Chronic pancreatitis is characterized by irreversible damage to the pancreas that eventually leads to pain and/or exocrine and endocrine insufficiency. It is a major health problem worldwide and is associated with considerable morbidity. Alcohol is the most common cause of chronic pancreatitis worldwide. Still in a large proportion of patients with chronic pancreatitis no etiology can be identified and these are labeled as idiopathic chronic pancreatitis. However, with medical advancement various other factors like genetic mutations, hypertriglyceridermia, hyperparathyroidism, and autoimmunity have been found to be causative for chronic pancreatitis.

Subgroup of chronic pancreatitis with no definite etiology has been labeled as idiopathic chronic pancreatitis which includes a number of well described disease entities like early and late onset idiopathic chronic pancreatitis, tropical pancreatitis, minimal change chronic pancreatitis and small duct chronic pancreatitis. Tropical pancreatitis is an interesting type of idiopathic chronic pancreatitis occurring in tropical regions. The patients may present as tropical calcific pancreatitis (TCP) characterized by multiple episodes of severe abdominal pain in childhood, extensive pancreatic calcification with large ductal calculi and signs of pancreatic dysfunction, but no diabetes mellitus at the time of diagnosis, or fibrocalculous pancreatic diabetes (FCPD) in which diabetes mellitus is presenting manifestation. In this article, we will describe the clinical form of chronic pancreatitis from North India.

**CLINICAL PROFILE OF CHRONIC PANCREATITIS FROM NORTH INDIA**

**Etiology**

In our study of 155 patients with chronic pancreatitis idiopathic chronic pancreatitis was the commonest etiology (n=64; 41.3%) followed by alcoholic chronic pancreatitis (n=59; 38.1%), pancreas divisum alone (n=23; 14.8%), pancreas divisum along with excessive alcohol consumption (n=4; 2.6%) and hyperparathyroidism (n=5; 3.2%). In a survey on chronic pancreatitis from north India, tropical pancreatitis was found to be the commonest etiology (58%), followed by alcohol related pancreatitis (41%) and other causes accounted for 1% of total cases. Another study on 270 patients of chronic pancreatitis from Lucknow, reported that 150 (55.5%) patients had tropical pancreatitis. A recent prospective multicenter survey from centres located both in north as well as south India involving 1086 subjects also reported that ICP is the most common form of chronic pancreatitis in India (622; 60.2% patients). A recent study from New Delhi in 411 patients with CP found that 58.9% of patients had idiopathic pancreatitis followed by alcohol in 38.2%, and hereditary in 2.4% patients. All these studies suggest that idiopathic chronic pancreatitis/tropical pancreatitis is the most common form of chronic pancreatitis with alcohol related chronic pancreatitis being the second most common cause of chronic pancreatitis in north India.

**Age and Sex distribution**

In our study, the age of patients with chronic pancreatitis ranged from 7 to 69 years (mean: 36.2 ± 12.4 years) and 121 of 155 (78%) patients of chronic pancreatitis were male. Majority of patients with idiopathic chronic pancreatitis (ICP) were young with mean age of 33.0 ± 13.0 years whereas patients with alcohol related chronic pancreatitis were significantly older than patients with ICP with the mean...
The study from New Delhi also reported that pseudocyst is a complication between ICP and alcoholic chronic pancreatitis. The mean age of patients from north India with chronic pancreatitis in another survey was reported to be 36.7 years with male: female ratio of 4:1. The study from Lucknow reported the mean age of patients with tropical pancreatitis being 23.2 ± 6.2 years. A study from New Delhi on 359 patients with chronic pancreatitis reported that majority of the patients (80%) with tropical pancreatitis were males. Based upon the results of these studies, it can be suggested that chronic pancreatitis in north India presents in the third and fourth decade of life and is seen more commonly in males. The male preponderance in patients with alcohol related chronic pancreatitis could be related to the cultural habit of people of north India where alcohol consumption is seen mostly in males.

**Clinical Features**

In our study, mean duration of symptoms at the time of presentation in patients with ICP was 40.2 ± 34.4 months whereas patients with alcoholic pancreatitis had significantly shorter duration of symptoms at the time of presentation (27.6 ± 20.6 months, p<0.05). Pain was the dominant symptom in patients with alcohol induced chronic pancreatitis as well as ICP [91.5% and 96.8% patients respectively]. There was no significant difference in the body mass index (BMI) between patients with ICP and 6.7% of patients with alcohol related chronic pancreatitis. Similarly, there was no significant difference in the frequency of increased fecal fat between ICP and alcohol related chronic pancreatitis and this difference was not statistically significant. None of the patients with diabetes had micro vascular or macro vascular complications of diabetes on presentation. The study from Lucknow reported diabetes in 26% of the patients with tropical pancreatitis on presentation. The authors from Lucknow also studied beta cell function in patients with tropical pancreatitis and found that it varies widely on presentation. They found that none of the patients with duration of diabetes less than 2 years had micro vascular complications. The study from New Delhi reported the frequency of diabetes to be 31% in patients with chronic pancreatitis and there was no significant difference in its frequency between ICP and alcohol related chronic pancreatitis (25% vs. 36% respectively). Khuroo et al from Kashmir reported the frequency of diabetes to be 24% in 50 patients of tropical pancreatitis they studied. Because of destruction of both alpha and beta cells diabetic ketoacidosis is usually not seen in patients with chronic pancreatitis but has been occasionally reported. A study from North India in 1988 reported frequency of diabetes to be 48% in 23 patients with chronic calcific pancreatitis of the tropics. These studies suggest that diabetes is seen in approximately one third of the patients with chronic pancreatitis in north India on presentation and in majority of these patients blood sugar can be controlled with diet or oral hypoglycemic agents. The profile of patients has changed over time and now the frequency of diabetes is less common and patients have improved nutritional status, and a more favorable prognosis.

**Diabetes Mellitus**

We found diabetes on presentation in 15/64 (23.4%) patients with ICP and in 13/59 (22%) of patients with alcohol related chronic pancreatitis and this difference was not statistically significant. None of the patients with diabetes had micro vascular or macro vascular complications of diabetes on presentation. The study from Lucknow reported diabetes in 26% of the patients with tropical pancreatitis on presentation. The authors from Lucknow also studied beta cell function in patients with tropical pancreatitis and found that it varies widely on presentation. They found that none of the patients with duration of diabetes less than 2 years had micro vascular complications. The study from New Delhi reported the frequency of diabetes to be 31% in patients with chronic pancreatitis and there was no significant difference in its frequency between ICP and alcohol related chronic pancreatitis (25% vs. 36% respectively). Khuroo et al from Kashmir reported the frequency of diabetes to be 24% in 50 patients of tropical pancreatitis they studied. Because of destruction of both alpha and beta cells diabetic ketoacidosis is usually not seen in patients with chronic pancreatitis but has been occasionally reported. A study from North India in 1988 reported frequency of diabetes to be 48% in 23 patients with chronic calcific pancreatitis of the tropics. These studies suggest that diabetes is seen in approximately one third of the patients with chronic pancreatitis in north India on presentation and in majority of these patients blood sugar can be controlled with diet or oral hypoglycemic agents. The profile of patients has changed over time and now the frequency of diabetes is less common and patients have improved nutritional status, and a more favorable prognosis.

**Complications**

In our study, pseudocyst was the commonest complication of chronic pancreatitis, being present in 58/155 (37.4%) patients. In patients with ICP also, pseudocyst was the commonest complication, being present in 22/64 (34.3%) patients. Similarly, pseudocyst was the most common complication recorded in patients with alcohol induced chronic pancreatitis (59/28, 47.4%). The frequency of portal hypertension in patients with alcohol related chronic pancreatitis and ICP was found to be 20.3% and 17.1% respectively. There was no significant difference in the frequency of various local and systemic complications between ICP and alcoholic chronic pancreatitis. The study from New Delhi also reported that pseudocyst is the most common complication of chronic pancreatitis being present in 32% of the patients. The investigators from New Delhi reported the frequency of pancreatic cancer to be 2.2% whereas one of patients in our study had pancreatic cancer. The conclusion of all these studies is that pseudocyst is the most common complication of chronic pancreatitis in north India and the frequency of its formation is similar between ICP and alcoholic chronic pancreatitis.
clinically evident steatorrhoea is uncommon in patients with chronic pancreatitis from north India.

**Pancreatic Calcification**

In our study, 21/59 (35.5%) patients with alcoholic pancreatitis and 30/64 (46.8%) patients with ICP had pancreatic calcification. The pattern of pancreatic calcification was also similar in both the groups and in majority of these patients it was small speckled calcification. Dense calcification was noted infrequently. We noted intraductal calculi in only 9/64 (14%) of our patients with ICP. The authors from Lucknow also reported that 57% of their patients with tropical pancreatitis had calcification and the frequency of diabetes was significantly higher in the calcific group when compared to the non-calcific tropical pancreatitis. The study from New Delhi reported that the frequency of calcification was significantly higher in patients with idiopathic chronic pancreatitis when compared with alcohol related chronic pancreatitis (88% vs. 50% respectively). Khuroo et al from Kashmir reported that 96% of the patients with tropical calcific pancreatitis had pancreatic ductal calculi. The studies from north India have shown that one third to half of patients with alcohol related chronic pancreatitis have pancreatic calcification. But the data on frequency and pattern of calcification in idiopathic chronic pancreatitis is heterogeneous with some centres reporting higher frequency of pancreatic calcification and ductal calculi whereas some having the pattern and frequency similar to alcohol related chronic pancreatitis.

**Pancreatography findings**

We performed ERCP in 46/59 (77.9%) patients with alcohol related chronic pancreatitis and in 58/64 (90.6%) patients with idiopathic chronic pancreatitis. Mild, moderate and marked changes of chronic pancreatitis as per Cambridge criteria were seen in 1 (2.1%), 5 (10.8%) and 40 (86.9%) patients with alcohol related chronic pancreatitis respectively. Ductal strictures were observed in 5 (10.8%) patients and 2 of these 5 patients (40%) had multiple strictures. Khuroo et al reported that 100% of the patients with tropical pancreatitis had large pancreatic calculi, absence of strictures/stenosis and absence of irregularity of the ductal wall. The studies on endoscopic retrograde cholangiopancreatography (ERCP) findings in patients with ICP from north India have yielded variable results and further multicentric studies using Cambridge classification are needed.

**Treatment**

In our study pancreatic endotherapy was effective in 91% of the patients undergoing ERCP and surgery was required in 9% of the patients with chronic pancreatitis. Endotherapy was also found to be effective in 96% of patients with ICP and these patients had immediate pain relief. The study from Delhi reported pain relief in 60% of the patients with chronic pancreatitis undergoing pancreatic endotherapy whereas short term pain relief was reported in 90% of the patients undergoing surgery. A recent randomized placebo-controlled double blind trial of antioxidant supplementation in painful chronic pancreatitis (age 30.5±10.5 years, 86 male, 35 alcoholic, and 92 with idiopathic CP) from Delhi reported that antioxidant supplementation was effective in relieving pain and reducing levels of oxidative stress in patients with chronic pancreatitis. Surgical drainage has been shown to be effective in management of painful idiopathic or tropical pancreatitis. The role of pancreatic enzymes in treatment of painful chronic pancreatitis is equivocal and good adequately powered studies are needed to evaluate the role of pancreatic enzymes in chronic pancreatitis. The various local complications of chronic pancreatitis can also be successfully treated with pancreatic endotherapy and various studies conducted by us have confirmed the efficacy of pancreatic endotherapy. We have also reported that endoscopic stenting if effective for relief of pain in chronic pancreatitis associated with pancreas divisum with 97.5% of the patients having successful outcome. There was no difference in outcome between calcific and no calcific chronic pancreatitis associated with pancreas divisum. The studies from North India suggest that pancreatic endotherapy is effective for treatment of pain as well as local complications of chronic pancreatitis. The role of antioxidants is interesting and requires further studies.

**Hyperparathyroidism and chronic pancreatitis**

We also investigated the clinical profile of patients with chronic pancreatitis associated with hyperparathyroidism and compared it with that of alcohol related chronic pancreatitis and ICP. Renal colic, nephrolithiasis, nephrocalcinosis, bone disease, palpable neck nodule and psychiatric abnormality were significantly more common in chronic pancreatitis due to hyperparathyroidism in comparison to alcoholic and idiopathic group. No significant difference was observed in the frequency of steatorrhoea, diabetes mellitus, pancreatic calcification and...
Is idiopathic chronic pancreatitis and tropical pancreatitis same or different entity?

We compared the clinical profile of our patients of ICP with the profile of classical tropical pancreatitis (as revealed by published reports in 1990s from various centers in South India) and found out various interesting differences. In contrast to ‘classical’ tropical pancreatitis, where most of the patients were between 10-30 years at the time of diagnosis, the mean age at presentation in our series was 33 years. Patients with ‘classical’ tropical pancreatitis were usually malnourished and abdominal pain was seen in 30-90% of the patients. But majority of our patients with ICP had normal mean body mass index and 96.9% of the patients had abdominal pain as one of the presenting clinical feature. More than 90% of the patients of tropical pancreatitis had pancreatic calcification and diabetes whereas in our study, the frequency of pancreatic calcification and diabetes was 46.9% and 23.4% respectively. Majority of patients with tropical pancreatitis frequently had large intra-ductal calculi whereas calculi were noted in only 9/64 (14%) of our patient population. Also, none of our patients had history of ingestion of cassava. In contrast to high risk of pancreatic malignancy in tropical pancreatitis, none of our patients with ICP had pancreatic cancer.

Another study from North India on idiopathic chronic pancreatitis reported that classical tropical pancreatitis was uncommonly seen with only 5.8% of the patients fitting into the standard criteria for diagnosis of tropical pancreatitis. The patients with ICP presented at a later age than the classical tropical pancreatitis, were not malnourished and diabetes was also uncommon at presentation, seen in only one third of the patients with ICP. Midha et al also reported better survival for patients with ICP with a 35 year probability of survival being 85%. This is in contrast to earlier studies on ‘classical’ tropical pancreatitis which had shown it to be an aggressive disease with many patients dying early in the course of disease. These observations from two large tertiary care centres in North India make us wonder whether the ICP of north India is different from the classical tropical pancreatitis described earlier, or is this indeed the same disease that has changed its' phenotypic expression over a period of time.

Balakrishnan et al in 2006 compared a cohort of 220 patients with chronic pancreatitis and hyperparathyroidism underwent parathyroidectomy and none had recurrence of pancreatic pain over a mean period of 14.3 months.

The etiopathogenesis of idiopathic chronic pancreatitis of tropics or tropical pancreatitis is still unclear. Various hypotheses like malnutrition or cassava ingestion (Tapioca, Manihot esculenta) have been hypothesized but not proven. Familial aggregation has been reported in about 8% of tropical pancreatitis patients with evidence of vertical transmission as well as horizontal distribution of the disease being reported in families. This familial aggregation suggests a genetic basis for tropical pancreatitis and genetic studies may hold considerable promise in unraveling the mystery of this enigmatic disease.

The first step in the development of pancreatitis is the inappropriate activation of trypsinogen within the pancreatic acinar cell. Cationic trypsinogen (PRSS1) the major form (65%) of trypsinogen has two calcium binding pockets that play a key role in the trypsinogen regulation. Calcium sensing receptors (CASR) maintain the homeostasis of calcium metabolism. Trypsinogen is contained in thezymogen granules and is protected from the proactive activation of cathepsin B present in lysosomes. Several other proteins keep trypsinogen in a safe inactive form. Serine protease inhibitor of Kazal type 1 (SPINK1) is an acute phase protein expressed primarily in pancreatic acinar cells, and acts a specific trypsin inhibitor. Cystic fibrosis transmembrane regulator (CFTR) maintains the normal function of the duct cell. It helps in flushing the alkaline pancreatic secretions into duodenum. Loss-of-function mutations of the protector genes or gain-of-function mutations of facilitator genes may lead on to premature inappropriate activation of trypsinogen to trypsin and/or failure to degrade the prematurely activated trypsin. The differences in the profile of chronic pancreatitis (CP) may be partly contributed by the diversity in the genetic profile of tropical pancreatitis (TCP).
patients in north and south India.

In north India, CFTR mutations were seen in half of the idiopathic CP (ICP) (50%), 11% of tropical CP (TCP). SPINK 1 mutations were seen in 42% of ICP, 17% of alcoholic CP (ACP) and 44% of TCP. In contrast, mutations in other candidate genes like PRSS1, leptin and CTSB play minor or no role in TCP.

Studies on south Indian patients revealed SPINK 1 mutations in 32.5% of ICP, 32%-46% of TCP, 26.8% of alcoholic CP, 73% of hereditary pancreatitis. Other genes like CFTR, CASR, CTRC and CTSB may interact with SPINK 1 to alter the disease expression. Association of CP with PRSS1, glycoprotein 2, ACE insertion/deletion polymorphisms and matrix metalloproteinase polymorphisms could not be demonstrated. There was no phenotype-genotype correlation noted in CP from both parts of India.

Summary: The chronic pancreatitis in north India presents in the third and fourth decade of life and is seen more commonly in males. Abdominal pain is the most common presenting symptom of both ICP and alcohol related chronic pancreatitis. The profile of ICP in north India seems to be changing with time and diabetes, steatorrhoea and malnutrition is less commonly seen. Pseudocyst is the most common complication of both ICP and alcohol related chronic pancreatitis and pancreatic cancer is infrequently seen complicating chronic pancreatitis. One third to half of patients with alcohol related chronic pancreatitis have pancreatic calcification but the data on frequency and pattern of calcification in idiopathic chronic pancreatitis is heterogeneous with some centres reporting higher frequency of pancreatic calcification and ductal calculi whereas some having the pattern and frequency similar to alcohol related chronic pancreatitis. Pancreatic endotherapy is effective for treatment of pain as well as local complications of chronic pancreatitis and surgery is infrequently required. The role of antioxidants in relief of pain has been demonstrated and requires further studies. The role of genetic mutations has also been investigated in idiopathic pancreatitis and SPINK 1 mutation has been reported to be more commonly associated with tropical pancreatitis and no association between cationic trypsinogen (PRSS1) gene and tropical pancreatitis has been reported.

In conclusion, ICP is the most common form of chronic pancreatitis seen in North India followed by the alcohol related chronic pancreatitis. Whether to call idiopathic pancreatitis in north India “tropical pancreatitis” or not requires genetic studies. Till that time we prefer this disease to be called as idiopathic chronic pancreatitis and reserve “Tropical Pancreatitis” for patients having classical features of younger age of onset, malnutrition and diabetes along with extensive pancreatic calcification and ductal calculi, which we see in minority of patients.

REFERENCES


