

Chapter 4

**Chronic pancreatitis: the AIIMS,
New Delhi experience**

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Summary

Tropical pancreatitis is a special type of chronic pancreatitis that is seen mainly in tropical countries. The prevalence of tropical pancreatitis is not known in northern India. The etiology is not known; genetic mutation such as SPINK1 gene mutation and environmental factors are the likely culprits. We have found SPINK 1 mutation in about 40% of our patients with idiopathic chronic pancreatitis. The disease usually affects young patients. Clinically, >90% of patients present with abdominal pain. About 25% of patients develop diabetes that generally requires insulin for its control but is ketosis resistant. Painless diabetes is another clinical presentation in some patients. Most patients develop malnutrition during the course of the disease. We have found that malnutrition is not a cause but an effect of the disease. Steatorrhoea is less common. The diagnosis can be established by plain x-ray of the abdomen, ultrasonography, a computerized tomography scan of the abdomen or ERCP. Management is directed towards pain relief and control of diabetes and steatorrhoea. Pain relief can be obtained by analgesics and enzyme supplementation with high protease content. Endotherapy coupled with stone fragmentation by ESWL is an effective therapy in about 50% of our patients. Surgical decompression of the main pancreatic duct by lateral pancreato-jejunostomy is reserved for patients with severe pain non-responsive to other forms of therapy.

Introduction

Tropical pancreatitis (TP) is a type of chronic pancreatitis seen in tropical countries and is characterized by pancreatic calcification and ductal dilatation in a young malnourished patient who presents with abdominal pain and/or diabetes¹. Initially described from Indonesia,² it has been reported from many other tropical countries including India, Nigeria, Uganda, West Indies, Kenya, Sri Lanka, Madagascar and Zaire^{3,4} and recently from other parts of India (6) and other countries such as China (7). It has been called by a variety of names such as chronic calcific pancreatitis of the tropics, juvenile tropical pancreatitis syndrome, idiopathic chronic calcific pancreatitis of the tropics, nonalcoholic tropical pancreatitis and nutritional pancreatitis. The largest series has however, been described from South India by Geevarghese⁷.

Epidemiology and clinical features

The prevalence of tropical pancreatitis is estimated to be ~126/100,000 population) in southern India according to a survey conducted by Balaji et al from the department of Gastroenterology, AIIMS, New Delhi (8). This is in contrast to the estimated prevalence of chronic pancreatitis of around 10-15/100,000 population in several western industrialized countries and 45.4/100,000 population in Japan ^{9,10}. Such a high prevalence of chronic pancreatitis in India suggests that it is an endemic zone for CP and points towards a possible genetic and/or environmental factor as playing an important etiologic role.

Most patients with CP are young in our experience, the mean age being 36.7 years. The majority of patients were male i.e. 80%. The duration of disease from the time of presentation to the hospital was 48 months.

Pain was the most common mode of presentation, being present in 97% of patients. The prevalence of diabetes in patients with CP was 31% but the prevalence of clinical malabsorption (maldigestion) was much lower at 5% (Table 1).

Among the complications (Table 2) of CP, pseudocysts were present in 32% of patients, bile duct stricture in 3.5% of patients, and splenic vein thrombosis in 7% of patients. The prevalence of cancer was in 2.2% of patients with TP.

The clinical features of hospital based TP patients also differed from those of alcoholic pancreatitis in many respects (table 3).

How is TP different from other forms of chronic pancreatitis?

The following features in a patient are characteristic of TP and distinguish it from other types of CP: young age of onset, residence in tropics, no history of alcoholism, no other discernible cause of CP, negative family history of pancreatitis, large duct disease with ductal dilatation, large pancreatic calculi predominantly in the head region, presentation with chronic abdominal pain, diabetes which is insulin requiring but ketosis resistant and finally, the coexistence of malnutrition.

Etiology

Tropical pancreatitis forms about 59 % of all our patients with chronic pancreatitis⁶. The etiology of tropical pancreatitis is not known and is still considered idiopathic. However, certain potential etiological factors have been identified. Among them, genetic predisposition is most likely. These factors are discussed below.

Malnutrition

Protein calorie malnutrition has long been suspected as a likely cause for TP because of the fact that the disease occurs predominantly in tropical countries where malnutrition is common and because of the reports from some of them including India, Uganda and Nigeria reveal that 80-90% of the subjects with calcific pancreatic come from poor socio-economic strata. Chronic protein undernutrition leads to structural as well as functional alterations in the pancreas. It also makes females more susceptible to pancreato-toxins. However, severe malnutrition is not associated with chronic pancreatitis but with pancreatic atrophy and insufficiency^{11,12}.

In a prospective study of 105 north Indian patients with chronic pancreatitis, we found that the mean BMI of patients was 22.89 ± 3.28 which was similar to that of controls. Only 12% of patients had a BMI <18.5. On the other hand, 80% of patients lost weight following the onset of disease and the percentage of patients with BMI <18.5 increased from 12% to 52%. The causes of weight loss were found to be (i) significant decrease in calorie intake due to pain compared with the recommended intake (1437 ± 574 vs. 2605 ± 313 kcal), (ii) subclinical steatorrhea in 60%, and (iii) diabetes in 29%. These data suggested that malnutrition was not a cause but an effect of tropical pancreatitis¹³.

Environmental toxins

The toxic hypothesis has been centered on consumption of cassava which has cyanogenic glycoside and is used liberally in southern India where TP is endemic.¹⁴ This theory has also not found wide acceptance because

of the following reasons: (i) cassava does not feature in the diet of many people who develop TP; (ii) there was no difference in cassava consumption between patients with TP and those without¹⁵; (iii) patients with TP from northern India do not consume cassava, and (iv) long-term cassava consumption did not produce diabetes or pancreatitis in a rat model¹⁶.

Free radical Injury

Braganza et al have shown that patients with alcoholic pancreatitis as well as other forms of chronic pancreatitis including TP are deficient in antioxidants and hence are more vulnerable to free radical injury¹⁷. They have further shown that supplementation with antioxidants may result in a significant decrease in analgesic requirements in patients with alcoholic pancreatitis¹⁸. We have also found that patients with TP do have increased free radical mediated injury as evidenced by high levels of malondialdehyde and decreased anti-oxidant levels¹⁹. In a recent ongoing study on the oxidative stress (OS) and total antioxidant capacity (TAC) in 48 consecutive patients with TP, we measured oxidative stress by lipid peroxidation products (LPO) and superoxide dismutase (SOD), and antioxidant capacity by Ferric reducing ability of plasma. Our results showed that patients with chronic pancreatitis had increased oxidative stress and decreased antioxidant capacity (Figure 1, 2)

Genetic factors

The landmark discovery by Whitcomb et al of a mutation in the gene for cationic trypsinogen on the long arm of chromosome 7 (7q35) in patients with hereditary pancreatitis verified the long held belief that a genetic defect underlies hereditary pancreatitis²⁰. A lot of interest has recently been generated in the possibility that there may be a genetic basis for TP because of the following similarities between TP and hereditary pancreatitis: (i) both diseases affect young individuals; (ii) calcification is very common in both; and (iii) there is an increased risk of pancreatic cancer in both. Moreover, Indians born in Kerala, but residing outside India continue to have an increased prevalence of TP¹⁵. An association of HLA DQ 9(A*0201-B*03003) has been shown with TP and diabetes (FCPD or fibrocalculous pancreatic diabetes)²¹. However,

one study from Bangladesh failed to show any mutation of the cationic trypsinogen gene among 13 patients with TP²². Another study did not find cationic trypsinogen gene mutation in 46 patients with FCPD²³.

Two groups demonstrated that the expected frequency of CFTR gene mutation was much higher among patients with idiopathic chronic pancreatitis i.e. 2.5 and 11.5 times the expected frequency seen in the general population^{24,25}. Affected patients with chronic pancreatitis were shown to have single gene CFTR mutations and/or 5T allele in intron 8 which resulted in a reduced activity of CFTR. In patients with typical cystic fibrosis, there are severe mutations affecting both alleles; the result is pancreatic insufficiency caused by atrophy of the pancreas. On the other hand, a mutation affecting only one allele may result in diseases such as chronic pancreatitis while retaining 'pancreatic sufficiency'.

More recently, a mutation in the pancreatic secretory trypsin inhibitor (PSTI, also known as serine protease Inhibitor Kojal type 1 or SPINK1) (N34S, chromosome 5) was found in 23% of patients with idiopathic pancreatitis versus 2% in the general population²⁶. SPINK I inhibits trypsin within the pancreas but accounts for inactivation of only ~20% of all activated trypsin²⁷. It is therefore unlikely that the SPINK I mutation alone will cause pancreatitis, but it might be a disease modifier lowering the threshold for pancreatitis²⁸. SPINK 1 mutation has been found in 32-44% of patients with TP from India^{29,30}.

We have analysed patients with chronic pancreatitis for common CFTR and SPINK1 gene mutations. One hundred patients with TP were studied for SPINK1 N34S mutation and CFTR gene mutation for Delta F508 and Intron 19 (3849+10 Kb C>T) and common variant of poly (T) sequence in intron 8 of *CFTR gene* (5T, 7T, 9T). We found 40% of patients having SPINK 1 gene mutation (table 4).

At present, intense search is on in many laboratories around the world to discover more mutations in patients with CP. There is every possibility that, in the near future, the genetic basis of CP will be further clarified. Further genetic analyses are also urgently required in patients with TP.

Diagnosis

The diagnosis of TP is based on a combination of clinical evaluation and imaging studies. In advanced disease, a plain film of the abdomen or a contrast enhanced computerized tomography (CECT) may show the pancreatic calcification and establish the diagnosis. In early cases, demonstration of ductal changes through endoscopic retrograde cholangio-pancreatography (ERCP) or magnetic resonance cholangio-pancreatography (MRCP) will establish the diagnosis. Pancreatic function tests are indeed the most sensitive tests to detect earliest changes in the exocrine pancreas³¹ but they may be abnormal in any cause of pancreatic insufficiency e.g. cystic fibrosis and not necessarily in chronic pancreatitis. Endoscopic ultrasonography has been touted as the most sensitive method of detecting earliest changes of pancreatitis in the parenchyma but its value remains to be established (Figure 3)³². The gold standard for diagnosis is histopathology but that is rarely obtained unless the patient undergoes a pancreatic resection.

Consequences of tropical pancreatitis

Tropical pancreatitis can lead to endocrine and exocrine insufficiency like any other chronic pancreatitis, the difference being that the degree of functional impairment is much more pronounced and early in tropical pancreatitis compared with other forms of chronic pancreatitis. Exocrine impairment leads to maldigestion and steatorrhea. Clinical steatorrhea is uncommon even in patients with advanced TP largely due to restriction of fat consumption by the patients. Steatorrhea can be managed well with supplementation of oral pancreatic enzymes with high lipase content.

Endocrine insufficiency leads to pancreatic diabetes. Diabetes is present in 25-90% of patients with tropical pancreatitis. Such a wide difference in the prevalence of diabetes is mainly due to the referral pattern. Patients presenting with diabetes as the major clinical problem get referred to diabetes clinics and data coming from such clinics often report a high prevalence of diabetes in patients with TP. On the other hand, diabetes is prevalent in about 31% of patients with TP in our gastroenterology clinic. There are many special characteristics of diabetes in TP which are discussed below.

Diabetes in TP

Patients with TP develop diabetes during the course of the disease. Patients with calcification are more likely to develop diabetes. Overall, up to 60% of patients with TP may develop diabetes. Many patients with painless TP present primarily with diabetes. These patients are initially misdiagnosed as having insulin requiring diabetes mellitus (IDDM). Fibrocalculous pancreatic diabetes (FCPD) is the term given to patients with painless calcific pancreatitis with diabetes³³. FCPD was earlier classified as malnutrition related diabetes mellitus (MRDM) by the WHO because most of the patients with FCPD are malnourished. Diabetes in patients with tropical pancreatitis is described as particularly severe, requiring high doses of insulin. Diabetes may be brittle in patients with TP with frequent episodes of hypoglycemia. This may be due to concomitant exocrine insufficiency. Patients with pancreatic diabetes usually require insulin for its control but the characteristics feature is that they are ketosis resistant even if insulin is withheld. The possible reasons for ketosis resistance are better insulin reserve compared with IDDM and low glucagon response to glucose load^{33, 34}. It was believed that more than 90% of patients with TP would require insulin for the control of diabetes. However, the current experience has shown that up to one third of patients of patients can be managed with oral hypoglycemic agents⁶. The insulin requirement was also thought to be very high up to 100 units per day but it has been shown that the majority of patients can be managed with regular doses of insulin. Patients with diabetes and TP may develop all macro- and micro-vascular complications of poorly controlled diabetes if they survive long enough³³.

Management

Medical treatment of TP is similar to that of any chronic pancreatitis and is aimed at relieving pain and steatorrhea and controlling diabetes¹.

Pain relief

For pain relief, initially non-opioid and later, opioid analgesics are used. Another approach has been to use pancreatic enzymes (proteases) based on the understanding that delivering these enzymes in the duodenum

could result in suppression of cholecystokinin (CCK) and hence a decrease in pancreatic exocrine secretion. Their role in relieving pain is however, questionable. The results of a meta-analysis of 6 randomised controlled trials showed no benefit of enzyme therapy in relieving pain³⁵. However, non-enteric coated pancreatic enzyme supplementation may relieve pain in patients with small pancreatic duct disease, idiopathic pancreatitis and in female patients³⁶. The Asia-Pacific consensus report on chronic pancreatitis also suggests pancreatic enzymes and non-opioid analgesics as the initial therapy for pain relief in patients with chronic pancreatitis¹.

Use of antioxidants has also been suggested recently for pain relief in chronic pancreatitis. A combination of antioxidants containing at least 2 grams of methionine per day may help relieve pain if continued for about a year³⁷. We have also shown that anti-oxidant supplementation relieves pain in tropical pancreatitis³⁸.

Surgery is required predominantly for intractable pain in about a third of patients. Its results are good only in patients with dilated ductal system which is the case in the majority of TP patients. The most common operation performed is lateral pancreateojejunostomy (modified Puestow's operation). In a study from our department, relief of pain was obtained in 90% of patients at 3 months after the operation and this relief was long lasting (5 years) in 82% of patients³⁹. The results of surgical drainage are less gratifying in chronic pancreatitis in the western world⁴⁰, as the predominant etiology there is alcohol abuse and the behaviour of alcoholic chronic pancreatitis may be different from that of TP.

Endoscopic therapy

What has been achieved by surgery can now be done by endoscopy. Thus, dilated pancreatic ductal system can be decompressed by endoscopic sphincterotomy and pancreatic ductal stone clearance by a combination of basketing and extracorporeal shock wave lithotripsy (ESWL). And these maneuvers have indeed yielded gratifying results. Various endoscopic series have reported 50-70% success for clearing the main pancreatic duct and 60-80% long term pain relief with

complications of <10%⁴¹⁻⁴³. We have also found good results of endotherapy in ~60% of patients with tropical pancreatitis⁴⁴. The results of endoscopic treatment are comparable with the surgical results but the problem is that all endoscopic series have been case series and no controlled prospective trial is available. Furthermore, long term results need to be interpreted in the light of the fact that many patients get spontaneous relief from pain due to “burning out of the disease”⁴⁵. Thus, it is important to find out the true benefit of endoscopic therapy in the long run. Randomized controlled studies comparing endoscopic and surgical treatment modalities are required. Till such time that these studies become available, however, most endoscopists would prefer giving a trial of endoscopic therapy before subjecting the patient to surgery if the medical therapy has failed as the initial results of endoscopic therapy are encouraging and the patients prefer less invasive procedures. One study has recently been published which has shown comparable results of surgical and endoscopic treatment for pain relief in chronic pancreatitis⁴⁶.

Conclusion

TP is a type of idiopathic CP that occurs in the tropics, but is also seen in northern India. It affects young patients. Its diagnosis is established by clinical evaluation and imaging, particularly plain film of the abdomen, ultrasound and/or CT scan of the abdomen showing pancreatic calculi. Many etiological factors have been suspected but genetic mutations, especially in the SPINK 1 gene appear as the most likely cause. Treatment is aimed at relieving pain and steatorrhoea and controlling diabetes.

Fig. 1: Oxidative stress in patients and controls

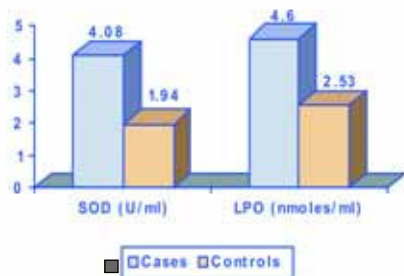


Fig 2: Antioxidant status of patients and controls

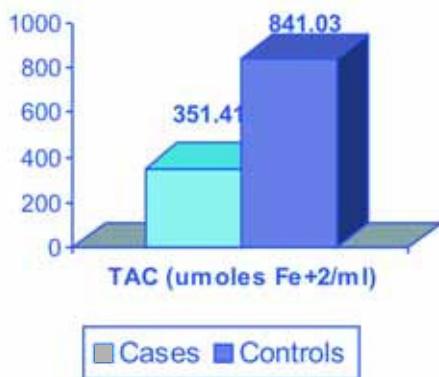


Fig. 3: EUS picture of (A) normal pancreas and (B) early chronic pancreatitis with honeycombing appearance

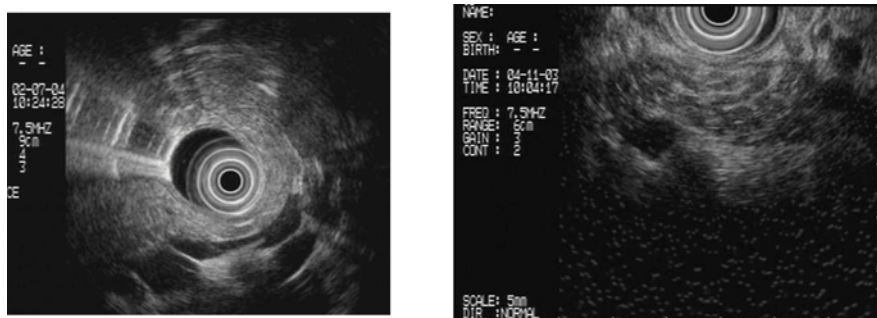


Table 1: Clinical features of patients with chronic pancreatitis

No. of patients	359
Mean age (years)	36.7
Sex (male : female)	4:1
Duration of disease (months)	48
Pain (%)	97
Diabetes (%)	31
Steatorrhea(%)	5

Table 2: Complications of chronic pancreatitis

Pseudocyst (%)	32.0
Bile duct stricture (%)	3.5
Splenic vein thrombosis (%)	7.0
Cancer (%)	2.2

Table 3: Comparison of Idiopathic with Alcoholic pancreatitis

	Idiopathic(%)	Alcoholic(%)	'p'
Acute pain	24	61	<0.05
Chronic pain	73	36	
Calcification	88	50	<0.05
Diabetes	23	11	
Pseudocyst	25	36	
Steatorrhea	2	1	

Table 4: Gene mutations in chronic pancreatitis

Gene tested	Mutation	Homozygous	Heterozygous
CFTR (n=100)	DeltaF508 3849+10kb C>T	0	3
SPINK 1 (n=100)	N34S	6	34

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