

CHAPTER

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Tropical Chronic Pancreatitis : An Update

V. Balakrishnan

Background

Chronic Pancreatitis (CP) is a worldwide disease. This disease is common in India, particularly in South India. Kerala state in India has the highest incidence of this disease. The etiopathogenesis of this disease is not clear despite a large number of studies conducted.

The term chronic pancreatitis implies a chronic ongoing irreversible destruction of the exocrine and endocrine tissues of the pancreas with morphological and functional changes. Acute and acute recurrent pancreatitis can often progress to chronic pancreatitis. The exact causes and mechanism of this progression is largely unknown. However many risk factors that can make the pancreas vulnerable to injury and damage have been postulated.

Alcoholic Pancreatitis

By and large, in Western countries and in Japan, the industrialized nations, alcohol has been found to be the major risk factor for CP. The association between alcohol and CP has been recognized since a few decades. This association has been established through epidemiological studies, observational and cohort studies, histopathological observations, electron microscopic study of biopsy tissues, from animal

experiments and by the study of autopsy material. These studies have shown that even though the risk of pancreatitis increases linearly with the increase in the quantity of alcohol consumed, no threshold level of alcohol intake has been shown beyond which pancreatitis occurs. Moreover, only about ten per cent of chronic alcoholics develop pancreatitis. The reasons for this have remained speculative. Additional genetic or dietary factors have been proposed in the past to account for this incongruity. More recent work has thrown light into the possible association of certain genetic mutations with chronic pancreatitis. The ball was set rolling by David Whitcomb when he discovered in 1996 that mutations in the PRSS1 gene were associated with the hereditary form of pancreatitis. However, subsequent work did not confirm an association between PRSS1 gene and either alcoholic or idiopathic forms of pancreatitis. Even so, later work has indicated an association between certain other genetic alterations, notably mutations in the SPINK1 and CFTR genes, with alcoholic as well as idiopathic pancreatitis.

Again, recent work has clearly shown an independent association between smoking and chronic pancreatitis. Thus, smoking is now considered, along with alcohol, an additional risk factor for chronic pancreatitis. There is enough epidemiological evidence too to incriminate

smoking as a strong risk factor in the progression of chronic pancreatitis to pancreatic cancer.

Yet another risk factor considered in the etiology of CP is dietary changes. A very high fat and high protein diet has been demonstrated by the Marseille group of Prof. Henri Sarles to be a risk factor for CP, while a very low fat intake also confers a risk for CP, second only to a high fat diet.

Chronic alcoholic pancreatitis in the West is now hypothesized to follow an acute or recurrent acute episodes of pancreatitis, initiated by aggressive factors such as alcohol and smoking, facilitated by weak defensive factors secondary to genetic mutations, and perpetuated by immunological changes, triggering of release of cytokines, tissue damage, more cytokine production, stimulation of pancreatic stellate cells, laying down of collagen and conversion to fibrous tissue. Extensive destruction of acinar tissue and later the islets of Langerhans, the endocrine tissue, and widespread fibrosis complete the picture of chronic pancreatitis.

Alcoholic pancreatitis constitute about 70% of CP in Western countries, another 10 to 15% are due to miscellaneous causes and around 15 to 20% are idiopathic, where the etiology cannot be determined by any of the known investigating modalities.

Tropical Pancreatitis

While Western workers had been preoccupied with the problem of alcoholic pancreatitis, a new form of pancreatitis had emerged in the deprived countries of Asia and Africa which is distinguished by its occurrence in the young, including children and adolescents, absence of a history of alcoholism and smoking, malnutrition, rapid progression, early development of diabetes mellitus and its complication, and death at the prime of life. This disease or syndrome was first described by Zudeima from Indonesia, though the first large series of cases were described from Kerala state in India by Prof. Geevarghese in the early sixties from the Trivandrum and Kottayam Medical Colleges in Kerala. Subsequently, there were many other

reports of similar patients from other parts of the state. The high prevalence of this unique disease in Kerala state and the absence of reports from most other parts of India presented an enigma not only to workers in India, but also from other parts of the world. The uniqueness of this disease and its peculiar geographic prevalence prompted the ICMR to start an ICMR Cell in the Medical College, Trivandrum during the sixties to study this disease further. As a result of the work of this Cell and the perseverance of Dr. Geevarghese and colleagues, the clinical features of the disease were largely characterized and several papers were published on the clinical features, the pathology and surgical treatment of this peculiar malady. However, the etiology of the disease remained a mystery. Meanwhile, there were a few reports of tropical pancreatitis, even though involving lesser number of patients, from Tamil Nadu, Karnataka and Andhra Pradesh, all from the South India, and surprisingly, none from the North. The only exception was the state of Orissa, from where Prof. B.B.Tripathy and his colleagues described a number of young malnourished diabetic patients who had pancreatic damage of varying degrees. In the ensuing years, reports of chronic pancreatitis with diabetes mellitus started coming in from several Asian countries such as Indonesia, Thailand, Ceylon (Sri Lanka), Malaysia and African countries such as Nigeria, Uganda, Ghana and Ivory Coast.

The common denominators of these countries were that they were all in the tropics, the standard of living and hygiene were poor, the diet was suboptimal, malnutrition was rampant and protein deficiency common. Another interesting observation was that cassava, a tuber very rich in carbohydrate and with negligible protein content was widely cultivated and consumed as a staple food by the population in these countries. These observations gave rise to a hypothesis that this disease was a consequence of protein malnutrition and/or perhaps as a result of cassava consumption in the diet. A cassava-based diet could lead to deficiency of protein and essential amino acids and

in addition, the cyanogenic content of many varieties of cassava (*Manihot esculenta* Crantz, tapioca) could be toxic to tissues, especially to the pancreatic tissue which has a high protein turnover. Moreover, the sparse essential amino acids methionine and cysteine, available in a malnourished person, are used up in the detoxification of the cyanogenic glycosides of cassava, resulting in a deficiency of these amino acids, thus depriving the pancreatic tissue, which has one of the highest protein turnovers in the body, of these essential amino acids.

Thus for a long time, protein malnutrition and cassava hypotheses held sway as etiological factors of this disease. As the etiology was only a matter of speculation, and since there were no other diagnostic markers for this disease, for the sake of differentiating it from the well characterized alcoholic pancreatitis, a convenient but inaccurate term of tropical pancreatitis was applied to refer to this disease. This term was obviously illogical, as we were comparing alcoholic pancreatitis (AP) named so based on etiology, to tropical pancreatitis (TP), named so on the basis of geographical prevalence.

Meanwhile, the endocrinologists were concentrating on the diabetes complicating this disease, and they emphasized the relation of the diabetes to malnutrition and thus the concept of malnutrition-related diabetes received coinage. In 1985, the World Health Organization (WHO), in a technical report on the revised classification of diabetes, introduced a new subtype of diabetes, "Fibrocalculous Pancreatic Diabetes" (FCPD), which has been considered by many workers as synonymous to "tropical pancreatitis" with diabetes. It was perhaps, a matter of semantics. The WHO thus endorsed malnutrition as a cause of pancreatic diabetes.

The World Health Organization in a Technical Report in 1985 described two types of diabetes mellitus, Fibrocalculous Pancreatic Diabetes mellitus (FCPD) and Protein-deficient pancreatic diabetes (PDPD). The former had pancreatic damage

with fibrosis, exocrine deficiency and pancreatic calcification, the latter without calcification or pancreatic exocrine deficiency, but associated with severe malnutrition.

A consensus conference conducted in Cuttack, Orissa in 1995 subsequently agreed upon to replace the term PDPD with the term malnutrition-modulated diabetes mellitus (MMDM). Most of the workers in this area are now agreed that TP and FCPD are the same disease, one in which diabetes has not yet developed, the other in which diabetes has set in. However this is an area of controversy - whether the two diseases are different stages of the same disease, or are two different diseases.

Our group has been engaged in studies into the etiology and pathogenesis of tropical pancreatitis over the past thirty and odd years, initially at the Medical College, Trivandrum, and now at the Amrita institute of medical Sciences at Cochin.

Examination of the theories of causation of tropical pancreatitis

Even though a geographical association has been observed between tropical pancreatitis and protein malnutrition, this association is not always consistent. There are many deprived populations, for example in Africa where TP is not seen. On the other hand, in the neighboring state of Tamil Nadu, TP has been described in better nourished subjects from the higher socioeconomic class. Moreover in the classical prototype of protein malnutrition, Kwashiorkor, typical changes of TP are not seen in the pancreas. In this condition the pancreatic changes are essentially reversible. Hence protein deficiency does not seem to be the major etiological factor in TP. In a case control study conducted by us, the protein intake by patients with TP, and age and sex matched controls from the same socioeconomic class and geographical region, did not differ significantly.

Similarly, even though there is considerable geographical overlap between cassava cultivating and consuming countries and regions of TP

endemicity, this correlation is not always borne out. There are many non-cassava eating populations who suffer from TP, such as in Tamil Nadu or Orissa, and similarly, many populations that are cassava eaters who do not contract the disease as in some of the African countries. Case control studies by our group and others have failed to show a positive correlation between cassava consumption and TP. A few cassava feeding studies in experimental animals have also not been successful in reproducing changes similar to those seen in TP. Even so, the contributory role of cassava in the progression of tropical pancreatitis cannot be completely excluded.

To summarize, while it is possible that protein malnutrition or toxins from cassava and similar cyanogen containing foodstuff intake might have an additive role, by available evidence, they by themselves do not seem to be the sole or major etiological factors in the causation of TP. This area needs to be explored further.

One of the remarkable features of TP noticed by all workers is the familial occurrence of the disease. There are many families with multiple affected members, including parents and siblings; and the high prevalence of TP in Kerala population compared to the rest of India and its occurrence in migrant Keralites in other parts of India and even abroad lend support to a theory of inheritance. However, early studies have not revealed a specific pattern of inheritance. Our studies on HLA antigens in TP patients with a family history of TP showed a higher frequency of AW10 and AW19 haplotypes in patients as well as other family members. In addition, we have noticed the common occurrence of non-calcific pancreatitis, type II diabetes and pancreatic cancer in family members of TP patients. When we were working on this problem many years earlier, we did not have the tools to study genetic factors. Work during the last two decades, spurred on by the discovery of the mutation of PRSS1 gene in hereditary pancreatitis, has shown an association between chronic pancreatitis - alcoholic, idiopathic and tropical- with mutations in the SPINK1 gene. In fact, Spink1 mutations have

been shown to be present to the tune of up to 4% in the normal population in our country. However, the disease occurrence is not proportionate to the high mutation frequency in the population; hence this genetic defect is now considered a disease modifier rather than the cause of the disease.

Another gene mutation that is under investigation in TP is the Cystic Fibrosis Transmembrane Conductance Regulator gene (CFTR). This gene controls the chloride-bicarbonate exchange in the pancreatic ductules and mutations result in an inspissated pancreatic juice prone to protein plug formation with subsequent calcification and calculus formation. It has been shown that a combination of SPINK1 and CFTR mutations in an individual raises the risk of developing chronic pancreatitis five hundred fold. Other candidate genes under study in the causation of chronic pancreatitis include the CASR (calcium sensor regulator gene), the Cathepsin B gene and the Cytokine gene. In a recent publication, our group has reported the presence of CASR mutations, SPINK1 mutations and a combination of both mutations in tropical pancreatitis.

Why is it important to investigate into the etiological factors of tropical pancreatitis?

Tropical pancreatitis has a very high incidence in the state of Kerala, and if we go by reports, perhaps the highest incidence in the world. What is the reason for this high prevalence? Are there environmental factors? Are there genetic factors? Are both these groups of factors interacting? If there are environmental factors that we could identify and if these are remediable, timely intervention might bring down the incidence of the disease. If there are genetic factors, one could offer genetic counseling, or by early detection of the disease, try genetic manipulations and try to abort the disease. Again it might be possible to identify a susceptible population and educate them regarding preventive measures.

Second, by identifying some of the etiological agents and the pathogenetic mechanisms, we may

be able to advance our knowledge about pancreatitis in general and about fundamental concepts on the genesis of pancreatitis. Having a highly susceptible population with a high endemicity of the disease, Kerala state may provide the right setting to study this disease in depth and prove some of the hypothetical issues in the initiation and progression of the process of chronic pancreatitis. It is possible that as in the case of the liver, even though the initiating injury may be different in different types of pancreatitis, say, alcoholic, idiopathic, autoimmune or tropical, the further course and perpetuating factors might be common to these different forms.

The problem of malignancy in tropical pancreatitis

It has been observed from the early years that tropical pancreatitis is a pre-malignant condition. Early workers such as P.A. Abraham, reported the high incidence of malignancy in operated cases. In our own series, operated by Prof. N. Rajan, there was a high incidence of carcinoma complicating pancreatitis. This observation has been confirmed by many later workers. Malignancy complicating TP occurs at a much younger age than de novo malignancy of the pancreas and is rapidly fatal. Surgery is of no avail. There are no markers for the early diagnosis of this complication. It has been quoted that TP has a hundred fold increased risk of developing pancreatic cancer than controls.

The impact of newer developments

Current thinking is that chronic pancreatitis most probably results from an interaction of genetic and environmental factors. If a genetically susceptible person is exposed to environmental factors such as alcohol, smoking, food toxins, environmental pollutants etc, there is initial injury to the pancreas. This results in premature activation of trypsin, which causes injury to pancreatic tissue. In the presence of genetic abnormality the activated trypsin cannot be destroyed as happens in a normal person. This lack of protection leads to pancreatic injury by the

injurious external agents with cytokine release, oxidant stress, etc., which results in pancreatic damage. Thus acute pancreatitis results. In persons in whom the injurious agents are removed and whose immune functions are normal the gland fully recovers from the injury. In those with recurrent or continuing injury, abetted by inappropriate immune responses, leads to perpetuation and progression of the damage and leads to chronic pancreatitis. In this process, cytokine release, oxidant stress, pancreatic stellate cell activation, laying of collagen tissue, fibrosis and further destruction of the gland, all occur in a cascading fashion resulting in a chronically destroyed gland. Many of the intermediate molecular events in this over-simplistic model are still poorly understood and require in depth studies.

We have also to study what are the peculiar factors that operate in the case of tropical pancreatitis.

Recent change in the epidemiological pattern of chronic pancreatitis

Three interesting developments in TP observed in recent years are:

1. The changing pattern of the disease. The disease is now seen to occur about one to two decades later i.e., in adults in contrast to early observations in children and adolescents. The diabetes is milder and in many instances controlled with oral hypoglycemic drugs. Patients now live longer. However the rate of malignancy does not seem to have come down.
2. Lesser quantities of cassava are now consumed by our population. And fewer people consume it regularly. This is due to better purchasing power, easier availability of cereals and improved public distribution system. Alcoholism and smoking have become widely prevalent in India and particularly in Kerala state during the last two to three decades.. About one third of the chronic pancreatitis patients we see now are labelled as "alcoholic pancreatitis". More than 80% of them

are heavy smokers. The non alcoholic chronic pancreatitis we now see are older and better nourished than the classic cases of tropical pancreatitis that we used to treat two or three decades earlier. Even in our “non alcoholic” pancreatitis, a good number now drink alcohol in quantities that are small or moderate, not enough to earn them the label of “alcoholic” pancreatitis. They also smoke moderately. We suspect that even such moderate drinking and smoking are contributory furthering pancreatic damage. They may also be contributory to the changing clinical characteristics of the disease observed by us.

3. Two to three decades back the disease was restricted to Southern Indian states such as Kerala, Karnataka, Tamil Nadu and Andhra Pradesh with Kerala perhaps having the highest reported incidence in the world. The only other region in India from where the disease has been reported in large numbers was Orissa in the east where it has been described as malnutrition-related diabetes mellitus. The reason for this peculiar geographical distribution was not clear. However, in recent years there are reports of TP coming in from some of the North Indian centres such as Delhi, Lucknow and Chandigarh and even countries like Bangladesh and China, which strictly are outside the tropics. The reasons for this geographical change in the disease incidence is unknown. Perhaps this changing pattern might offer some insights into the etiological factors of the disease.

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