

Chronic Pancreatitis: A Changing Etiology?

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Introduction

In 1998, Lankisch and Banks reported that the prevalence of chronic pancreatitis appeared to be in the range of 3-10 per 100,000 people in many parts of the world [1]. They also emphasized that the most important medical problems associated with the disease included abdominal pain, steatorrhea, diabetes mellitus and the possibility that chronic pancreatitis may be considered a premalignant condition [2, 3]. In 2002, in a well-written review, Banks pointed out that the two important forms were alcoholic and tropical pancreatitis [4].

There is no doubt that that, in Western countries, alcohol is the most frequent associated factor of chronic pancreatitis, that alcoholic chronic pancreatitis presents clinically in young adults of 30-40 years of age, with a higher prevalence of the male gender, that the histological lesions are chronic “*ab initio*” and that, from a clinical point of view, the disease is characterized by recurrent attacks of abdominal pain. In Western countries, in the period from 1940 to 2003, alcohol frequency increased as an etiological factor of chronic pancreatitis from 19 [5] to 50% [6] and even up to 80% [7, 8]. The results of the latter study regarding the etiology of chronic pancreatitis were subsequently confirmed by others in Europe [9, 10, 11, 12, 13, 14, 15, 16] as well as in Brazil [17], Australia [18] and South Africa [19]. On the other hand, four consecutive surveys carried out in Japan (from 1979 to

1977, from 1978 to 1984, in 1994, and in 1999, respectively) [20] showed that alcohol as an etiological factor accounted for fewer than 60% of the cases of chronic pancreatitis in this country. The study of Sarles *et al.* [8] reported that India is the most characteristic country in which patients with chronic pancreatitis were mainly malnourished in childhood, assuming a low fat and low protein diet; they were also not alcoholics. Thus, this particular form of the disease was named “tropical pancreatitis”. Subsequent studies from India and Africa confirmed this finding as was reported in the review article published by Mohan *et al.* in 2003 [21].

The Importance of the Etiology

From a practical point of view, understanding the pathogenesis may lead to the identification of novel molecular targets and the development of new potential therapeutic agents. Thus, the role of alcohol is the cornerstone of the pathogenesis of chronic pancreatitis, at least in Western countries. Durbec and Sarles [7] clearly demonstrated that alcohol is a risk factor for chronic pancreatitis; in fact, they showed that the relative risk would be multiplied approximately by a factor of 1.4 when passing from one 20-gram intake to the next. Furthermore, the increase appears to be more rapid when passing from the class of non-drinkers to that of 20-gram of alcohol intake per day. The mechanism which determines the main manifestation of chronic pancreatitis, i.e., fibrosis of the pancreatic

gland, has been well-summarized by Taludkar *et al.* [22]. In brief, the oxidation of ethanol to acetaldehyde determines the activation of the pancreatic stellate cells in the quiescent state without any pre-activation; this process generates a state of oxidant stress within the pancreatic stellate cells which subsequently activates the downstream pathways of the fibrogenesis. This finding implies that, in the human pancreas, pancreatic stellate cells may be stimulated early during chronic alcohol intake even in the absence of necro-inflammation. The importance of the oxidative stress in chronic pancreatitis patients has also been reported using breath analysis [23]. Regarding tropical pancreatitis, several hypotheses have been made, in particular, the malnutrition theory, the cassava hypothesis and the oxidant stress hypothesis [21]. Thus, also in this particular form of the disease, it is possible that there is activation by certain substances of the pancreatic stellate cells.

However, according to this postulated pathogenesis, alcohol seems to induce pancreatic fibrosis as has frequently been found in autopsic series of alcoholics without clinical history of chronic pancreatitis [24, 25, 26].

Furthermore, animal models of alcoholic chronic pancreatitis have not been able to induce pancreatic damage similar to that observed in human chronic pancreatitis; alcohol requires prior sensitization with other agents (viruses, obstruction) in order to produce damage similar to that found in humans.

In summary, alcohol represents a defined risk factor for chronic pancreatitis; it is capable of inducing pancreatic fibrosis by its action on the pancreatic stellate cells, but its role in the etiopathogenesis of the disease is still being debated.

New Advances in Etiology

Genetic Factors

The possibility of evaluating the mutations of the cystic fibrosis transmembrane conductance regulator-gene (CFTR-gene)

[27], as well as the discoveries of mutations of cationic trypsinogen gene (protease-serine-1 gene, PRSS-1) [28] and serine protease inhibitor, Kazal type 1 gene (SPINK-1) [29], has led to better evaluating the familial/hereditary forms as well as idiopathic forms of chronic pancreatitis in Western countries. In tropical pancreatitis it has also been noted that this disease has been highly associated with the SPINK-1 N34S mutation [30, 31] whereas the frequency of CFTR mutations was lower than in white subjects [32]. The PRSS1 mutations appear capable of inducing chronic pancreatitis whereas CFTR and SPINK-1 seem to be “gene modifiers” capable of inducing the disease in the presence of a risk factor such as alcohol [31, 33].

Autoimmune Diseases

In 1961, Sarles *et al.* [34] reported the case of a non-drinker suffering from pancreatitis associated with hypergammaglobulinemia. The authors hypothesized that the disease in this patient was an autonomous pancreatic disease of autoimmune origin. After this report, other authors around the world described similar cases. In 1995, Yoshida *et al.* [35] suggested the term “autoimmune pancreatitis” for this disease and, therefore, this term has become largely accepted for pancreatic disease of an autoimmune origin. In the past 10 years, an increasing number of cases have been reported in all countries [36] and the frequency of autoimmune pancreatitis will probably increase in the next few years.

Changing Lifestyle

The impact of changing lifestyle, especially in developing countries, may contribute to modifying the etiology of chronic pancreatitis. For example, alcohol consumption in developing countries may increase [37] and this could change the etiology of chronic pancreatitis in those countries. On the contrary, in Europe, there was a progressive reduction of alcohol consumption from 1961 to 1991 [38]. Furthermore, taking into account the lifestyle of chronic pancreatitis patients, it has been

reported that the pancreatic functional changes caused by alcoholic pancreatitis progress even after cessation of alcohol use, but the progression is slower and less severe when alcohol intake is stopped [39].

The Frequency of Change in Etiology

All these new factors and changing lifestyle may contribute to changing the frequencies of the various etiologies of chronic pancreatitis. This is the reason why, from 2004 to the present, the etiological features of chronic pancreatitis have been reported to be different than in the past. Four studies are examples of this. In Korea [40], the main etiological factor remains alcohol (64.3%) followed by an unknown etiology (20.8%), obstruction (8.6%) and autoimmune pancreatitis (2.0%). In a recent survey on chronic pancreatitis in the Asian-Pacific region [41] there was a great variability in the frequency of alcoholic pancreatitis, accounting for about 19% of chronic pancreatitis cases in China to 95% in Australia whereas tropical pancreatitis was 46.4% in China and, obviously, was not present in Australia. In a recent survey of chronic pancreatitis in Italy [42], chronic pancreatitis associated with alcohol abuse accounted for less than 50% of cases and this figure is lower than that reported by Gullo *et al.* in 1977 [9]. However, some regional differences regarding the frequency of alcoholic chronic pancreatitis exist in Italy. In fact, in Bologna (located in Northern Italy), alcohol as an etiological factor remains high (80.4%) [43] whereas, in Sicily (located in the Southern Italy), the percentage of alcoholic chronic pancreatitis is about 60% [44]. In a survey of chronic pancreatitis in Italy [42], alcohol as an etiological factor of chronic pancreatitis is followed by obstruction (27%), pancreatitis of unknown origin (17%), autoimmunity (4%) and hereditary/genetic factors (4%). The most surprising results come from India. In a prospective nationwide study in India [45], the authors found that the majority of patients had pancreatitis of unknown origin (60% of the cases); alcoholic chronic pancreatitis accounted for a third of the cases whereas tropical pancreatitis was

present in only 3.8% of the cases. It seems that alcohol tends to be increasing in frequency in India as is chronic pancreatitis of unknown etiology. However, the data reported by the Indian researchers (60% were idiopathic forms of chronic pancreatitis) need to be better re-evaluated. In this regard, it is worth noting that the frequency of unknown origin chronic pancreatitis is 17% in the Italian survey [42] ranging from about 12% in Bologna to 38% in Sicily [43, 44].

Conclusions

The evidence of recent surveys on chronic pancreatitis carried out around the world shows that alcohol remains the main factor associated with chronic pancreatitis, even if at a frequency lower than that reported in the past. Autoimmune pancreatitis accounts for 2-4% of all forms of chronic pancreatitis, but this frequency will probably increase over the next few years. The rise of idiopathic chronic pancreatitis, especially in India, represents a black hole in recently published surveys. Despite the progress made so far regarding the possibility of establishing the hereditary forms of chronic pancreatitis and the recognition of autoimmune pancreatitis, is it possible that we are more inaccurate today than in the past in identifying the factors associated with chronic pancreatitis in our patients?

Keywords Cohort Studies; Combined Modality Therapy; Data Collection; Genetics, Pancreatitis, Alcoholic; Pancreatitis, Chronic; Population

Conflict of interest The authors have no potential conflicts of interest

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