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Idiopathic and Rare Causes of Chronic Pancreatitis

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Introduction

Chronic pancreatitis (CP) is now recognized as a heterogeneous inflammatory disease that can develop in individuals with multiple risk factors, including environmental and genetic factors [1,2]. Many risk factors have been described in the TIGAR-O and M-ANNHEIM classifications, which include alcoholic, smoking, genetic, autoimmune, obstructive, nutritional, and rare metabolic factors [3,4]. However, recent international consensus guidelines strongly agree that alcohol, smoking, and certain genetic alterations are risk factors for CP [5].

Idiopathic CP (ICP) is identified after ruling out other potential causes, including rare ones [2,6]. It has been proposed that ICP can be further classified into three types, primarily based on clinical features: early-onset ICP (EO-ICP), late-onset ICP (LO-ICP), and tropical pancreatitis (TP) [3]. This chapter mainly focuses on the clinical features of ICP, including EO-ICP and LO-ICP described in recent reports. Moreover, we discuss the background risk factors for ICP, which include environmental risk factors, such as smoking and consuming small amounts of alcohol, and genetic risk factors (7–11]. In addition, rare causes of CP are also described.

Idiopathic Chronic Pancreatitis

Definition

To date, heavy alcohol drinkers (usually 50–80 g or more per day) with CP have been defined as having alcoholic CP (ACP). In others, CP has been defined as ICP after excluding all known rare causes such as obstructive, hereditary, and autoimmune diseases. Therefore, patients with ICP may include moderate or social drinkers [6]. Originally, ICP in patients with absolute abstinence from alcohol has been classified as EO-ICP or LO-ICP [12,13]. Thus, it is necessary to strictly distinguish between two categories of ICP, one that excludes all drinkers and one that includes people who drink small amounts of alcohol (light drinkers).

Classification

Early-Onset and Late-Onset

Patients with ICP who abstain from alcohol and were diagnosed at the Mayo Clinic had a bimodal age distribution. Their ICP has been classified into two types: EO-ICP or LO-ICP [6,12]. Age 35 is used as a cutoff for distinguishing between these two types of ICP [12]. A bimodal age distribution among patients with ICP has also been reported in Italy and among patients of European ancestry in the United States [13,14]. Although the peaks occurred at higher ages in a report from Japan, ICP showed a bimodal age distribution [15]. However, a bimodal distribution was not found in Chinese patients with ICP [16]. Since the latter two reports included light drinkers with ICP, light alcohol consumption might have affected the distribution of onset age [9,13]. Smoking and racial differences are other potential factors that should be studied in the future [6,17].

Tropical Pancreatitis

TP is a type of ICP seen in tropical countries. It is characterized by large pancreatic calculi and ductal dilatation in a young malnourished patient who presents with abdominal pain, diabetes, or both [18]. It has been reported in many parts of tropical Asia and Africa, but mostly in India, especially in the states of Kerala and Tamil Nadu [19]. Although malnutrition and cassava

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intake were previously thought to be causally associated with TP, they are no longer implicated as causative factors [17].

Prevalence

Table 49.1 shows the etiologies of CP from recently published epidemiologic analyses in population-based, multicenter, or nationwide cross-sectional studies [20–28]. In most studies, alcoholic was the most common etiology of CP, accounting for 33.6% to 72.0% of cases. The proportion of ICP cases was between 12.9% and 28.6% in the presented studies except for a nationwide study from India. The study showed the most common etiology was idiopathic, accounting for 60.2% of cases [25]. ICP was prominent in India. This finding was confirmed by three observational studies from single-centers in both northern and southern India [29–31].

Table 49.1 Etiology of CP in epidemiologic studies.

Author [ref]	Nation or region	Study period	Study design	Number of patients	Etiology
Lankisch et al. [20]	Germany / Lüneburg County	1988–1995	Population-based study	74	ACP 71.6% ICP 28.4%
Wang et al. [21]	China	1994–2004	Retrospective multicenter study	2008	ACP 35.1% Biliary 34.4% Hereditary 7.2% ICP 12.9%
Frulloni et al. [22]	Italia	2000–2005	Prospective multicenter study	893	ACP 33.6% Obstruction 26.7% Alcohol + obstruction 9.2% Autoimmunity 3.8% Dystrophy 6.2% Hereditary 4.0% ICP 16.6%
Coté et al. [23]	United States	2000–2006	Prospective multicenter study	539	ACP 44.5% Genetic 8.7% Autoimmune 2.2% Obstructive 8.7% Other 7.2% ICP 28.6%
Ryu et al. [24]	Korea	2001–2004	Retrospective multicenter study	814	ACP 64.3% Obstructive 8.6% Autoimmune 2.0% Other 4.4% ICP 20.8%
Balakrishnan et al. [25]	India	2005–2007	Prospective multicenter study	1033	ACP 38.7% Other 1.1% ICP 60.2%
Hirota et al. [26]	Japan	2007	Cross-sectional study	1236	ACP 69.7% Obstructive 1.1% Hereditary 0.9% Other 7.3% ICP 21.0%
Conwell et al. [27]	United States	2008–2012	Prospective multicenter study	521	ACP 45.7% Genetic 9.8% Obstructive 6.9% Autoimmune 1.5% Other 11.9% ICP 24.2%
Masamune et al. [28]	Japan	2016	Cross-sectional study	2102	ACP 72.0% Hereditary 1.6% Obstructive 0.4% Autoimmune 0.4% Other 1.9% ICP 23.7%

Ref: reference; ACP: alcoholic chronic pancreatitis; ICP: idiopathic chronic pancreatitis.

Tropical Pancreatitis

It has been reported that the prevalence of TP has significantly decreased. Previously, it was reported that TP accounted for more than 50% of CP cases in India [18]. However, a nationwide study conducted from 2005 to 2007 in India demonstrated TP made up only 3.8% of CP cases [25]. This finding was supported by a single-center observational study that demonstrated the proportion of typical TP was 5.8% [30]. Malnutrition, a typical feature of TP, has been rarely observed among patients with ICP in India. The prevalence of diabetes has decreased from 90% to 50% of ICP cases [17,30]. Furthermore, it has been pointed out that the number of drinkers is increasing due to lifestyle changes. The prevalence of ACP has been increasing in India [25]. The spectrum of clinical features in ICP has been changing in India and possibly other places.

Clinical Characteristics

Idiopathic vs. Alcoholic

ACP is generally recognized to cause severe symptoms [32]. To clarify the clinical characteristics of patients with ICP, seven reports comparing ICP and ACP from the United States, East Asia, and India were reviewed (Table 49.2). In these studies, ICP included light drinkers. Since the three studies were single-center observational studies, selection bias was possible [29,30,33]. The background of patients might be different between multicenter studies at specialty hospitals [23,24] and nationwide cross-sectional surveys [15,28] that included general hospitals because young symptomatic patients are expected to concentrate in specialty hospitals. The two studies from Japan are nationwide surveys conducted in different years [15,28]. Therefore, many of the participants in these studies might be duplicated.

Table 49.2 Comparison of clinical features between ACP and ICP.

Author [ref]	Coté et al. [23]	Hao et al. [33]	Ryu et al. [24]	Hirota et al. [15]	Masamune et al. [28]	Bashin et al. [29]	Midha et al. [30]
Country	United States	China	Korea	Japan	Japan	India	India
Study period	2000–2006	2000–2013	2001–2004	2011	2016	1999–2004	2004–2008
Number of patients (ACP/ICP)	240 / 154	404 / 1633	523 / 169	1171 / 347	1513 / 498	59 / 64	157 / 242
Males, % (ACP/ICP)	70.0 / 41.6[a]	98.3 / 63.1[a]	96.0 / 66.7[a]	92.2 / 54.6[a]	91.0 / 60.0[a]	100 / 65.6[a]	99.4 / 63.6[a]
Age at onset, years (ACP/ICP)	–	38.1 / 41.6[a]	–	51.5 / 57.2[a]	–	–	37.9 / 24.7[a]
Age at study, years (ACP/ICP)	50.9 / 50.0	42.6 / 47.0[a]	50.7 / 50.4	60.4 / 67.2[a]	–	41.5 / 33.0[a]	40.2 / 27.5[a]
Ever smoker, % (ACP/ICP)	92.9 / 58.6[a]	80.7 / 22.8[a]	–	85.0 / 39.8[a]	79.8 / 41.5[a]		70.7 / 12.8[a]
Pain, % (ACP/ICP)	–	94.6 / 91.8[b]	–	68.1 / 54.8[a]	–	91.5 / 96.9	–
Calcification, % (ACP/ICP)	66.2 / 53.9[a]	83.9 / 73.0[a]	72.3 / 64.5	71.7 / 63.4[a]	70.3 / 59.7[a]	35.6 / 46.9	68.8 / 82.6[a]
Diabetes, % (ACP/ICP)	29.2 / 26.4	38.9 / 26.3[a]	35.0 / 26.0[a]	40.1 / 30.5[a]	43.1 / 40.3	22.0 / 23.4	36.3 / 35.5
Exocrine insufficiency, % (ACP/ICP)	30.8 / 28.6	29.7 / 20.8[a]	–	–	33.6 / 30.5	28.0 / 12.0	6.3 / 16.9[a]
Pseudocyst, % (ACP/ICP)	38.3 / 13.0[a]	23.3 / 14.7[a]	33.5 / 21.9[a]	–	29.6 / 11.2[a]	47.4 / 34.3	40.1 / 14.5[a]
Biliary stricture, % (ACP/ICP)	21.7 / 8.4[a]	17.8 / 15.9	13.6 / 14.8	–	16.8 / 7.0[a]	–	29.3 / 10.7[a]
Surgery %, (ACP/ICP)	–	16.6 / 20.7	No difference[c]	–	17.8 / 12.1[a]	–	–

[a] $P < 0.05$.
[b] Type of pain was different ($P < 0.001$).
[c] No specific numbers were given.
Ref: reference; ACP: alcoholic chronic pancreatitis; ICP: idiopathic chronic pancreatitis.

Taking these potential biases into account, some characteristic features were demonstrated. First, compared to ACP, which has a male predominance, the proportion of male patients with ICP was relatively low. The majority of patients with ACP were smokers. Second, there were likely regional differences in the age of patients with ICP. In the United States and East Asia, age at onset was in the 40s and 50s, and age at the time of the study was approximately in the 40s to 60s. In India, age at onset was in the 20s and age at time of the study was approximately in the 20s and 30s. Patients with ICP in India were shown to be approximately 20 years younger than those in other countries. Conversely, patients with ICP in Japan were 10 years older than those in other East Asia countries and the United States. Third, in the United States and East Asia, patients with ACP tended to have a higher incidence of calcification and diabetes than patients with ICP. However, patients with ICP in India had more calcification than those with ACP. There were no significant differences between the proportion of patients with ICP and patients with ACP who have diabetes in India. Finally, a higher proportion of patients with ACP had pseudocyst formation. This finding was seen in almost all reports.

In summary, patients with ACP were predominantly male and smokers in all countries. They tended to have more severe clinical features than patients with ICP. Compared with ACP, a higher proportion of patients with ICP are women. In the United States and East Asia, patients with ICP are as old as or slightly older than patients with ACP, except for patients in India, who developed ICP at a very young age. However, patients with ICP in India tended to have a high rate of pancreatic calcification and diabetes as complications, even though they were very young.

Early-Onset and Late-Onset

Comparisons of clinical features between EO-ICP and LO-ICP were reported in five papers, two from the United States and three from India (Table 49.3). Layer et al. reported the results of a single-center observational study from the Mayo Clinic [12]. Lewis et al. reported a multicenter study with 26 participating institutions in the United States [13]. These studies defined patients with ICP as strictly abstinent from alcohol, which excluded even social and light drinkers. The latter study only included patients of European ancestry. Conversely, three studies from India, which were all single-center observational studies, did not define patients with ICP as strictly abstinent from alcohol [29–31].

According to Table 49.3, which shows a comparison of clinical features between EO- and LO-ICP, regional

Table 49.3 Comparison of clinical features between EO-ICP and LO-ICP.

Author [ref]	Layer et al. [12]	Lewis et al. [13]	Bashin et al. [29]	Midha et al. [30][c]	Rajesh et al. [31][d]
Country	United States	United States	India (North)	India (North 61%, Other 39%)	India (South)
Study period	1976–1985	2000–2014	1999–2004	2004–2008	2004–2010
Number of patients (EO/LO)	25 / 41	61 / 69	41 / 23	171 / 71	111 / 94
Males, % (EO/LO)	44.0 / 56.1	37.7 / 18.8[a]	75 / 48	63.2 / 64.8	61.3 / 50.0
Age at onset, years (EO/LO)	19.2 / 56.2[a]	20 / 58[a]	23 / 44[b]	18.7 / 39.1[a]	15.0 / 38.1[a]
Age at study, years (EO/LO)	–	30.1 / 64.3[a]	–	–	28.2 / 42.5[a]
Ever smoker, % (EO/LO)	–	33.3 / 43.5	–	9.9 / 19.7	8.1 / 12.1
Pain, % (EO/LO)	100 / 75.6[a]	96.1 / 69.2[a]	95.1 / 100	88.3 / 84.5	No difference[e]
Calcification, % (EO/LO)	56.0 / 36.6	45.9 / 50.7	46.3 / 47.8	–	95.5 / 97.9
Diabetes, % (EO/LO)	32.0 / 41.5	29.5 / 27.5	17.1 / 34.8	33.3 / 40.8	41.4 / 69.1[a]
Exocrine insufficiency, % (EO/LO)	44.0 / 46.3	29.5 / 36.2	7.3 / 0	16.4 / 18.3	34.4 /53.2[a]
Pseudocyst, % (EO/LO)	16.0 / 14.6	11.5 / 27.5[a]	–	11.7 / 21.1	7.4 / 10.6
Biliary stricture,% (EO/LO)	0 / 7.3	–	–	8.2 / 16.9[a]	–
Surgery %, (EO/LO)	60.0 / 31.7[a]	23.0 / 29.0	–		–

[a] $P < 0.05$.
[b] No statistical results were shown.
[c] EO-ICP was defined based on age at diagnosis <30 years. LO-ICP was defined based on age at diagnosis >30 years.
[d] EO-ICP was defined based on age at onset <30 years. LO-ICP was defined based on age at onset ≥30 years.
[e] No specific numbers were given.
Ref: reference; EO: early-onset idiopathic chronic pancreatitis; LO: late-onset idiopathic chronic pancreatitis; ICP: idiopathic chronic pancreatitis.

differences between the United States and India are remarkable. First of all, the patient composition was different. More patients in the United States had LO-ICP while more patients in India had EO-ICP. Compared with EO-ICP patients in the United States, EO-ICP patients in India were predominantly male. Age at EO-ICP onset was approximately 20 years in both the United States and India. Patients with EO-ICP in the two countries had generally similar clinical features with predominantly complaints of pain and similar complication rates to LO-ICP even though they were younger. Second, the clinical characteristics of patients with LO-ICP were different between the two countries. The age at LO-ICP onset was in the late 50s in the reports from the United States, while it was approximately 40 years in the reports from India. In the US studies, significantly fewer patients with LO-ICP complained of pain compared to patients with EO-ICP. Conversely, most patients with LO-ICP in India complained of pain. Patients with LO-ICP in India had similar rates of pancreatic calcification and diabetes as patients in the United States, even though they were on average more than 10 years younger. Finally, in particular, patients with LO-ICP in southern India had high rates of pancreatic calcification, diabetes, and exocrine insufficiency [31]. In this report, although patients with EO-ICP were very young, almost all of them had pancreatic calcification [31]. One reason for these differences might be explained by differences in patient background such as a small amount of alcohol intake and smoking, but further research including genetic analysis would be required.

Background Risk Factors

Smoking

Cigarette smoking has been identified as an independent risk factor for the development of CP [7,8]. Smoking facilitates the development of pancreatic calcification and diabetes in patients with CP [15,34]. As shown in Table 49.2, the association between ACP and smoking is strong. The combination of alcohol abuse and smoking produces a higher cumulative risk for CP [35]. An association between ICP and smoking has also been reported. Among patients in Italy, smoking increased the risk of pancreatic calcification and heavy smoking (>20 cigarettes per day) was associated with diabetes [36]. A report from the Mayo Clinic showed that smoking increases the risk of pancreatic calcification in LO-ICP but not in EO-ICP. However, smoking did not affect development of exocrine or endocrine insufficiency [37]. In patients with EO-ICP in southern India, smoking was an independent significant risk factor for diabetes according to a multivariate analysis [31].

Small Amount of Alcohol Intake

As mentioned above, in general ICP includes patients who drink small amounts of alcohol (<50 g per day). Lankisch et al. reported the effect of a small amount of alcohol intake on the clinical course of ICP. Patients with LO-ICP drinking less than 50 g of alcohol per day were younger at disease onset and reported more frequent and severe pain than patients with LO-ICP who did not drink any alcohol [9]. A systematic review and meta-analysis demonstrated a linear dose–response relationship between alcohol consumption and development of CP, which was monotonically increasing with no identifiable threshold [10]. This indicates that even intake of a small amount of alcohol is a risk factor for CP.

Genetic Factors

Associations have been identified between several gene variants and ICP risk. In idiopathic disease, full sequence analysis of the following genes has been recommended in international consensus guidelines: cationic trypsinogen (*PRSS1*), carboxypeptidese A1 (*CPA1*), serine protease inhibitor Kazal type 1 (*SPINK1*), chymotrypsinogen C (*CTRC*), carboxyl ester lipase (*CEL*), and cystic fibrosis transmembrane conductance regulator (*CFTR*) [5]. Variants of these genes are classified into three categories according to mechanisms in the pathogenesis of CP. Variants of *PRSS1*, *SPINK1*, and *CTRC* are involved in the trypsin-dependent pathway. Variants of *CPA1* and *CEL* are involved in the misfolding-dependent pathway, which is associated with protein misfolding and endoplasmic reticulum stress. Variants of *CFTR* are involved in the ductal pathway, which is related to disruption of chloride-bicarbonate channel activity in pancreatic duct cells [2,11]. Mutations in *PRSS1* and *CPA1* are associated with >300-fold and 25-fold higher risk of CP, respectively; thus, they are occasionally referred to as hereditary CP. The other gene variants have relatively low risk effects and are associated with sporadic CP with no family history [5].

A US multicenter study reported that 49% of patients with EO-ICP carried a pathologic variant associated with one or more of the following genes: *CFTR*, *SPINK1*, and *CTRC*. A *SPINK1* mutation significantly accelerated the onset of symptoms in the EO-ICP group, from age 22 to age 12 [13]. A study from India reported that the *SPINK1* N34S mutation was present in 42% of patients with ICP, which was significantly higher than the percentage in patients with ACP (17%) and controls (4%). This study also reported that 50% of patients with ICP and 10% of controls had *CFTR* variants [30]. Heterozygous *SPINK1* mutations reportedly do not cause pancreatitis. It appears that patients with heterozygous *SPINK1* mutations must also have a mutation in other susceptibility genes (e.g., *PRSS1* or *CFTR*) in order to develop recurrent acute pancreatitis (RAP) or CP [38].

Other Rare Causes

Pancreatic divisum

Pancreatic divisum (PD) is the most common congenital malformation of the pancreas. It involves a congenital disconnection between the main pancreatic duct and the major papilla. PD is classified as an obstructive cause of CP [3]. Although increased pressure in the dorsal pancreatic duct and minor papilla have been reported in PD, the majority of patients with PD are asymptomatic. Therefore, there is considerable debate as to whether it is causally associated with pancreatitis or abdominal pain [39]. Some reports indicate that the existence of a genetic cofactor plus PD leads to the development of CP. Garg et al. reported *SPINK1* mutations in 41.7% of patients with PD and ICP, which was significantly higher than 2% in healthy controls. They also reported that 41.7% of patients carried *CFTR* gene polymorphisms [40]. Bertin et al. reported the frequency of PD in patients with RAP or CP is significantly associated with *CFTR* mutations or polymorphisms [41].

Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) is a distinct form of pancreatitis. Therapeutically, AIP has a dramatic response to steroids. AIP is classified into type 1, which is a type of IgG4-related systemic disease, and type 2, which frequently accompanies inflammatory bowel disease [42]. Currently, the long-term prognosis of AIP is not well understood. However, an international study group reported pancreatic duct stones in 7% of patients with type 1 AIP, but not in patients with type 2 AIP [43]. According to a report from Japan, among 52 patients with type 1 AIP who had no pancreatic stones at diagnosis, 20 (38.5%) of them developed *de novo* pancreatic stones after 3 or more years of follow-up [44]. The relationship between AIP and classic CP will become clearer in the future.

Hyperparathyroidism

The causal relationship between primary hyperparathyroidism (hypercalcemia) and RAP or CP is debatable. A systematic review demonstrated AP or CP occurred in 1.5% to 15.3% of patients with primary hyperparathyroidism, but the included studies had confounding factors, biases, and a lack of appropriate controls. In addition, the authors suggested the pancreatitis in this setting is likely the result of additional genetic and environmental factors [45]. Aslam et al. reported that hyperparathyroidism accounted for 1.94% of RAP or CP cases. In patients with CP associated with hyperparathyroidism, severe pain was a predominant symptom. After parathyroidectomy and subsequent decreases in serum calcium levels, there was a reduction in their symptoms [46].

Hyperlipidemia

Hypertriglyceridemia is a well-established but underestimated cause of AP and RAP. However, whether hypertriglyceridemia can cause CP has not been well studied [47]. Vipperla et al. performed a retrospective study that reviewed the medical records of 121 patients with serum triglyceride levels of ≥500 mg/dL who experienced 225 attacks of AP between 2001 to 2013 at their institute in the United States. They found 20 (16.5%) of 121 patients were diagnosed with CP (9 with preexisting CP, 11 with new-onset CP during follow-up) [48]. Their relatively small single-center retrospective study needs to be validated in future prospective or large multicenter studies with simultaneous analysis of confounding factors such as alcohol intake and smoking.

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