

Chapter 3

Tropical pancreatitis in North India

Gourdas Choudhuri, Eesh Bhatia, Sadiq S Sikora, George Alexander

Summary

While tropical calcific pancreatitis (TCP) was first reported in Kerala, the disease is prevalent throughout India. At our center in North India, we found a high frequency of SPINK1 N34S mutations. In addition, 80% of our patients belonged to the middle or upper income groups. Similarly, only half of our patients were lean, less than a third had low serum albumin levels, while parotid gland enlargement and nutritional edema were not encountered. Patients with low BMI had a shorter duration of pain, suggesting that their pancreatitis may be more severe. In older reports, as well as in some recent studies, most FCPD patients had severe insulin-requiring diabetes at onset. In our studies, we found that surgery does indeed improve pain and exocrine function, but recovery of endocrine dysfunction is a controversial issue.

Introduction

Tropical calcific pancreatitis (TCP) is a unique form of chronic, non-alcoholic pancreatitis, which is limited to the tropical developing countries. Patients present at a young age with severe abdominal pain, weight loss and insulin-requiring diabetes. The pancreas is often shrunken with dilatation of the main pancreatic duct due to multiple intraductal calculi and strictures. At time of presentation patients have markedly diminished pancreatic exocrine function and beta cell reserve. A subset of patients with TCP presents with diabetes without significant abdominal pain. This subset is also known as fibrocalculous pancreatic diabetes (FCPD).

The disease has most commonly been reported from Kerala, but is prevalent throughout India. The etiology of TCP is obscure. Established risk factors such as alcohol intake, hyperparathyroidism and biliary stones are absent. It has been proposed that environmental factors, such as protein energy malnutrition or the consumption of cassava (a source of cyanogenic glycosides) may play a pathogenic role. However, TCP is frequently found in regions where cassava is not consumed and is also observed in patients from higher economic levels, in whom malnutrition is unlikely. The familial clustering of TCP suggests that genetic defects may predispose to the disease.

TCP in North India

One of the genetic causes of TCP that has been identified is mutation in the cystic fibrosis transmembrane regulator (CFTR) gene. Several reports from the world have shown that such mutations in the CFTR gene are high in patients with idiopathic pancreatitis. Many subjects with CFTR mutations diagnosed in childhood, present in adulthood with chronic pancreatitis. We tried to detect mutations in the entire CFTR gene by the multiplex heteroduplex analysis and direct sequencing in 18 consecutive TCP patients. (Bhatia E et al. *AJG* 2000). The screening comprised of the promoter region as well as all 27 exons including flanking intron sequences with estimated mutation detection rate of 95%. The patients were also tested for the 5-thymidine variant of the polythymidine tract of intron 8. CFTR gene mutations, including the 5T variant, were detected in only 2 (11%) TCP subjects, both females. The overall frequency of CFTR gene mutations was 0.083 (3/36), which is far lower than that observed in white Caucasian subjects with idiopathic chronic pancreatitis (0.20-0.24). Among female patients, the gene frequency was 0.25 (3/12), similar to that reported by Cohn et al (0.20, 9/44). This higher apparent frequency of CFTR mutations among female patients with TCP is of interest, because a female preponderance among patients with idiopathic pancreatitis is also a consistent observation. Based on the very low frequency of CFTR gene mutations in our patients, we concluded that this genetic abnormality had a very small etiologic role, if at all, in our patients with TCP.

Chronic pancreatitis is thought to result from inappropriate trypsin activity within the pancreatic parenchyma. Protective mechanisms capable of inactivating any trypsin activated within the pancreas prevent autodigestion in normal subjects, but these fail to act upon mutated trypsin. Gain-of-function mutations of the cationic trypsinogen (PRSS1) gene have been found to be associated with hereditary chronic pancreatitis. However its role in TCP appears unlikely. Pancreatic secretory trypsin inhibitor (serine protease inhibitor, Kazal type 1; SPINK 1) is a 56-amino-acid peptide that specifically inhibits trypsin by physically blocking its active site and acts as the first line of defence against prematurely activated trypsinogen. Mutations in the SPINK1 gene have been reported to be associated with chronic pancreatitis in Europe and the United States and a substitution of asparagines by serine (N34S) in

exon 3 was the most common SPINK1 mutation found in them. We prospectively studied these two mutations (PRSS1 and SPINK1) in 66 of our TCP patients. (Bhatia E et al. *Gastroenterology* 2002) Twenty-nine patients (44%) carried the N34S missense mutation, of which 9(14%) were homozygotes. In contrast only 2 (2.2%) control subjects were N34S heterozygotes ($p < 0.001$), suggesting a strong association of this genetic mutation with TCP. We noted however that in patients with TCP the frequency of N34S carriers and homozygotes were similar in those with or without diabetes. The high frequency of SPINK1 N34S mutation in our patients with TCP compared with controls suggested a possible etiologic or predisposing role in a subset of our patients. Our observation that the frequency was similar in TCP patients with and without diabetes suggests that these two subtypes have a similar genetic predisposition. Mutations in the PRSS1 gene were not detected in any patient, confirming earlier reports and suggesting that mutations in this gene are not associated with TCP. While these findings are exciting, few new questions arise. In our study, N34S homozygotes did not reveal greater severity in their clinical features, when compared with heterozygotes. This would suggest that while a heterozygous N34S mutation is strongly associated with TCP, it might not be adequate to cause the disease without other genetic and/or environmental factors.

Earlier reports described the disease as occurring among adults of a poor socioeconomic status. The patients presented with emaciation, nutritional deficiencies and severe IDDM (but ketosis resistant). The prognosis was described as dismal with most patients succumbing to the disease within a few years of diagnosis. More recently Yajnik et al from Pune have described a high mortality rate from infections and acute complications related to diabetes among FCPD patients. But as a result of improvements in the socioeconomic status and standards of medical care, the clinical presentation and prognosis of patients with TCP have changed.

Of 270 patients of chronic pancreatitis being followed up in our pancreatic clinic, 150 (55.5 %) had TCP. The median age of onset of pancreatitis in these patients was 23.2 +/- 6.2 years. Fifty-eight percent of patients had onset of pain at age less than 20 years. On presentation 26 % had diabetes mellitus and a further 26 % developed diabetes on follow-up. In patients in whom diabetes appeared after pain, the median

time of onset of diabetes after symptoms of pancreatitis was 59.7 +/- 24.5 months. The patients' body mass index (BMI) was 18.1 +/- 3.4 kg/m²; a low BMI (<18 kg/m²) was found in 53% of the patients at presentation. Pain was a prominent symptom and it was seen that the duration of pain was longer in those who had diabetes compared to those without.

Calcification was seen in 57% patients of TCP of whom 47% had diabetes. In patients without calcification diabetes was present in only 17.5 % (p<0.05). Most of the patients had severely diminished exocrine function with mean fecal chymotrypsin being 2.2 +/- 2.2 U/g stool. Thirty-three percent of patients with exocrine deficiency (low fecal chymotrypsin) had diabetes compared to 40 % in those without exocrine deficiency. (p=ns) Therefore development of diabetes mellitus in patients with TCP was related to the duration of pain and calcification and not to presence or absence of exocrine deficiency. Comparing our patients with TCP without diabetes with those with FCPD, we did not find any significant difference in median age, age at onset of pain, BMI or degree of exocrine insufficiency (fecal chymotrypsin).

Eighty of our patients of FCPD were separately evaluated for their nutritional status, clinical presentation, beta-cell function and exocrine function (*Mittal N et al. Nat Med J of India 2002*). The patients in our study differed in many aspects from those reported earlier. In previous reports TCP occurred predominantly in economically deprived people, who were emaciated and suffered from numerous nutritional deficiencies. In contrast, 80% of our patients belonged to the middle or upper income groups. Similarly, only half of our patients had a low BMI, less than a third had low serum albumin levels, while parotid gland enlargement and nutritional edema were not encountered. Patients with low BMI had a shorter duration of pain, suggesting that their pancreatitis may be more severe. In older reports, as well as in some recent studies, most FCPD patients had severe insulin-requiring diabetes at onset. In contrast in our study, 2/3 were initially controlled on diet or oral hypoglycemic agents. The only clinical characteristics differentiating patients requiring diet/oral medications or insulin were that the latter were younger and had worse glycemic control. Fasting C-peptide levels did not differ significantly between these two groups of patients.

In our study as well in previous studies, beta cell function varied widely at presentation. (*Mehrotra R et al. Metabolism 1997*) This may be the result of a variable rate of loss of beta cell function or because patients presented at different stages of pancreatitis. We also observed that beta cell function was negatively associated with a longer duration of diabetes. This is the likely reason for a large proportion of our FCPD patients on diet/oral medications requiring insulin within 5 years of diagnosis. We detected a high prevalence of microvascular complications in this population and the prevalence increased with duration. But unlike type 2 diabetes none of the patients with duration of diabetes less than 2 years had any microvascular complications. This may reflect the relatively abrupt onset of symptoms of hyperglycemia in most FCPD patients.

In contrast to beta cell function, exocrine function was markedly diminished in all FCPD patients by time of presentation. There was no correlation between FCT and C-peptide levels. It is possible that by the time glucose intolerance manifests, exocrine function is already markedly diminished in most patients. Our data are in contrast to an earlier study by Yajnik et al, in which beta cell and exocrine function were directly correlated. Despite having severely diminished FCT levels, most of the patients exhibited a sustained and significant improvement in weight on enzyme supplements. In our prospective study of 32 patients of FCPD, only 2 (6 %) died. Renal failure and carcinoma of pancreas were the cause of mortality. These data are in contrast to older studies, and to a more recent study by Yajnik and Shelgikar, where a high mortality rate was observed mainly due to infectious diseases, malnutrition and acute diabetes-related complication.

The exact pathogenesis of pain and progressive pancreatic dysfunction in chronic pancreatitis is not clear. Increased intraductal pressure and its effects on the pancreatic parenchyma, may play a role in a subset of patients who present with dilatation or strictures. In these patients with "obstructive pancreatitis", the pain responds well to decompressive procedures. We conducted a prospective study to evaluate the effect of drainage of the pancreatic duct on beta cell and exocrine function in TCP patients. (*Agarwal G et al. World J Surg 2002*) While the pain score improved significantly following ductal decompression, there was no

change in beta cell function. FCT was diminished in all patients prior to intervention and did not normalize after ductal drainage in any patient. All 4 subjects with elevated baseline trypsin levels had a sharp fall after intervention. However serum trypsin did not normalize after ductal drainage in any patient with a diminished baseline value. A fall in elevated trypsin suggests that there may be relief of subclinical inflammation after intervention, however there is no improvement in exocrine function after a follow up of 1 year.

References

1. Bhatia E, Durie P, Zielenski J, Lam D, Sikora SS, Choudhuri G, Tsui LC. Mutations in the cystic fibrosis transmembrane regulator gene in patients with tropical calcific pancreatitis. *Am J Gastroenterol* 2000; 95:3658-3659
2. Bhatia E, Choudhuri G, Sikora SS, Landt O, Kage A, Becker M, Witt H. Tropical calcific pancreatitis: strong association with SPINK1 trypsin inhibitor mutations. *Gastroenterol* 2002; 123:1020-1025
3. Mittal N, Mehrotra R, Agarwal G, Rajeshwari J, Choudhuri G, Sikora S, Bhatia E. The clinical spectrum of fibrocalculous pancreatic diabetes in north India. *The Nat Med J of India* 2000; 15:327-330
4. Mehrotra R, Bhatia E, Choudhuri G. Beta-cell function and insulin sensitivity in tropical calcific pancreatitis from north India. *Metabolism* 1997; 46:441-444
5. Agarwal G, Sikora S, Choudhuri G, Bhatia E. Prospective study of pancreatic beta cell and exocrine function following duct decompression in tropical calcific pancreatitis. *World J Surg* 2002; 26:171-175

