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Clinical characterization of the silent chronic pancreatitis patient: a single-center retrospective cohort study

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Abstract

Background Silent chronic pancreatitis (SCP) is a poorly understood subtype of chronic pancreatitis (CP) in which individuals describe little to no abdominal pain. The risk factors for SCP are unclear, and it is unknown whether there are differences in the clinical outcomes of SCP and painful CP. We set out to investigate the clinical features of SCP and the risk factors associated with this condition.

Methods This was a retrospective cohort study using data from the Penn State Milton S. Hershey Medical Center from 2019-2022. Two patient groups, the SCP cohort (23 patients) and the painful CP cohort (94 patients), were identified from consecutive clinics. Descriptive statistics and bivariate and logistic regression analyses (including variables with a P-value <0.1 on bivariate analysis) were performed to characterize the study cohort and to evaluate for independent associations with SCP.

Results SCP was independently associated with older age (odds ratio [OR] 1.06, 95% confidence interval [CI] 1.01-1.11; P=0.03) and male sex (OR 5.38, 95%CI 1.38-20.96; P=0.02), and inversely associated with current opioid use (OR 0.18, 95%CI 0.03-0.96; P=0.04). There was no association between SCP and current pain medication or diabetes mellitus.

Conclusions Our study adds to the growing body of literature describing SCP as a condition associated with older age and male sex, and inversely associated with opioid use. We found no greater association of diabetes with SCP. Future larger longitudinal studies are needed to gain a better understanding of SCP.

Keywords Silent chronic pancreatitis, painless chronic pancreatitis, risk factors, clinical characteristics

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Introduction

Chronic pancreatitis (CP) is a progressive inflammatory syndrome that results from repetitive irreversible pancreatic injury, leading to extensive fibrotic tissue replacement in the pancreas [1,2]. The incidence of CP in the USA has increased over time, with a reported prevalence ranging from 42-73 cases per 100,000 adults [3,4]. Risk factors associated with CP include environmental factors, such as alcohol and smoking, and genetic factors, such as the serine protease inhibitor Kazal type 1 (*SPINK1)* gene and the *CFTR* gene that leads to cystic fibrosis [5,6]. CP is more frequently seen in black patients than in Caucasians, and about 2/3 of the patients are male [1,7].

Abdominal pain is a principal symptom of CP, reported to occur in about 85% of patients [8]. The pathophysiology of pain in CP is poorly understood. Multiple theories have been proposed for CP-associated pain. These include pancreatic nociceptive afferent injury leading to neuropathic pain, and ductal obstruction from recurrent inflammation, which results in ductal distension and pain [5,9]. However, about 12% of patients with CP are reported to have painless or silent chronic pancreatitis (SCP) [10,11]. These patients do not have pain and/or a prior diagnosis of acute pancreatitis. They are incidentally

found to have radiologic features of CP, such as pancreatic calcifications and or ductal changes on abdominal imaging studies undertaken for other reasons [10]. SCP may also be diagnosed in patients who undergo abdominal imaging for evaluation of symptoms and signs of pancreatic insufficiency [10].

The risk factors associated with SCP are not clearly defined. Some studies have reported smoking, alcohol, older age and genetic/hereditary CP as risk factors [10,11]. A study by Vujasinovic *et al* showed that SCP is more common in patients older than 55 years, and found no difference in the rate of development of diabetes mellitus and exocrine pancreatic insufficiency between SCP and painful CP [12]. Other studies, however, reported an a greater association of SCP with exocrine pancreatic insufficiency and diabetes mellitus [10,13].

It remains unclear whether there are unique risk factors that predispose to SCP, and whether there are significant differences between the clinical outcomes of SCP and painful CP. Since SCP is asymptomatic, patients may present later in their clinical course, with multiple advanced complications that may not be amenable to therapy [10]. An in-depth understanding of the risk factors of SCP could unearth key findings that may be crucial to the management of SCP. Additionally, targeted therapies for CP might be enhanced if we had a better understanding of the nociceptive pathways of CP [14]. We undertook this study to evaluate the clinical characteristics of SCP and to identify potential risk factors associated with this condition.

Patients and methods

Study design and study participant identification

This was a retrospective cohort study using data from a single tertiary care center between 2019 and 2022. All components of this study were approved by the Institutional Review Board of Penn State University (STUDY00017310). Potential participants were initially identified using ICD-10 diagnosis codes: K86.1 ("other CP") and K86.81 ("exocrine pancreatic insufficiency"). Two independent expert reviewers then assessed each patient chart to abstract relevant clinical data. We defined CP according to the American College of Gastroenterology (ACG) 2020 clinical guidelines on CP [15]. In brief, these guidelines recommended defining CP using the presence of appropriate clinical symptoms, imaging findings, and/or endoscopic and/or histologic findings [15]. Imaging findings using computed tomography and/or magnetic resonance imaging were based on the Cambridge Classification of chronic pancreatitis [16]. Endoscopic ultrasound findings based upon the Rosemont criteria were used if imaging findings were inconclusive [17]. Pancreatic exocrine deficiency was diagnosed with stool elastase as the first screening test, followed by total stool fat content.

Inclusion and exclusion criteria

In order to be included in this study, individuals had to be at least 18 years of age, and to have met the ACG 2020 clinical guideline diagnostic criteria for CP (noted above). Patients were excluded if their pain was attributed to a cause other than CP, or if they had undergone pancreaticobiliary surgery prior to the first clinic visit. Individuals were categorized as having SCP based on 2 provider assessments, during the index clinic visit and 1 other subsequent clinic visit, separated by at least 3 months. Each study participant was cared for by an expert pancreatologist. Participants were asked at each visit about the presence of abdominal pain (currently and/or at any time since their last clinic visit), as well as the location and characteristics of the abdominal pain. Individuals who reported abdominal pain that was determined to be consistent with chronic pancreatitis during at least 1 clinic visit were characterized as having painful CP. It should be noted that we did not have reliable information about abdominal pain severity or frequency, so we did not include this information in our analyses. Patient demographics, the presence of a pancreatic duct stent, diabetes, alcohol, tobacco and illicit substance use, and pain medication use were also abstracted. A total of 286 patients were initially identified, of whom 117 met the inclusion criteria (Fig. 1).

Statistical analysis

Descriptive statistics were computed, and bivariate analyses were performed using either Fisher's exact test or the Wilcoxon rank sum test. A multivariable logistic regression model was fit, including variables with a P-value <0.1 on bivariate analysis, to characterize the study cohort and evaluate associations with SCP while controlling for potential confounders. Age, female sex, CP etiology (alcohol vs. gallstone), diabetes, and prescription opioid use were controlled for in the multivariate logistic regression model, as was any current analgesic medication use, including acetaminophen, non-steroidal anti-inflammatory drugs, opioids, antidepressants/anxiolytics (selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants), and neuromodulators (gabapentin, dopamine norepinephrine reuptake inhibitors). Prior alcohol use was excluded, as it was deemed duplicative considering that we were already including alcohol-related chronic pancreatitis. All analyses were performed using R 4.2.0 (R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2022) [18].

Results

A total of 117 patients with CP were included in this study. Table 1 summarizes the baseline characteristics of the study participants. The mean age was 57.2 years and males formed 61.5% of the population. There were 23 (19.7%) patients with SCP, compared to 94 patients with painful CP. SCP patients were more likely to be male (82.6%) compared to painful CP (53.4%) (P=0.03). It was noteworthy that 65.2% of SCP patients had diabetes mellitus, compared to only 38.3% with painful CP (P=0.03). SCP patients were less likely to use opioids compared

Table 1 Clinical characteristics of patients with silent versus painful chronic pancreatitis

Variable	Total (n=117)	Silent (n=23)	Painful (n=94)	P-value
Age at index visit (mean±SEM years)	57.2±1.4	67.3±2.9	54.7±1.4	<0.001
Disease duration (mean±SEM years)	3.4±0.2	2.9±0.4	3.5±0.3	0.47
Male sex (%)	72 (61.5%)	19 (82.6%)	53 (53.4%)	0.03
Pancreatic duct stent in place (%)	7 (6.0%)	0 (0%)	7 (7.4%)	0.46
Diabetes (%)	51 (43.6%)	15 (65.2%)	36 (38.3%)	0.03
Current tobacco use (%)	39 (33.3%)	6 (26.1%)	33 (35.1%)	0.47
Current alcohol use (%)	13 (11.1%)	1 (4.35%)	12 (12.8%)	0.46
Current pancreatic enzyme use (%)	40 (34.2%)	6 (26.1%)	34 (36.2%)	0.47
Current APAP use (%)	38 (32.5%)	6 (26.1%)	32 (34.0%)	0.62
Current NSAID use (%)	21 (17.9%)	7 (30.4%)	14 (14.9%)	0.13
Current antidepressant or anxiolytic use (%)	44 (37.6%)	7 (30.4%)	37 (39.4%)	0.48
Current neuropathic pain medication use (%)	20 (17.1%)	3 (13.0%)	17 (18.1%)	0.76
Current opioid use (%)	44 (37.6%)	2 (8.7%)	42 (44.7%)	0.001
Any current pain med use (%)	92 (78.6%)	13 (56.5%)	79 (84.0%)	0.009

SEM, standard error of the mean; APAP, acetaminophen; NSAID, non-steroidal anti-inflammatory drug

to the painful CP cohort (8.7% vs. 44.7%, P=0.001). Additionally, any current pain medication use was less frequent in the SCP cohort compared to the painful CP group (56.5% vs. 84%, P=0.009) solely because of the difference in opioid use between thee cohorts. There was no significant difference between these cohorts with regard to the use of pancreatic enzyme supplements, tobacco, alcohol, or use of APAP, NSAID, antidepressant/anxiolytic or neuropathic medications. Pancreatic duct stents had been placed in 7.4% of the painful CP cohort participants, but in none of the SCP cohort (this difference was not statistically significant). There was also no difference between the study cohorts in the mean disease duration.

Table 2 summarizes the multivariable analysis, which evaluated for associations between the presence of SCP and any of the clinical characteristics found to be significantly associated during the bivariate analyses described above. Older age (odds ratio [OR] 1.06, 95% confidence interval [CI] 1.01-1.11; P=0.03) and male sex (OR 5.38, 95%CI 1.38-20.96; P=0.02) were each found to be independently positively associated with SCP. Conversely, current opioid use (OR 0.18, 95%CI 0.03-0.96; P=0.04) was found to be independently inversely associated with SCP. Notably, neither current analgesic medication use (OR 0.86, 95%CI 0.24-23.07; P=0.82) nor a diagnosis of diabetes mellitus (OR 2.43, 95%CI 0.77-7.61; P=0.13) was found to be significantly associated with SCP.

Table 2 Multivariate analysis for association between clinical characteristics of silent versus painful chronic pancreatitis

Variable	Odds ratio	95% confidence interval		P-value
Age	1.06	1.01	1.11	0.03
Male sex	5.38	1.38	20.96	0.02
Diabetes	2.43	0.77	7.61	0.13
Current opioid use	0.18	0.03	0.96	0.04
Any current pain medication use	0.86	0.24	23.07	0.82

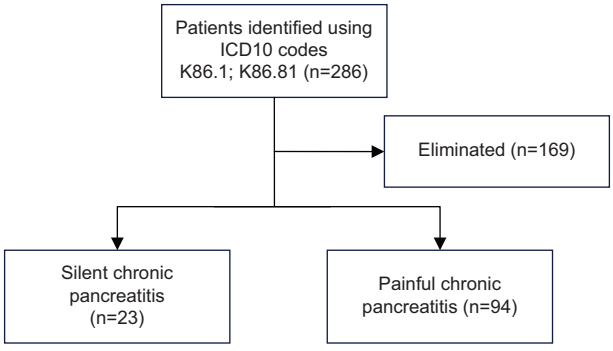

Figure 1 Study cohort identification

Discussion

This report describes one of the few studies to have investigated the risk factors and clinical features of SCP, an important clinical condition that is generally understudied and poorly understood. We found that SCP is relatively common, as approximately 1/5 of the study cohort was determined to have this condition. SCP is independently associated with male sex and older age, and inversely independently associated with current opioid use. Notably, while there was an association on bivariate analysis, we did not find diabetes mellitus to be significantly associated with SCP on multivariate analysis.

Several findings of this study are similar to those of previous investigations. For example, the mean age of our SCP cohort

was relatively advanced (67.3 years). Amodio *et al* reported 60.8 years as the mean age of SCP diagnosis in their study [13], while a separate study reported a mean age at diagnosis of 61.2 years [12]. One potential explanation for this observation is that older adults have more comorbidities, and are therefore likely to undergo more, or more frequent tests that may incidentally lead to a diagnosis of SCP. Additionally, the natural history of CP may lead to complications, such as endocrine and exocrine insufficiency or pancreatic cancer, which become apparent with increased age, requiring evaluations that may reveal underlying SCP. Our study also demonstrated an independent association between male sex and SCP. This finding was also reported in a study by Dite *et al*, who reported that 70.4% of their SCP population were male [11]. While the explanation for sexual dimorphism in this context is not entirely clear, it is important to note that the prevalence of CP is generally reported to be higher in men compared to women, in part because of greater alcohol use [1,7,19].

In this study, the majority of individuals in the SCP cohort were diagnosed with diabetes (65.2%), and this was significantly higher than the rate observed in the painful CP cohort. However, this association did not reach significance in the multivariable analysis. It should be noted that previous studies have yielded mixed findings in regard to the relationship between SCP and diabetes. A 2023 study reported diabetes rates of 28.4% in SCP and 31.6% in painful CP; however, the difference was not statistically significant [12]. Bhullar *et al* found that approximately 50% of SCP patients had diabetes [10], while Amodio *et al* reported that 72% of their SCP patients were diagnosed with this disorder [13]. Given the frequency with which diabetes mellitus is diagnosed in the setting of SCP, and the fact that it is a recognized complication of CP in general, regular monitoring for this disorder (and its complications) remains an important consideration in this setting.

There were also some relatively novel findings in this study. We found that the SCP cohort was less likely to use opioids or any analgesic when compared to the pain-perceiving cohort. Additionally, SCP was inversely independently associated with current opioid use on multivariable analysis. These findings are important because they demonstrate that the lack of pain in the SCP cohort described in this study was not attributable to a greater use of pain medications.

While this study and other investigations have provided clues to the factors that lead to SCP, the pathophysiology of this condition is still poorly understood. Based upon the findings presented here and in other studies, it is evident that SCP cannot be explained purely based upon behavior and/or medication-related influences. As discussed above, advanced age and male sex appear to play roles that warrant further investigation.

Another possibility is that there are genetic factors influencing individual pain perception. There is evidence that genetic factors have significant influence over pain experience in CP [20]. While the role that genetics may have in SCP is less clear, there are other similar conditions that may provide clues in this regard. One such model is silent inflammatory bowel disease (SIBD). In this condition, individuals perceive little to no abdominal pain during active phases of intestinal inflammation [21]. A study by Gonzalez-Lopez *et al* found that SIBD patients were more likely to be homozygous for a polymorphism within the gene (*SCN10A*) encoding the voltage-gated sodium channel, $Na_v1.8$ [22]. This is relevant because $Na_v1.8$ has been shown to be critically important for transmission of pain-related signals from the periphery [23,24]. It is possible that individuals with SCP are more likely to harbor this or other genetic variants that lead to diminished visceral pain perception.

It is essential that further clarity is gained regarding the pathophysiology of CP and SCP. We know that CP is associated with a myriad of complications, including, but not limited to, exocrine and endocrine pancreatic insufficiency, duodenal strictures, bile duct strictures, pancreatic pseudoaneurysms (which can predispose to life-threatening bleeds) and pancreatic cancer [1,21,22]. Individuals with CP also tend to have a higher mortality rate, particularly from pancreatic cancer, compared to the general population [25]. Poorly managed CP patients are at risk of these complications. Importantly, individuals with SCP tend to be at even higher risk, since they are frequently diagnosed only after developing one of these complications [11]. A better understanding of the pathophysiology, risk factors and clinical outcomes of SCP will lead to improved treatment outcomes.

We recognize that there are specific limitations to this study. First, this was a single-center study and the risk factors found to be associated with SCP may not be generalizable to other clinical settings. It is also possible that, as it was performed in a tertiary referral center, this study overestimated the incidence of SCP, as a result of referral bias. Additionally, this was a retrospective cohort study, and some relevant data may not have been considered and/or collected during the time when the study participants were being evaluated and cared for. As an example, we did not have reliable information about anxious and/or depressive symptoms in our study cohort, and it has previously been reported that these variables are strongly associated with pain experience in CP [26]. It was also impossible for us to determine the cause of certain complications in each case (e.g., diabetes). This was important as it relates to the potential risk(s) of SCP. Screening for abdominal pain relied upon patient self-reporting and appropriate documentation in the clinic note. It was also unclear how persistent the lack of abdominal pain was, as we did not have repeated clinical examinations for each study participant. There may have been cases where the true patient experience was not accurately documented. Our study cohort was also relatively small, and it is possible some associations were not detected and/or were not found to be significant because of this.

In conclusion, the findings of this study add to the growing body of literature describing the clinical and demographic variables associated with SCP, a relatively common condition. This study also demonstrates that this condition is not driven by analgesic medications (including opioids). The exact pathophysiology and overall impact of silent chronic pancreatitis remain unclear, however. Future studies should focus on investigating larger cohorts of carefully phenotyped individuals, preferably on a longitudinal basis, and in

comparison to additional study cohorts (e.g., healthy matched controls), to glean further insights about this important and still poorly understood phenomenon.

Summary Box

What is already known:

- Chronic pancreatitis can exist as a "silent" subtype in some patients, where there are no symptoms indicating the inflammatory syndrome
- Silent chronic pancreatitis (SCP) is often an incidental radiologic finding and may go unnoticed until complications arise
- Few studies have investigated the clinical characteristics and potential risk factors associated with SCP

What the new findings are:

- Approximately 20% of chronic pancreatitis patients were found to have SCP
- SCP was more likely to be found in older individuals and males
- Individuals with SCP were less likely to use opioids

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