value
Findings (CT/MRI/EUS)			
Peripancreatic inflammation/fat stranding	3/16 (19%)	58/154 (38%)	0.133
Findings (CT/MRI/MRCP/ERCP/EUS)			
Cysts/Pseudocysts	4 (20%)	41/178 (23%)	1.0
Findings (MRCP/ERCP)			
Main Pancreatic Duct - Abnormal	15/18 (83%)	135/168 (80%)	1.0
Abnormal Side Branches	8/18 (44%)	77/157 (49%)	0.712
Intraductal filling defects of Calculi	10/18 (56%)	49/161 (30%)	0.032
Pancreas Divisum	3/18 (17%)	24/163 (15%)	0.736

Magnetic resonance cholangiopancreatography (MRCP), Endoscopic retrograde cholangiopancreatography (ERCP), Computed tomography (CT), Endoscopic Ultrasound (EUS).

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Table 4

Treatment modalities.

Variables	Silent CP (n = 20)	Traditional CP (n = 185)	p-value
Medical therapies (from provider response)	13 (65%)	126/178 (71%)	0.592
Medications (from patient response)			
Pain medications	5/17 (29%)	81/166 (49%)	0.127
Pancreatic enzymes	7/18 (39%)	95/166 (57%)	0.137
Vitamins/anti-oxidants	7/18 (39%)	81/166 (49%)	0.424
Steroids	3/18 (17%)	4/166 (2%)	0.022
Diabetic medications	0/18 (0%)	18/167 (11%)	0.224
Medication helpful in controlling/treating pancreatitis (from patient response of those using medication)			
Pain medications helpful	3/5 (60%)	47/58 (81%)	0.273
Pancreatic enzymes helpful	2/2 (100%)	43/54 (80%)	–
Vitamins/anti-oxidants helpful	1/5 (20%)	12/40 (30%)	1.0
Steroids helpful	–	3/3 (100%)	–
Diabetic medications helpful	–	6/12 (50%)	–
Procedures			
Any ERCP	14 (70%)	125/179 (70%)	0.988
Biliary sphincterotomy	4 (20%)	45/172 (26%)	0.550
Pancreatic sphincterotomy	9 (45%)	86/170 (51%)	0.636
Pancreatic duct stent	9 (45%)	75/174 (43%)	0.871
Biliary stent	1 (5%)	14/174 (8%)	1.0
Pancreatic duct stone removal	8 (40%)	40/173 (23%)	0.107
Surgeries			
Surgical therapies	4 (20%)	74/180 (41%)	0.066
Cholecystectomy	3 (15%)	33/180 (18%)	1.0
Celiac nerve block	0 (0%)	6/180 (3%)	1.0
Cyst/pseudo-cyst operation	1 (5%)	9/180 (5%)	1.0
Lateral pancreatojejunostomy	0 (0%)	17/180 (9%)	0.228
Partial pancreatectomy	0 (0%)	4/180 (2%)	1.0

Variables	Silent CP (n = 20)	Traditional CP (n = 185)	p-value
Total pancreatectomy/islet auto transplant	3 (15%)	39/179 (22%)	0.577