

Chapter 7

Chronic pancreatitis in Orissa

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Summary

In Orissa, experience with chronic pancreatitis is shared between the gastroenterologist and the endocrinologist. However, exciting work is in progress to unravel the basis of this illness, and we discuss the results from autoantibody testing, HLA-linked susceptibility studies as well as SPINK-1 mutations amongst subjects with this illness. In addition, we also summarize unusual presentations of the disease and our experience with ultrasound assessment in this setting.

Introduction

Any discussion on chronic pancreatitis (CP) in Orissa, especially tropical calcific pancreatitis (TCP) brings to mind the verses of The Blind Men and the Elephant written by John Godfrey Saxe. The story of tropical pancreatitis in Orissa is a tale of two departments. The clinical features of tropical pancreatitis as presented and published from the two departments – endocrinology and gastroenterology are totally at variance.

Etiology of chronic pancreatitis in Orissa:

The majority of cases of CP in Orissa are due to tropical calcific pancreatitis (TCP). Alcoholic pancreatitis is very uncommon in Orissa; it constitutes only 10% of all cases of CP seen in Orissa. Tropical calcific pancreatitis (TCP) is a chronic pancreatitis unique to developing countries in tropical regions. The cause of TCP is obscure. Whereas environmental factors such as protein energy malnutrition and ingestion of cassava have been implicated, a genetic predisposition to the disease also may be important.

Cassava and CP in Orissa

Heavy consumption of cassava has been implicated in the etiopathogenesis of tropical pancreatitis in Kerala. However, cassava is seldom consumed in Orissa, except in some pockets in coastal southern Orissa. However, paradoxically, TCP is seldom reported from this part of Orissa. Most patients hail from the eastern coastal region, although it is also seen in western Orissa.

Malnutrition

Besides, there is insufficient evidence to implicate protein and energy malnutrition in the causation of tropical pancreatitis. However, Tripathy et al found that 85% of the FCPD (Fibrocalculous pancreatic diabetes) patients hail from areas of predominantly low or very low socioeconomic status. History of alcoholism was not found in a single case.

Alcohol and chronic pancreatitis in Orissa

Alcohol is responsible for about 10% of cases of CP in Orissa today. This is in contrast to the scenario two decades ago when history of significant alcohol intake was not present in a single case of a published series of CP. With increasing industrialization and increase in alcohol consumption, the frequency of alcoholic pancreatitis is going to increase, as we are seeing a surge in the cases of alcohol related acute pancreatitis getting admitted to the medical wards.

Autoimmunity and chronic pancreatitis in Orissa

The prevalence of GAD65 antibodies was studied in 46 FCPD patients of Orissa by Kanungo and associates, and they found that none of the FCPD patients were positive for GAD65 antibodies. In contrast, autoantibody frequency was 4% in healthy controls, 49% in type 1 DM patients, 32% in PDDM patients, and 42% in type 2 DM patients. This suggests that autoimmunity does not have any role in the etiopathogenesis of FCPD in Orissa.

HLA Class II gene polymorphism

There is limited data from genetic studies of malnutrition related diabetes. HLA class II gene polymorphism were analyzed in different types of diabetes mellitus patients from Cuttack, and an association of DQ9 with FCPD was found; FCPD was positively associated with DQ9 (A*0201-B*0303). The investigators suggested that there were differences in the genetic background for susceptibility between type 1 DM and MRDM in the Cuttack population.

SPINK1 gene mutation

As a modifier role has been proposed for trypsin inhibitor (serine protease inhibitor, Kazal type I; SPINK1) mutations, the role of SPINK1 mutations in TCP patients of Orissa is also being analysed. We are investigating SPINK1 gene mutation in both tropical calcific pancreatitis patients and controls. The frequency of N34S in SPINK1 was studied in 20 patients and was found to be 55%; in controls it was 2.3%, not too different from what has been reported in other studies. The mother of a girl with chronic calculous pancreatitis had shrunken hyperechoic pancreas with a dilated pancreatic duct and the mother was diabetic too. Both the mother and daughter had mutated *SPINK1*. These data suggest a common genetic basis for tropical calcific pancreatitis with additional genetic/environmental factors responsible for the variability of phenotype as has been speculated in other similar studies.

Clinical features of chronic pancreatitis in Orissa

The profile of clinical features of chronic pancreatitis in Orissa depends upon the subset of patients who are seen by the reporting investigator. The earlier picture based on FCPD patients presenting predominantly with diabetes mellitus to the physicians or diabetologists was quite different from that of the patients consulting the gastroenterologists for pain. Analysis of two decades old data on pancreatic diabetes patients admitted to the medical and endocrinology wards reveals that the incidence of pancreatic diabetes among all diabetics admitted to the medical wards was 3.7% and among young diabetics below 40 and 35 years 9.8% to 11.7% respectively. Most of these patients with pancreatic diabetes (74%) were between age ranges of 10-30 years. Most (88%) of the patients belonged to poor or very poor socioeconomic status. The nutritional status was poor in the majority of patients; about 90% of the patients were underweight and clinical signs of malnutrition were seen in about 40% patients. Family history was positive in less than 10% of cases. History of abdominal pain, often elicited by direct questioning, was elicited in 42% patients. Pain was rare as a presenting feature among the diabetics. Most of the patients had severe diabetes with gross hyperglycemia. However, it has been observed that after surgery, there is not only remarkable amelioration of the symptoms,

improvement in nutrition and quality of life, but also that the insulin requirement is reduced. Uncommonly, the patient does not require insulin after surgery. The presenting features of these patients with FCPD are as shown in Table 1.

Table 1: Presenting features of FCPD patients in Orissa

Weakness (asthenia)	100%	Fatty stools	24%
Thirst (polydipsia)	80%	Ketosis	16%
Abdominal pain	42%	Infection	16%
Neuropathy	45%	Gallstones	6%
Parotid enlargement	30%	Retinopathy	4%

Although at one time it was difficult to think of a patient with chronic pancreatitis without pain, the position now is quite different; a good number of patients with chronic pancreatitis particularly patients with diabetes mellitus have no pain. Interestingly, early studies from Cuttack⁶ found severe pain in only 12% patients; this was similar to the 10% pain prevalence reported from Diabetes Research Centre, Chennai. It is important to note here that these data pertain to FCPD patients presenting with diabetes mellitus. These figures often gave a wrong impression that tropical calcific pancreatitis in Orissa was generally painless. On the contrary, the prevalence of pain as a presenting feature in TCP patients attending the gastroenterology department is 79%, which is similar to the pain prevalence reported from Trivandrum (82%).⁸

The clinical profile of TCP patients attending the gastroenterology outpatient department is quite different from that of the FCPD patients. The clinical profile of TCP patients attending a gastroenterology clinic is shown in Table 2.

Table 2: Clinical profile of TCP patients in the gastroenterology clinic

Male : female	2:1
Age below 35	75%
Poor nutrition	33%
Overt diabetes	25%
Pancreatic pain	79%
Fatty stool	12%
Pancreatic cancer	2 cases

TCP today, is not as formidable a disease as it used to be considered, thanks to better diabetic care and management of complications. Patients of TCP from the better socio-economic status have now a much better prognosis than earlier.

Tropical pancreatitis and pancreatic carcinoma in Orissa

Pancreatic carcinoma is believed to be a dreaded complication of TCP and published literature would make us believe that patients with TCP are at least 8 times more likely to develop carcinoma than controls. Indeed, TCP is considered by many as a premalignant disease. An analysis was undertaken to study the association of pancreatic carcinoma with TCP in Orissa. This involved 499 patients studied and followed up over a period of two decades from 1975 to 1995. Diagnosis of TCP was made by X-ray and/or ultrasonography. These patients were followed up at intervals varying from 6 to 12 months for a mean period of 8.2 years. Ultrasound was performed at intervals of 12 to 24 months in 312 patients to study the pancreatic morphology and to detect the development of malignancy. Surprisingly none of the patients developed pancreatic carcinoma during follow up. However, during the same period, 10 new patients with pancreatic carcinoma were seen and two of them had pancreatic calculi.

It is concluded that contrary to what has been reported from other parts of the country, patients with TCP did not have an increased predilection for pancreatic carcinoma in this part of the country. However, this issue needs to be carefully examined. Two questions need to be answered: what is the true frequency of pancreatic malignancy in these patients? Does surgery alter the predisposition to malignancy? Data from published literature are inadequate and prospective studies are needed.

Unusual presentations

There were two unusual presentations that are worth mentioning. One of our patients presented with hematemesis and melena; he gave recurrent history of abdominal pain suggestive of pancreatitis and gastroscopy revealed fundal varices as the source of bleed. Ultrasonography revealed chronic calcific pancreatitis with splenic vein occlusion.

About 5% patients presented with cholestatic jaundice due to ampullary obstruction by pancreatic calculi. In one of the patients, biliary dilatation and jaundice resolved after spontaneous passage of the stone across the ampulla into the duodenum. In another patient, relief was obtained after endoscopic removal of the stone. Most of these patients more the less required subjected to surgery.

Ultrasonography and TCP

Ultrasound can pick up a good number of cases missed on routine plain X-ray of the abdomen. In about 50% of the cases in whom diagnosis was made by sonography, plain X-ray of the abdomen missed the calculi. With ultrasonography increasing number of patients with this disease are picked up early even before conventional X-rays can detect calculi/ calcification. Increasing referrals for ultrasonography has resulted in increased detection of TCP. In the pediatric age group too, thanks to sonography, a fair number of patients who were earlier treated for parasitosis or unexplained recurrent abdominal pain have been diagnosed to be suffering from TCP. This has resulted in a relative increase in detection of patients presenting predominantly with pain.

Twenty-four patients who were initially diagnosed as PDDM, with X rays negative for calcification, revealed calculi when ultrasonography was done. (Table-3) and about half of them (45%) complained of abdominal pain. Thus, there may be an overlap between cases of PDDM and FCPD. None of these patients had ever consumed alcohol. It is difficult to classify some of these patients. The daughter of one of these patients had chronic calcific pancreatitis with pain and a markedly dilated main duct, necessitating surgery, but did not have diabetes mellitus.

Table 3: Observations from an ultrasonographic study of 108 patients

Group-I (77.8%)	No pancreatic abnormality on ultrasonography.
Group-II(14.8%)	Shrunken irregular hyperechoic pancreas with dilated irregular PD, but no stones/calcifications. Pain was present in 44%.
Group-III(7.4%)	Shrunken irregular hyperechoic pancreas with bright echogenic areas & irregular dilated PD without stones, pain was present in 50%.

In the light of our clinical and ultrasonographic data, we feel there is a definite need for a reappraisal of the definition of chronic calcific pancreatitis of the tropics. It would be interesting to look for SPINK1 gene mutation in these patients.

Conclusion

Very little progress has been made in our knowledge of the etiology of TCP. It is time there should be a combined multi-disciplinary approach by clinicians, radiologists, endocrinologists, therapeutic endoscopists and surgeons if we are to unravel the mysteries of this enigmatic disease and optimize therapy for patients

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Reference

1. Sanjeevi CB, Kanungo A, Shtauvere A, Samal KC, Tripathi BB. Association of HLA class II alleles with different subgroups of diabetes mellitus in Eastern India identify different associations with IDDM and malnutrition-related diabetes. *Tissue Antigens* 1999;54:83-7.