

Classic chronic pancreatitis is associated with prior acute pancreatitis in only 50% of patients in a large single-institution study

Yasuki Hori ^{a, b}, Santhi Swaroop Vege ^{a, *}, Suresh T. Chari ^a, Ferga C. Gleeson ^a, Michael J. Levy ^a, Randall K. Pearson ^a, Bret T. Petersen ^a, Michael L. Kendrick ^c, Naoki Takahashi ^d, Mark J. Truty ^c, Rory L. Smoot ^c, Mark D. Topazian ^a

^a Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

^b Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

^c Department of Surgery, Mayo Clinic, Rochester, MN, USA

^d Department of Radiology, Mayo Clinic, Rochester, MN, USA

ARTICLE INFO

Article history:

Received 1 February 2019

Received in revised form

6 February 2019

Accepted 7 February 2019

Available online 12 February 2019

Keywords:

Acute pancreatitis

Chronic pancreatitis

Recurrent acute pancreatitis

Sentinel acute pancreatitis event

ABSTRACT

Background: The sentinel acute pancreatitis event (SAPE) hypothesis for pathogenesis of chronic pancreatitis (CP) postulates that acute pancreatitis (AP), especially recurrent AP (RAP), precedes development of CP. However, in a recent population-based study, 52/89 (58.4%) of CP had no prior episodes of AP. In a large clinic-based CP cohort, we aimed to determine the incidence and timing of prior AP in patients diagnosed with CP.

Methods: We retrospectively identified 499 consecutive patients with classic CP diagnosed at our institution from January 2013 through December 2015. We abstracted their demographic and clinical data, especially regarding prior AP.

Results: We identified 3 cohorts: 1) CP with no AP (n = 231 [46.3%]), 2) AP before CP (n = 250 [50.1%]), and 3) AP after CP (n = 18 [3.6%]). At CP diagnosis, 249 patients (49.9%) had no prior AP. Compared with the “CP preceded by AP” cohort, the “CP without AP” cohort was older (59.2 ± 13.9 vs 48.6 ± 15.7 years; $P < .001$), had a higher prevalence of diabetes mellitus (30.3% vs 12.4%; $P < .001$), reported less pain (52.8% vs 87.6%; $P < .001$), and had a lower rate of endoscopic interventions (16.0% vs 39.2%; $P < .001$). In the “CP preceded by AP” cohort, 117 (46.8%) had a single episode of AP and 133 (53.2%) had RAP.

Conclusion: Nearly half the patients with classic CP did not have prior AP. Only a quarter of patients had CP that could potentially have evolved from prior RAP. Development of CP may be attributable to an altogether different pathogenesis (a non-SAPE pathway) for a considerable proportion of patients.

© 2019 IAP and EPC. Published by Elsevier B.V. All rights reserved.

Introduction

Chronic pancreatitis (CP), first described by Comfort et al. [1], is a progressive, fibroinflammatory disease and the resultant loss of pancreatic parenchyma leads to endocrine and exocrine failure, which manifests eventually as leads to diabetes mellitus and

Abbreviations: AIP, autoimmune pancreatitis; AP, acute pancreatitis; CP, chronic pancreatitis; CT, computed tomography; ER, endoplasmic reticulum; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; OCP, obstructive chronic pancreatitis; RAP, recurrent acute pancreatitis; SAPE, sentinel acute pancreatitis event; UPR, unfolded-protein response.

* Corresponding author. Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN, 55905, USA.

E-mail address: vege.santhi@mayo.edu (S.S. Vege).

<https://doi.org/10.1016/j.pan.2019.02.004>

1424-3903/© 2019 IAP and EPC. Published by Elsevier B.V. All rights reserved.

steatorrhea [2,3]. Considerable advances in the areas of diagnosis, treatment, and prevention have been made in recent years, but many gaps still remain in the understanding of CP. Although the 1963 Marseilles classification [4] suggested that the primary lesion responsible for the disease resided in the pancreatic duct, Comfort and colleagues [5] subsequently proposed an alternative necrosis-fibrosis hypothesis, which suggested that CP was the result of repeated attacks of acute pancreatitis (AP). However, after this hypothesis was proposed, several high-quality studies of surgical and autopsy specimens suggested that CP was already established by the time of the first attack of alcoholic pancreatitis and hence not the result of prior AP [4,6–12].

The long-term, prospective, clinicopathologic study by Amman and colleagues [13] strongly supported the necrosis-fibrosis

hypothesis. However, their study did not include patients with acute alcoholic pancreatitis; hence, they could not determine whether CP was already established by the time of the first attack of alcoholic pancreatitis. Subsequently, Whitcomb [14] published the sentinel AP event (SAPE) hypothesis, noting that some patients with hereditary pancreatitis or alcoholism progressed to CP with little evidence of pancreatic necrosis. The SAPE hypothesis is a 2-hit model, in which a single episode of AP causes infiltration of inflammatory cells and activation of stellate cells, with subsequent ongoing injury or stress promoting fibrosis through the activated immune cells. This process is proposed as the underlying mechanism of CP development in patients with no prior necrosis. This hypothesis has gained widespread acceptance in the pancreatic community and also states that in those patients with CP where there is no history of prior AP, the AP might be a subclinical event. However, AP as recognized currently is a clinical entity with quite significant abdominal pain, enzyme elevation and/or imaging abnormalities. Hence it would be difficult to comprehend a term like subclinical AP in support of SAPE hypothesis, if one would like to explain the absence of clinical attacks of AP in patients with CP.

However, the relationship between AP and CP is far from simple. Numerous studies and meta-analyses have reported that approximately 10% of all patients with AP will have subsequent CP, especially if they have recurrent acute pancreatitis (RAP) [15]. Patients with a history of smoking and alcoholism have much higher frequency of RAP and subsequent CP. However, the literature is unclear about how often AP is the initial clinical event for patients with CP.

This complex relationship between AP and CP becomes even more perplexing with the reports that many patients with a diagnosis of idiopathic AP and idiopathic RAP subsequently receive the diagnosis of CP [16,17]. Whether CP is the original disease and AP is the first clinical presentation, or whether the initial AP subsequently leads to CP (the SAPE hypothesis), is not clear from the available evidence, and large-scale, population-based, prospective studies to address this question are lacking. CP as commonly described (classic or usual CP) implies exclusion of well-recognized subsets such as obstructive pancreatitis (OCP; due to pancreatic tumors, ductal strictures due to trauma, and necrotizing pancreatitis) and autoimmune pancreatitis (AIP). However, classic CP may have further subsided like painless CP, hereditary CP, and early onset and late onset CP. Alcoholic CP is still being considered as the classic example of classic or usual CP.

Thus, to further elucidate the relationship between CP, AP, and RAP, we decided to retrospectively study the most recent group of patients at our institution with CP. The objectives were to determine the frequency of AP and RAP and the temporal relation of those events to the diagnosis of CP. We also aimed to characterize patients who had AP as the initial presentation and compare them with patients who had CP but no prior AP. Lastly, we aimed to define the etiologic spectrum of CP in this recent cohort.

Methods

This study was approved by the Mayo Clinic Institutional Review Board. Written informed consent was obtained from all participating patients about the use of their medical records for research purposes.

Patients

We retrospectively identified consecutive adult patients (aged 18 years and older) with a diagnosis of CP treated at Mayo Clinic (Rochester, Minnesota), from January 1, 2013, through December 31, 2015. The Mayo Clinic Advanced Cohort Explorer tool was used

to query institutional databases and identify patients with CP (*International Classification of Diseases, Ninth Revision* code 577.1; *International Classification of Diseases, Tenth Revision* codes K86.0 and K86.1).

Definitions

CP was diagnosed according to accepted criteria for findings on computed tomography (CT), magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography (Cambridge classification), endoscopic ultrasound (EUS) (presence of ≥ 5 findings or Rosemont criteria [18]), pathology, or a combination thereof. AIP was diagnosed on the basis of the International Consensus Diagnostic Criteria [19]. OCP was defined according to the following criteria: 1) normal proximal pancreas, 2) stricture at the beginnings of dilated ducts, 3) dilated pancreatic duct, and 4) atrophy of distal pancreas [4,20,21]. We excluded patients with AIP and OCP from the study (because they are now recognized as distinct entities) and categorized the remaining patients as having classic CP.

All patients in our cohort were considered to have definitive CP. For patients with AP, the interval from AP to CP was defined as the period from the first AP episode to CP diagnosis. Patients were considered to have alcohol-related CP if they had a habit of alcohol abuse from history and the physician recorded the etiology as alcohol. However, the amount and duration of alcohol history was not ascertained. Patients with a convincing family history of pancreatitis or CP-related gene mutation were categorized as having a genetic cause. Smoking was considered the cause of CP if patients smoked ≥ 1 pack per day for ≥ 5 years.

We considered the initial diagnostic imaging (or pathologic findings) that could be confirmed in our institution as the method used to establish the diagnosis. If the patient had received a diagnosis at another institution and the diagnosis was established only from the medical record, we defined the diagnostic method as “medical history.” The initial symptom of CP was recorded, if the patient had multiple symptoms at the time of the hospital visit, we included only the first symptom that was attributable to CP.

CP treatment was categorized as “medical” for patients who required medication for pain, diabetes mellitus, or steatorrhea related to CP. Treatment was categorized as “endoscopic” if patients had endoscopic drainage or treatment for pancreatolithiasis or ganglion block. Treatment was categorized as “surgical” if patients had pancreatic resection or surgical drainage. If a patient required multiple treatments, every administered treatment was counted for the same patient.

For clinical outcomes, patients were considered to have exocrine pancreatic insufficiency if they required pancreatic enzyme replacement therapy. Pancreatic function tests were not available in majority of patients. Patients were considered to have diabetes mellitus if they required oral hypoglycemic agents or insulin. New-onset diabetes mellitus was defined as diabetes that was diagnosed for the first time after CP was diagnosed.

Data collection

Patient data were abstracted from the electronic medical records. We collected 1) characteristics of patients (age, sex, body mass index at the time of CP diagnosis, history of alcohol consumption, smoking habits, cause of CP, diabetes mellitus before CP diagnosis, initial symptom prompting the hospital visit); 2) method of diagnosing CP; 3) outcome measures (exocrine and endocrine decrease, patients achieving symptom relief, duration of follow-up); 4) administered treatment (medical, endoscopic, surgical, as defined above).

Statistical analyses

Categorical variables were compared by using the χ^2 [2] test and Fisher exact test. Continuous variables were compared by using the student *t*-test or Mann-Whitney *U* test. All analyses were performed with SPSS statistical software, version 23 (IBM Corp., Armonk, NY, USA). Results were considered statistically significant if the 2-tailed *P* value was $<.05$.

Results

Patient characteristics

We retrospectively reviewed records from 758 consecutive patients seen from 2013 to 2015. We excluded 83 cases of AIP and 176 cases of OCP; the remaining 499 cases were categorized as classic CP. As shown in Fig. 1, 249 patients (49.9%) did not have AP before CP was diagnosed. Among them, 18 patients had AP after the diagnosis of CP, whereas 231 had no AP throughout the follow-up period. In contrast, 250 cases (50.1%) had an episode of AP before CP was diagnosed. In the “CP preceded by AP” cohort ($n = 250$), 117 (46.8%) had a single episode of AP and 133 (53.2%) had RAP. No pancreatic events other than AP were observed before the diagnosis of CP in any patient.

Patient characteristics at the time of CP diagnosis are shown in Table 1. The cause of CP was attributed to alcohol for 190 patients (38.1%) and to smoking for 180 (36.1%). We noted considerable overlap between these groups, with 107 patients categorized as both alcohol users and smokers.

Table 2 summarizes the initial symptoms that prompted the hospital visit and the treatments administered to patients with classic CP. Three hundred and fifty-six patients (71.3%) reported pain. This pain is chronic abdominal pain, similar to the pain seen in classic CP. None of these patients had acute abdominal pain typical of AP, nor imaging evidence of AP. Meanwhile, 74 patients (14.8%) had no symptoms associated with CP. Diabetes mellitus was diagnosed after CP in 62 of 395 patients (15.7%). In total, 166 patients (33.3%) required an oral hypoglycemic agent or insulin, and 219 (43.9%) received pancreatic enzyme replacement therapy.

Comparison of patients who did or did not have AP preceding CP

Table 3 shows the clinical characteristics, interventions, and outcomes of patients with CP who did or did not have preceding AP. Patients without prior AP differed from those with prior AP in terms of older age (mean $\pm$ SD, 59.2 ± 13.9 vs 48.6 ± 15.7 years; $P < .001$), a

Table 1

Patient characteristics and method of diagnosing classic chronic pancreatitis ($n = 499$).

Characteristic	Value
Age, mean $\pm$ SD, y	53.8 $\pm$ 15.6
Sex, # (%)	
Male	303 (60.7)
Female	196 (39.3)
Body mass index, mean $\pm$ SD, kg/m ²	25.9 $\pm$ 6.2
Diabetes mellitus, # (%)	104 (20.8)
Cause of chronic pancreatitis, # (%)	
Alcohol only ^a	83 (16.6)
Smoking only ^b	73 (14.6)
Both alcohol and smoking	107 (21.4)
Hereditary	29 (5.8)
Idiopathic	141 (28.3)
Other	66 (13.2)
Diagnostic method ^c , # (%)	
Computed tomography	230 (46.1)
Magnetic resonance imaging	42 (8.4)
Endoscopic ultrasonography	165 (33.1)
Endoscopic retrograde cholangiopancreatography	6 (1.2)
Surgery	15 (3.0)
Medical history ^d	41 (8.2)

^a Alcohol abuse.

^b Cigarette smoking, ≥ 1 pack per day and ≥ 5 years.

^c Initial diagnostic method, confirmed at our institution.

^d Diagnosed at another institution and noted in the patient's medical record by physician.

Table 2

Initial symptom prompting hospital visit and subsequent treatment of patients with classic chronic pancreatitis ($n = 499$).

Initial symptom, # (%)	
Pain	356 (71.3)
Diarrhea	42 (8.4)
Weight loss	16 (3.2)
Jaundice	7 (1.4)
Other	4 (0.8)
Asymptomatic	74 (14.8)
Treatment, # (%)	
Medical ^a	298 (59.7)
Endoscopic ^b	141 (28.3)
Surgical ^c	87 (17.4)
No treatment	133 (26.7)
Clinical outcomes, # (%)	
New-onset diabetes mellitus	62/395 (15.7)
Exocrine insufficiency	219 (43.9)
Duration of follow-up, median (range), mo	16 (0–252)

^a Continual medication for pain, diabetes mellitus, or “exocrine insufficiency” associated with chronic pancreatitis.

^b Endoscopic drainage, treatment for pancreatolithiasis, or ganglion block.

^c Pancreatic resection or drainage.

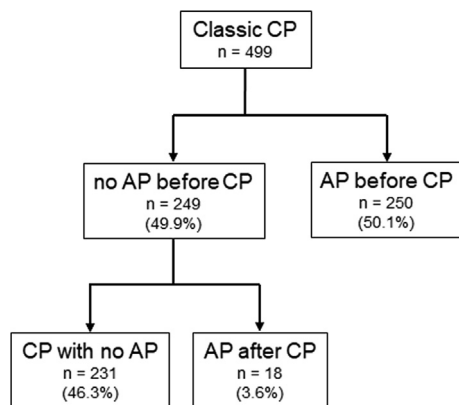


Fig. 1. Flow Diagram of Patients With Classic Chronic Pancreatitis. AP indicates acute pancreatitis; CP, chronic pancreatitis.

higher prevalence of diabetes mellitus at the time of CP diagnosis (30.3% vs 12.4%; $P < .001$), less pain (52.8% vs 87.6%; $P < .001$), and a lower rate of endoscopic interventions (16.0% vs 39.2%; $P < .001$). For the initial symptoms, the rate of diarrhea (12.1% vs 5.6%; $P = .02$) and body weight loss (5.2% vs 0.8%; $P = .004$) were significantly higher in patients without prior AP.

Clinical characteristics of patients with RAP or a single episode of AP before CP

Among patients with CP who initially presented with AP, 133 (53.2%) had RAP. The cause or association of RAP was alcohol for 23 patients (17.3%), smoking for 36 (27.1%), with 14 patients (10.5%) categorized as both alcohol users and smokers. Idiopathic RAP was diagnosed in 32 (24.1%), accounting for 6.4% of all CP cases. Meanwhile, 29 cases (21.8%) had multiple causes. The intervals

Table 3Comparison of patients who did or did not have AP preceding CP (n = 481)^a.

Characteristic	CP Without AP (n = 231)	CP Preceded by AP (n = 250)	P Value
Age, mean $\pm$ SD, y	59.2 $\pm$ 13.9	48.6 $\pm$ 15.7	<.001
Sex, # (%)			.82
Male	141 (61.0)	150 (60.0)	
Female	90 (39.0)	100 (40.0)	
Body mass index, mean $\pm$ SD, kg/m ²	26.2 $\pm$ 6.3	25.7 $\pm$ 6.2	.44
Diabetes mellitus, # (%)	70 (30.3)	31 (12.4)	<.001
Initial symptom, # (%)			
Pain	122 (52.8)	219 (87.6)	<.001
Diarrhea	28 (12.1)	14 (5.6)	.02
Body weight loss	12 (5.2)	2 (0.8)	.004
Jaundice	6 (2.6)	1 (0.4)	.06
No symptoms associated with pancreatitis	59 (25.5)	14 (5.6)	<.001
Treatment, # (%)			
Medical ^b	140 (60.6)	147 (58.8)	.69
Endoscopic ^c	37 (16.0)	98 (39.2)	<.001
Surgical ^d	35 (15.2)	49 (19.6)	.20
No treatment	72 (31.2)	56 (22.4)	.03
Clinical outcomes, # (%)			
New-onset diabetes mellitus	21/161 (13.0)	38/218 (17.4)	.25
Exocrine insufficiency	97 (42.0)	114 (45.6)	.43
Duration of follow-up, median (range), mo	17 (0–252)	15 (0–236)	.52

Abbreviations: AP, acute pancreatitis; CP, chronic pancreatitis.

^a Eighteen patients had their initial episode of AP after CP was diagnosed.^b Continual medication for pain, diabetes mellitus, or steatorrhea associated with chronic pancreatitis.^c Endoscopic drainage, treatment for pancreatolithiasis, or ganglion block.^d Pancreatic resection or percutaneous surgical treatment.

between the initial diagnosis of AP and subsequent diagnosis of CP are detailed in Fig. 2.

Table 4 summarizes characteristics of patients with a single episode of AP before CP and patients with RAP. Patients with RAP were different from those of patients with single episode of AP in terms of younger age (mean $\pm$ SD, 44.8 $\pm$ 5.1 vs 53.0 $\pm$ 15.3 years; P < .001) and lower prevalence of diabetes mellitus (7.5% vs 17.9%; P = .01) at CP diagnosis. New-onset diabetes mellitus (after the diagnosis of CP) was significantly more common in patients with RAP (30/123 [24.4%] vs 8/96 [8.3%]; P = .002).

Discussion

This recent single-center cohort study of 499 consecutive patients with CP had several important findings. Nearly half the patients (49.9%) did not have AP before CP was diagnosed, and another 3.6% had AP after the diagnosis of CP. Of the 250 patients with prior AP, only 53.2% had RAP, and approximately a quarter were diagnosed with CP within 12 months after the episode of AP. Of the patients with RAP, 24.1% had an idiopathic cause; these

patients constituted 6.4% of the full CP cohort. These observations have significant clinical implications and are useful for critically assessing some key concepts and controversies regarding the relationship between AP and CP.

A number of studies have monitored patients with AP for subsequent development of CP. In these cohorts, all (or nearly all) patients with CP had a history of AP, which might explain why the dominant hypotheses for pathogenesis of CP consider AP as an important initiator of the process. The most recent consensus paper on CP divided the clinical course into 5 stages: stage A is exposure to risk factors (alcohol, smoking etc); stage B, SAPE, then RAP; stage C, early CP; stage D, established CP, and stage E, advanced CP [22]. According to the SAPE hypothesis (the most widely accepted hypothesis for pathogenesis of CP) an immune reaction to a sentinel AP event triggers CP development. In the absence of a preceding AP event, either a subclinical AP event has occurred, which would be difficult to prove or disprove, or the SAPE hypothesis does not apply to these patients. Another hypothesis of CP pathogenesis posits that recurrent attacks of pancreatitis causes progressive inflammatory damage, micronecrosis, and fibrosis (necrosis-fibrosis sequence) [17,22–25]. With general agreement with SAPE hypothesis, investigators started looking at cohorts of AP for subsequent occurrence of RAP and CP [16,17]. A recent meta-analysis reported a 10% rate of progression to CP in patients with AP and a much higher rate of 36% progression to CP in patients who had RAP (22% of all AP) [16]. While there are many studies looking at cohorts of AP for subsequent development of CP, studies looking at cohorts of CP for prior attacks of AP were very limited and is the main reason for our study.

We compared our study findings with those of others that had assessed prior AP in cohorts of patients with CP (Table 5). We identified 2 studies of CP in which the data were obtained from multicenter cohorts [26,27]. Although these studies reported data from 14 to 13 centers, respectively, they included only 229 and 477 patients seen during an approximately equivalent period. In those cohorts, 34% and 83% of patients did not have a history of AP and approximately half the patients in both studies had alcohol listed as the cause of CP. Thus, this evidence supports the observations of the

Interval between first attack of AP and subsequent CP diagnosis

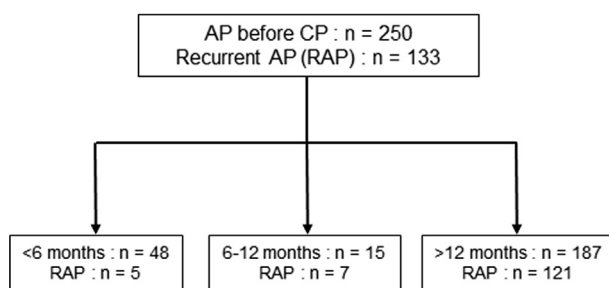


Fig. 2. Interval Between First Attack of AP and Subsequent Diagnosis of CP. The patients with RAP are a subset of the patients with AP before CP. AP indicates acute pancreatitis; CP, chronic pancreatitis; RAP, recurrent acute pancreatitis.

Table 4

Comparison of patients with a single episode of AP or with RAP (n = 250).

Characteristic	Single Episode of AP (n = 117)	RAP (n = 133)	P Value
Age, mean $\pm$ SD, y	53.0 $\pm$ 15.3	44.8 $\pm$ 15.1	<.001
Sex, # (%)			.76
Male	69 (59.0)	81 (60.9)	
Female	48 (41.0)	52 (39.1)	
Body mass index, mean $\pm$ SD, kg/m ²	25.6 $\pm$ 7.1	25.8 $\pm$ 5.4	.82
Diabetes mellitus, # (%)	21 (17.9)	10 (7.5)	.01
Cause of acute pancreatitis, # (%)			
Alcohol only	16 (13.7)	9 (6.8)	.09
Smoking only	15 (12.8)	22 (16.5)	.48
Both alcohol and smoking	34 (29.1)	14 (10.5)	<.001
Hereditary	4 (3.4)	20 (15.0)	.002
Idiopathic	18 (15.4)	32 (24.1)	.11
Treatment, # (%)			
Medical	61 (52.1)	86 (64.7)	.04
Endoscopic	48 (41.0)	50 (37.6)	.58
Surgical	19 (16.2)	30 (22.6)	.21
None	31 (26.5)	25 (18.8)	.15
Clinical outcome, # (%)			
New-onset diabetes mellitus	8/96 (8.3)	30/123 (24.4)	.002
Exocrine insufficiency	47 (40.2)	67 (50.4)	.11
Follow-up, median (range), mo	16 (0–236)	13 (0–235)	.40

Abbreviations: AP, acute pancreatitis; RAP, recurrent acute pancreatitis.

Table 5

Studies assessing prior AP in cohorts of CP.

Study	Patients, #	Study Period	Centers, #	Types of CP	No Prior AP, # (%)	Alcohol, # (%)
Szűcs et al. [26] (2017)	229	2012–2014	14	All	78 (34.1)	103/228 (45.2)
Conwell et al. [27] (2017)	477 ^a	2008–2011	13	AIP, obstructive excluded	396 (83.0)	238/521 (45.7)
Machicado et al. [32] (2018) ^b	89	1997–2006	Olmsted county	AIP, obstructive excluded	52 (58.4)	46 (51.7)
Current study	499	2011–2013	1	AIP, obstructive excluded	251 (50.3)	190 (38.1)

Abbreviations: AIP, autoimmune pancreatitis; AP, acute pancreatitis; CP, chronic pancreatitis.

^a The total cohort included 521 patients. After excluding cases of AIP and obstructive CP, 477 patients remained.^b Olmsted County population-based study.

present study, in which nearly half the patients with CP did not have prior AP, and alcohol was felt to be the cause in 38% of patients. However, retrospective studies can be limited by missing information, e.g., prior AP may be forgotten or unreported by the patient, or the physician might not have asked for or documented information appropriately. We therefore looked for population-based studies, which presumably would have more accurate documentation of the occurrence of prior AP and subsequent diagnosis of CP. A study of residents of Olmsted County, Minnesota, described 89 patients with CP from a 10-year period and reported that 58% did not have a history of AP. Multiple previous publications validated the reliability of Olmsted County data, as most of these patients receive medical care in just two institutions and any attack of AP would be unlikely to be missed. Fifty-two percent of that group had alcohol noted as the cause of CP, which is similar to the proportion in our study and the other 2 studies. This population-based study further supports our findings that a considerable proportion of patients with classic CP do not have a history of AP.

The hypothesis of subclinical AP causing CP is difficult to substantiate because of the lack of human data. An altogether different mechanism may be possible for patients with no episodes of AP before CP or perhaps more universally in CP. A recently published mouse model study [28] strongly supports our notion that low-level inflammation can cause progressive CP without overt acute attacks. Chronic alcohol consumption and smoking are well-known causes of endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR). As noted by Chaudhari et al. [29], “Chronic ER stress and activation of the UPR through endogenous or exogenous insults may result in impaired calcium and redox homeostasis [and] oxidative stress via protein overload, thereby

also influencing vital mitochondrial functions.” We hypothesize that chronic ER stress in acini due to alcohol, smoking, or an unknown cause leads to patchy, subclinical acinar damage and fibrosis. Progression to CP is not so much due to AP or RAP but to low-grade subclinical inflammation triggered by ER stress and UPR. This model may explain the short interval between AP and CP in many patients with prior AP, and it does not preclude the possibility of some patients with the first attack of alcoholic AP having no evidence of underlying CP [13]. Furthermore, UPR could be universal in people who chronically abuse alcohol and smoke, with recent reports from surgical pathology [6,30] suggesting that CP is already established before the first clinical attack of AP for patients who abuse alcohol. Nevertheless, most alcohol users will not have AP or CP. A recent study [31,32] has suggested mechanisms that may protect against development of pancreatitis due to alcohol-induced UPR, although the triggers of an attack of clinical pancreatitis are unknown. Another notable study [33] has identified a novel mechanism of synergy between alcohol and cigarette smoke in causing unresolved ER stress and acinar cell death which subsequently worsens pancreatitis responses. Therefore, on the basis of previous and recent reports, pancreatitis pathogenesis is considered to be related to “multiple hits on multiple targets” model [34] caused by alcohol abuse and cigarette smoking.

The study provides strong evidence that CP develops without prior AP for a considerable proportion of patients. In our study of nearly 500 patients with CP, nearly half had no history of AP. One strength of the study is that we present the most recent data on CP, which reflects current practice patterns, from a cohort that is nearly the same size as that of a 4-year study from 13 US academic centers [27]. Our findings are further strengthened by the fairly uniform

diagnostic and therapeutic approaches used at our institution, and we believe this uniformity decreases the clinical diversity of data compared with prior studies from multicenter cohorts.

Our study has many limitations that are associated with retrospective studies. Ours was a cross-sectional study, and long-term follow-up to assess other aspects of the disease was not possible. It is conceivable that some patients who did not have AP before CP may have had mild (or subclinical) episodes and did not report them to the clinician. However, it is very unlikely that half the cohort would have had mild and unreported attacks of AP. The pain that was observed in 122 patients with no prior AP was not the typical abdominal pain of AP, but chronic abdominal pain that is typically the symptom in CP which requires treatment. In addition, none of these patients had imaging evidence of AP, neither at our institution, nor from outside records.

In conclusion, nearly half the patients with CP did not have a history of AP. These patients had different clinical characteristics compared with patients who had a history of AP before CP was diagnosed. Only a quarter of patients in the cohort had a history that was consistent with the model of CP developing from prior AP and subsequent RAP. CP may be the cause, rather than the result, of AP in nearly a quarter of the patients with prior AP, in whom the subsequent diagnosis of CP was made within 1 year after the initial AP episode. These observations raise the possibility that, for a considerable proportion of patients, their CP is not attributable to progression from AP. In those patients, CP may have an altogether different mechanism of pathogenesis, a possibility that requires further study.

Conflict of interest

Guarantor of the article

Santhi Swaroop Vege, MD.

Specific author contributions

Conception and design: Hori Y and Vege SS.

Analysis and interpretation of the data: Hori Y, Topazian MD, Chari ST, Gleeson FC, Levy MJ, Pearson RK, Petersen BT, Kendrick ML, Takahashi N, Truty MJ, Smoot RL, and Vege SS.

Drafting of the article: Hori Y, Chari ST, and Vege SS.

Critical revision of the article for important intellectual content: Chari ST.

Final approval of the article: Vege SS.

Financial support

This study was not externally funded.

References

- [1] Comfort MW, Gambill EE, Baggenstoss AH. Chronic relapsing pancreatitis: a study of twenty-nine cases without associated disease of the biliary or gastrointestinal tract. *Gastroenterology* 1946;6:239 [passim].
- [2] Majumder S, Chari ST. Chronic pancreatitis. *Lancet* 2016;387:1957–66.
- [3] Braganza JM, Lee SH, McCloy RF, et al. Chronic pancreatitis. *Lancet* 2011;377:1184–97.
- [4] Sarles H, Sarles JC, Camatte R, et al. Observations on 205 confirmed cases of acute pancreatitis, recurring pancreatitis, and chronic pancreatitis. *Gut* 1965;6:545–59.
- [5] Comfort MW, Gambill EE, Baggenstoss AH. Chronic relapsing pancreatitis. A study of twenty-nine cases without associated disease of the biliary or gastrointestinal tract. *Gastroenterology* 1968;54(Suppl):760–5.
- [6] Migliori M, Manca M, Santini D, et al. Does acute alcoholic pancreatitis precede the chronic form or is the opposite true? A histological study. *J Clin Gastroenterol* 2004;38:272–5.
- [7] Payan H, Sarles H, Demirdjian M, et al. Study of the histological features of chronic pancreatitis by correspondence analysis. Identification of chronic calcifying pancreatitis as an entity. *Rev Eur Etud Clin Biol* 1972;17:663–70.
- [8] Gullo L, Costa PL, Fontana G, et al. Effect of adrenocorticotrophic hormone on pure exocrine pancreatic secretion in man. *Gastroenterology* 1977;73:762–4.
- [9] Sahel J, Cros RC, Durbec JP, et al. Multicenter pathological study of chronic pancreatitis. Morphological regional variations and differences between chronic calcifying pancreatitis and obstructive pancreatitis. *Pancreas* 1986;1:471–7.
- [10] Sarles H, Bernard JP, Gullo L. Pathogenesis of chronic pancreatitis. *Gut* 1990;31:629–32.
- [11] Hanck C, Singer MV. Does acute alcoholic pancreatitis exist without preexisting chronic pancreatitis? *Scand J Gastroenterol* 1997;32:625–6.
- [12] Gullo L, Barbara L, Labo G. Effect of cessation of alcohol use on the course of pancreatic dysfunction in alcoholic pancreatitis. *Gastroenterology* 1988;95:1063–8.
- [13] Ammann RW, Heitz PU, Kloppel G. Course of alcoholic chronic pancreatitis: a prospective clinicomorphological long-term study. *Gastroenterology* 1996;111:224–31.
- [14] Whitcomb DC. Hereditary pancreatitis: new insights into acute and chronic pancreatitis. *Gut* 1999;45:317–22.
- [15] Sankaran SJ, Xiao AY, Wu LM, et al. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. *Gastroenterology* 2015;149:1490–1500.e1.
- [16] Lankisch PG, Breuer N, Bruns A, et al. Natural history of acute pancreatitis: a long-term population-based study. *Am J Gastroenterol* 2009;104:2797–805. quiz 2806.
- [17] Ahmed Ali U, Issa Y, Hagenaars JC, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. *Clin Gastroenterol Hepatol* 2016;14:738–46.
- [18] Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. *Gastrointest Endosc* 2009;69:1251–61.
- [19] Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatologists. *Pancreas* 2011;40:352–8.
- [20] Laugier R, Camatte R, Sarles H. Chronic obstructive pancreatitis after healing of a necrotic pseudocyst. *Am J Surg* 1983;146:551–7.
- [21] Chan DK, Kendrick ML, Farnell MB, et al. Prior acute pancreatitis is the most common cause of obstructive pancreatitis: a surgical series of distal pancreatectomy. *JOP* 2015;16:449–51.
- [22] Whitcomb DC, Frulloni L, Garg P, et al. Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. *Pancreatol* 2016;16:218–24.
- [23] Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 2013;144:1252–61.
- [24] Samokhvalov AV, Rehm J, Roerecke M. Alcohol consumption as a risk factor for acute and chronic pancreatitis: a systematic Review and a series of meta-analyses. *EBioMedicine* 2015;2:1996–2002.
- [25] Greer JB, Thrower E, Yadav D. Epidemiologic and mechanistic associations between smoking and pancreatitis. *Curr Treat Options Gastroenterol* 2015;13:332–46.
- [26] Szucs A, Marjai T, Szentesi A, et al. Chronic pancreatitis: multicentre prospective data collection and analysis by the Hungarian Pancreatic Study Group. *PLoS One* 2017;12. e0171420.
- [27] Conwell DL, Banks PA, Sandhu BS, et al. Validation of demographics, etiology, and risk factors for chronic pancreatitis in the USA: a report of the North American pancreas study (NAPS) group. *Dig Dis Sci* 2017;62:2133–40.
- [28] Hegyi E, Sahin-Toth M. Human CPA1 mutation causes digestive enzyme misfolding and chronic pancreatitis in mice. *Gut* 2019;68:301–12.
- [29] Chaudhari N, Talwar P, Parimisetty A, et al. A molecular web: endoplasmic reticulum stress, inflammation, and oxidative stress. *Front Cell Neurosci* 2014;8:213.
- [30] Pitchumoni CS, Glasser M, Saran RM, et al. Pancreatic fibrosis in chronic alcoholics and nonalcoholics without clinical pancreatitis. *Am J Gastroenterol* 1984;79:382–8.
- [31] Lugea A, Waldron RT, Pandolfi SJ. Pancreatic adaptive responses in alcohol abuse: role of the unfolded protein response. *Pancreatol* 2015;15:S1–5.
- [32] Lugea A, Tischler D, Nguyen J, et al. Adaptive unfolded protein response attenuates alcohol-induced pancreatic damage. *Gastroenterology* 2011;140:987–97.
- [33] Lugea A, Gerloff A, Su HY, et al. The combination of alcohol and cigarette smoke induces endoplasmic reticulum stress and cell death in pancreatic acinar cells. *Gastroenterology* 2017;153:1674–86.
- [34] Sahin-Toth M, Hegyi P. Smoking and drinking synergize in pancreatitis: multiple hits on multiple targets. *Gastroenterology* 2017;153:1479–81.