24

Epidemiology of Chronic Pancreatitis

An Infrequent Disease or an Infrequently Diagnosed Disease?

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Why is Chronic Pancreatitis Epidemiology so Imprecise?

The epidemiology of chronic pancreatitis (CP) is much less precisely known than that of acute pancreatitis (AP). There are several reasons. AP is a clearly defined disease that is easily diagnosed, and then coded in databases, using classical criteria: characteristic acute abdominal pain, elevation of serum lipase over three times the upper limit of normal and, in case of doubt, typical images on computed tomography (CT).

On the other hand, CP is a long-lasting disease in which a formal diagnosis usually requires several years, a delay necessary for the development of ductal abnormalities or pancreatic calcifications. Clinical presentation may vary widely from one patient to another: CP might be diagnosed after one or several flares of AP, because of diabetes mellitus or exocrine pancreatic insufficiency, or after fortuitous discovery of pancreatic calcifications.

Classically, the natural history includes a number of different phases [1,2]. The first phase is preclinical without symptoms (or very mild nonspecific ones) during which it is supposed that histological lesions are already present. Acute bouts occur during the second phase but there are still no unequivocal signs of CP on imaging studies. During the third phase, acute bouts become rarer. Pancreatic calcifications and ductal abnormalities become visible and both endocrine and exocrine insufficiencies appear. Then, acute and chronic pain episodes decrease and the majority of patients develop diabetes mellitus or exocrine insufficiency. These different phases typically last 5–10 years but huge variations are seen, depending on the cause of CP, continuation or not of chronic alcoholism or tobacco smoking and, eventually, on individual variability (probably sustained by genetic polymorphisms and other environmental factors) [3].

Besides clinical variation, CP diagnosis is not easy. No simple and reliable diagnostic test exists for early CP and definitive diagnosis can take years to be obtained. Histology is usually not available, so the diagnosis of CP is primarily based on the demonstration of pancreatic ductal or parenchymal morphological and/or functional changes [4]. Diagnosis of CP is thus mainly based on imaging procedures such as magnetic resonance cholangiopancreatography (MRCP), CT, and endoscopic ultrasound (EUS). Functional testing of exocrine secretion in this context may help in cases with inconclusive morphological findings but is rarely used in clinical practice since values are often in the normal range, at least during the first phase of the disease [5]. CT is an accurate method for detecting pancreatic calcifications and main duct dilation, but is not effective for earlier pancreatic changes such as mild parenchymal changes due to fibrosis. MRCP, with or without secretin-induced stimulation of pancreatic secretion, associated with diffusion-weighted magnetic resonance imaging (MRI) or contrast (gadolinium)-enhanced MRI, allows accurate evaluation of pancreatic ductal and parenchymal changes.

EUS is currently considered the most sensible method for diagnosing CP as it demonstrates the presence and severity of pancreatic parenchymal and ductal changes with a high degree of accuracy [6]. The presence of five or more EUS criteria offers a high probability of CP diagnosis, whereas the diagnosis is unlikely in patients with none to two EUS criteria. Patients with three or four EUS criteria are in a gray zone where the disease can be overdiagnosed. However, EUS evaluation is subjective and there is a lack of standardization in terms of technique, nomenclature, and quantitative criteria used for CP. In addition, the use of EUS is questionable: it is an invasive procedure usually requiring general anesthesia or deep sedation, and sometimes several EUS procedures may be

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needed to obtain a firm diagnosis that frequently have no therapeutic consequences.

Last but not least, some issues remain unsolved.

- Until recently, AP, recurrent AP (RAP) and CP were considered as distinct diseases. This is now considered incorrect. They are part of the same spectrum. AP might evolve to CP whatever the cause [7]. For example, biliary AP was considered as the archetype of AP, never evolving to CP. This is also incorrect since all pancreatic necroses including pancreatic disconnection may lead to upstream CP with pancreatic calcifications and ductal abnormalities.
- Clinical and imaging manifestations may vary according to the cause. For example, hereditary CP usually starts in young children aged around 9 years old in both genders [8], whereas alcoholic CP becomes symptomatic between the ages of 35 and 50 years, mainly in men. Because of these clinical variations, several specialties might be involved in the care of CP patients, such as gastroenterologists, general or digestive or hepatobiliary-pancreatic surgeons, internists, pain specialists, diabetologists, or general practitioners. This underscores the difficulties of collecting valid data outside referral centers in which there is a huge recruitment bias.
- Some causes of CP have completely different physiopathological mechanisms leading to specific imaging and histological abnormalities. The best examples are autoimmune CP types 1 and 2 whose imaging characteristics are completely different from those of alcoholic CP for instance.
- Some imaging signs are considered pathognomonic for diagnosis of CP, such as pancreatic ductal calcifications. Once again a wrong assertion! Intraductal papillary mucinous neoplasms (IPMNs) are calcified in only 10–15% of cases, and pancreatic ductal calcifications are part of the diagnosis of acinar cell cystadenoma [9,10].
- Ductal anomalies evoking CP are sometimes very difficult to distinguish from those of main pancreatic duct IPMN. This is the same in obstructive pancreatitis upstream of an ampullary obstacle or a pancreaticodigestive anastomosis.

All these considerations explain why a formal and rigorous diagnosis of CP in clinical practice is rather difficult. However, for clinical trial or epidemiological studies, we need tools to achieve an appropriate and accurate diagnosis of CP at an early stage. Understanding whether or not a case of AP or RAP is the beginning of CP is not a clinical issue; the most important point is to find the cause and, as far as possible, to treat the cause to avoid subsequent episodes of the disease or to slow evolution.

Eventually, most cases of CP are identified from their clinical context (e.g. RAP in heavy alcoholics or in well-known families with hereditary pancreatitis) and confirmed several years later by abnormal duct imaging or pancreatic calcifications.

These data strongly suggest that CP is often misdiagnosed in excess or by default. That said, clinicians and researchers alike should examine the literature.

Epidemiology

The data on incidence and prevalence of CP are scarce and somewhat imprecise due to previously emphasized reasons. The reported incidence rates are roughly the same whatever country is examined, varying from 4 per 100 000 in the UK and United States to 13.4 per 100 000 in Finland, with intermediate incidence rates reported for Denmark (10), Poland (5.0), Germany (6.4), Czech Republic (7.8), and France (7.7) [1].

The crude prevalence of chronic pancreatitis was estimated at 26.4 per 100 000 inhabitants in France but this figure was probably an underestimate since the recruitment of patients was mainly performed by gastroenterologists and not by general practitioners or endocrinologists [11]. More recently, prevalence of CP was estimated in the commercially insured population of the United States. Of 48.67 million eligible enrollees, the age- and sex-adjusted period prevalence of CP per 100 000 was 73.4, 98.7 for adults and 8.3 for children. Prevalence of CP was slightly higher in males (sex ratio 1.05) and highest in the age group 46–55 years (135 per 100 000) [12]. In another study from United States in 2014, the prevalences of pediatric and adult CP were 5.8 and 91.9 per 100 000, respectively [13].

A study of the incidence and prevalence of CP was performed in Olmstead County, Minnesota, USA. In this county, nearly all medical care is provided by a central hospital and a single primary care center. This permits more complete insight into epidemiological data. Interestingly, this study provided estimates of incidence (4.05 per 100 000) and prevalence (41.8 per 100 000) [14].

Time trends of incidence are scarce. In a Finish study, incidence increased by 26% between 1977 and 1989 [15]. A study from China showed a marked increase in the prevalence of CP between 1996 and 2003 (from 3.08 per 100 000 to 13.52 per 100 000) [16]. The most recent study aimed at determining incidences of AP and CP, and the prevalence of CP, in children and adults with commercial inpatient and outpatient insurance from 2007 through 2014 in the United States. The incidence of CP decreased over time in children (2.2 per 100 000 in 2007 to 1.9 per 100 000 in 2014) and adults (31.7 per 100 000 in 2007 to 24.7 per 100 000 in 2014) [13].

Another means of understanding the epidemiology of CP is to assess the number of admissions. However, this methodology is associated with many flaws. First, all the criticisms made previously about the difficulties in performing the diagnosis are applicable. Moreover, all patients with CP are not hospitalized during one year, especially during late phases of the disease. That said, the age-standardized hospital admission rate of CP increased twofold in England between 1989–1990 and 1999–2000 (4.3 to 8.6 per 100 000) [17]. The same trend was observed in the Netherlands between 1992 and 2004, where admission rate increased by 75%. The incidence rate of CP increased over the same time period from 5.2 to 8.5 per 100 000 inhabitant-years [18].

We cannot exclude that this augmentation of admission rate was due to overdiagnosis of CP due to diagnosis at an earlier stage and better knowledge of physicians. There is also the risk of misdiagnosis due to the use of nonspecific criteria such as EUS criteria.

Why are Reported Data on Incidence and Prevalence of Chronic Pancreatitis Discrepant?

In the literature, there is a discrepancy between the incidence and prevalence of CP. In the French study, the estimated prevalence was 15 830 cases and the incidence was 4646 per year (crude annual incidence 7.8 per 100 000). These results would imply a duration of illness of around 3.4 years [11]. An older study in Poland (in a hospital setting) determined both incidence and prevalence and the ratio of prevalence to incidence suggested a duration of illness in the same range, which is far from clinical experience [19]. The study from Olmstead County, Minnesota gave figures more in accordance with life expectancy estimates for patients with CP [14].

CP patients are typically referred to a gastroenterologist or a surgeon for their first bouts of illness due to AP and abdominal pain. Later, pain is not usually a feature and AP is rarer. At that stage, the main problems encountered are pancreatic exocrine insufficiency and diabetes mellitus (and other consequences of alcohol and tobacco overuse), and long-term care is normally in the hands of general practitioners or diabetologists. These patients with long-standing disease are therefore invisible for studies recruiting via gastrointestinal specialists.

General Characteristics of Patients with Chronic Pancreatitis

The peak of incidence of CP is between 40 and 60 years of age, and there are no striking differences between countries or genders. Males usually represent 70–90% of patients. Chronic alcohol abuse is the prime cause, accounting for 70–80% of patients [11].

However, the cause of CP is multifactorial. As an example, only about 4% of chronic alcohol abusers will develop CP, underscoring the role of other factors. The M-ANNHEIM classification reflects the multiplicity of favoring factors: *a*lcohol consumption, *n*icotine consumption, *n*utritional factors, *h*ereditary factors, *e*fferent duct factors, *i*mmunological factors, and *m*iscellaneous and metabolic factors [20].

Mortality

In 1984, Ammann et al. [21] reported on 245 patients with CP. The median survival time in alcoholic CP was 20–24 years after disease onset. Lowenfels et al. [22] evaluated the survival of 2015 CP patients as part of an international multicenter study; overall survival was 70% at 10 years and 45% at 20 years. Cavallini et al. [23] followed 715 CP patients seen at the University of Verona, Italy for a median follow-up of 10 years. The 5-, 10-, 15- and 20-year mortality rates were 3, 13.7, 25.7, and 37%, respectively. Thuluvath et al. [24] studied 193 consecutive patients admitted to the Johns Hopkins Hospital, Baltimore, USA for the control of pain or complication of CP. The 5-, 10- and 15-year mortality rates were 14, 18, and 20%, respectively. Schnelldorfer et al. [25] followed 228 patients who underwent surgery for CP at the Medical University of South Carolina, Charleston, USA and found 1-, 3-, and 5-year survival rates of 97, 87, and 82%, respectively. Pedrazzoli et al. [26] followed 170 patients who underwent and survived surgery for CP in Padova, Italy for a median duration of 15.5 years. Death rate after 5, 10, 15, 20, 25, and 30 years was 15.3, 34.4, 48.4, 62.0, 71.9 and 76.5. The median survival was 15.5 years (95% confidence interval 13.3–18.5).

It is noteworthy that the majority of deaths (60–75%) is due to the extrapancreatic consequences of alcohol and smoking overuse (e.g. lung or esophageal cancer, liver cirrhosis, heart attack) rather than CP itself.

Only a single study has compared the mortality of CP with that of the population as a whole. A study in France compared the mortality and causes of mortality in 240 CP patients with that of a matched control group from the general population. The mean age at onset of CP was 41.5 years and the mean age at death for the 57 patients who died during 8.7 years of follow-up was 52.3 years. The excess mortality, compared with a matched French population, was 35.8% over a 20-year course of illness [27].

The median survival of CP patients is therefore between 15 and 20 years from onset.

Conclusion

The epidemiology of CP is not well known for a number of reasons:

- an unclear definition, which is complicated by a narrow distinction between AP and CP, when in fact they are two faces of the same disease;
- the absence of reliable and reproducible tools for early diagnosis;
- care which is performed by different medical specialties at different stages of the disease.

However, the incidence should be between 4 and 32 per 100 000 and prevalence between 26 and 99 per 100 000. These wide ranges reflect the imprecision of the figures. Males are overrepresented and the main cause is alcohol abuse, although interaction with other intrinsic or environmental factors, tobacco use being in the first rank, is necessary to explain CP onset. The excess of mortality is mainly due to extrapancreatic complications of alcohol and tobacco overuse.

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