Tropical Pancreatitis

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The term "tropical pancreatitis" (TP) was coined in 1955 when Zuidema described 18 cases of disseminated pancreatic calcification in young nonalcoholic individuals in Indonesia. These patients were diabetic and had marked edema resembling kwashiorkor. Zuidema considered this entity to be a degenerative disease of the pancreatic parenchyma (pancreatic cirrhosis) secondary to protein-caloric malnutrition. However, there had been reports of surgery for this disease from India even earlier; Kini operated on a 39-year-old man with pancreatic calculi in 1937. The pancreas was hard and nodular, and the duct was dilated; external drainage was performed, but the patient died on the third day after operation. In 1959, Mahadevan presented his experience with 17 cases of "pancreatic lithiasis" treated by surgery. He treated several patients by external tube drainage of the pancreatic duct followed by washouts of stones and calcareous material for over three months. Pain relief lasted up to 14 years.

Over the next 10 years, there were several reports of a similar syndrome from Asia (India, Ceylon, Thailand, Malaysia), Africa (Nigeria, Uganda, Burundi, Zaire and Malawi), and South America (Brazil). The largest series was described by Gecvarges and colleagues from the southwestern Indian state of Kerala where the disease was found to occur in endemic proportions. The disease is relatively less common in northern and western India; sporadic reports have however appeared from Orissa, Punjab, Delhi and Maharashtra.

TP resembles the alcoholic form of chronic pancreatitis seen in the West, except that the patients are young and do not consume alcohol. Over the last three decades, there have been several changes in clinical presentation.

Definition

Chronic pancreatitis implies an irreversible destruction of pancreatic parenchyma and ductal elements. TP is a syndrome characterized by abdominal pain, pancreatic calculi, and diabetes mellitus occurring in nonalcoholic individuals. The disease has also been referred to as 'tropical calcific pancreatitis', juvenile tropical pancreatitis, nutritional pancreatitis and chronic pancreatitis of the tropics. The term fibrocalsal pancreatic diabetes has been used to describe the associated diabetes.

Prevalence

The highest incidence of TP in the world appears to be in Kerala. Data from two large teaching hospitals in Kerala reveal that 12% to 16% of diabetics admitted have pancreatic calcification. The frequency of calcific pancreatitis among autopsies performed in Trivandrum is 5.5%, but this figure is likely to be an overestimate because of the low overall autopsy rates. Two population surveys have been performed during this decade. Balaji reported a prevalence of 1 in 793 based on a survey of 28,357 individuals screened by a field study which included clinical examination, abdominal X-ray, pancreatic function tests (bentiromide test), and ultrasonography. A second field study, performed by Augustine and Ramesh, revealed a prevalence of 1 in 500 (unpublished data).

The belief that the prevalence of TP is on the decrease is not supported by evidence. Now several centers with facilities to investigate and treat pancreatic disease have come up, and therefore a single center may see fewer cases. An average of 100 new cases are diagnosed every year at our center.

Etiology

The etiology of TP is unknown. The following factors have been implicated:

Malnutrition

Protein-caloric malnutrition has long been regarded as a likely causative factor because: malnutrition can cause suppression of pancreatic function and render it susceptible to damage by toxins; most reports of TP were from developing countries; early reports described a state of severe malnutrition, with edema, pot-belly and pedal edema.

However, there are several arguments against this theory. First, pancreatic structural changes and fibrosis are rare in patients with malnutrition, calculi never occur, and the functional changes can be reversed by protein supplementation. Second, Kerala enjoys the best health standards and the lowest infant mortality rate in the country. Malnutrition may thus represent the effect and not the cause of TP. A similar nutritional depletion has been reported in patients with long-standing, insulin-dependent diabetes mellitus.

The extreme emaciation described in early reports of the disease is no longer seen; this may reflect the fact that patients are being diagnosed earlier. It has been postulated that a low dietary fat intake (common in Kerala) may predispose to pancreatic calcification. Dietary surveys at our center showed no significant difference in diet between patients and controls (daily intake of 40.8 ± 12.1 g fat, 52.8 ± 9.7 g protein, 279.4 ± 7.7 g carbohydrate in patients versus 34.4 ± 11.0 g fat, 47.8 ± 11.3 g protein, 284.0 ± 6.5 g carbohydrate among controls).

Food toxins

The cyanogenic glycosides linamarin and methyl linamarin...
present in the tuber of cassava, *Manihot esculenta*, have been implicated as a possible cause. These glycosides react with gastric hydrochloric acid, liberating hydrocyanic acid which is toxic to cells. The enzyme rhodanese acts on hydrocyanic acid converting it into thiocyanates. This requires sulfur donors like methionine or cystine. The resultant depletion of methionine can cause pancreatic damage.

This tuber has been the staple diet of a large section of the population in Kerala. Narendramanthan, in a case-control study, examined the association between cassava consumption and TP and failed to find a relationship despite controlling for confounding factors like low socioeconomic status and vegetarian diet. Furthermore, fewer people of Kerala consume the tuber now than did earlier, and the disease is also seen among those who have never consumed cassava.

**Other factors**

Deficiency of micronutrients (selenium, copper, vitamin A) has also been implicated. Braganza and Mohan found a lower bio-availability of beta-carotene and ascorbic acid in south Indian patients compared with controls from Manchester, England and suggested that culinary practices were responsible.

Genetic factors may well play a part and this may account for the development of disease in children of migrants from Kerala to the West. Familial clustering has been reported. No specific pattern of inheritance has however been found on HLA studies.

Ductal abnormalities occur in only about 1% of cases and are unlikely to play a part in a majority of patients. Isolated reports of increased frequency of antibodies against coxsackie B, *Mycoplasma pneumoniae*, mumps and cytomegalovirus may suggest an infective cause. Immunologic causes have also been postulated.

**Pathogenesis**

Like in other forms of calcifying pancreatitis, in TP too calcification is present in the minute side branches of pancreatic ducts rather than in the parenchyma. These stones are predominantly calcite with small amounts of protein (less than 1% is a fibrillar, insoluble, 133-amino-acid residue of pancreatic stone protein, called PSP-S1 or PTP, now called lithostatin).

A study of pancreatic juice composition in TP patients revealed the following: decrease in volume of pancreatic juice; normal bicarbonate concentration; high calcium concentration; increase in nonstimulated protein concentration; and lack of response to cerulein. There is some controversy regarding the role of protein plugs in the pathogenesis of TP. Geeverghese and Balaraman Nair found plugs in the ducts but Sarles, in a study of 14 surgical specimens from our center in Kerala, found a striking paucity of protein plugs.

**Pathology**

The pancreas may look normal in the early stage of the disease. Later it appears small and is firm to touch. Changes may be focal or diffuse. In more advanced stages, two types can be recognized: a fibrotic type and an adipose type. Microscopic features include the presence of calculi, patchy lobular distribution of lesions, and canalicular regression of tubular complexes. Eventually, acinar atrophy and replacement by fibrous tissue occur.

Balaraman Nair found that islets are spared even in advanced stages of the disease; hypertrophy of islets causing what he termed a ‘pseudonodularlobulosis’ is often seen. Unlike in alcoholic pancreatitis, TP is characterized by an intact pancreatic ductal epithelium, paucity of protein plugs, and absence of necrosis and inflammatory infiltrates.

**Clinical features**

In 1968, Geeverghese succinctly described the features of TP as “recurrent abdominal pain in childhood, diabetes around the age of puberty, and death at the prime of life.” In his series, most patients had marked emaciation with bilateral parotid enlargement and a peculiar cyanotic hue of the lips. Thirty years later, such extreme emaciation is rare. The age of presentation has risen from the teens and early twenties to the fourth decade (average age of presentation to our center was 39 years). This is true not only among patients reporting to the hospital, but also of asymptomatic individuals detected by population surveys.

The male-female ratio among hospital patients is 1.7:1 in Kerala, 2:1 in Nigeria, and 5:1 in the Congo. However, it is 1:1.8 in field studies. This may be because fewer women attend hospitals.

The main symptoms of TP are abdominal pain (35%), diabetes mellitus (55%), weight loss (60%), obstructive jaundice (10%), and steatorrhea (30%). Rarely, patients may present with an abdominal mass, ascites or gastrointestinal bleeding.

Abdominal pain is typically pancreatic in nature and episodic. It may be severe and unrelenting or mild with long pain-free intervals. Data from our center indicate that about 15% of asymptomatic patients develop symptoms over a period of three years.

Diabetes in TP presents most often in the third decade. A history of diabetes in parents can be obtained in 20% of cases. Nearly half the patients can be controlled on oral hypoglycemic agents, but the remainder require insulin. Insulin resistance develops in about 25% of cases. Ketosis is relatively uncommon due to a higher fasting and postprandial C-peptide levels as compared with other insulin-dependent diabetics. These higher levels may reflect an intact islet cell mass, despite which an absolute or relative deficiency of insulin occurs in many cases. The reason for this phenomenon is not clear. Plasma glucagon levels in TP are usually low, and this may predispose the patient to dangerous hypoglycemia. Vascular complications occur as in other forms of diabetes. Improvement in evaluation and treatment of diabetes mellitus may account for the older age at presen-
Steatorrhea is not a prominent symptom owing to the low dietary fat intake. However, on a standard fat diet, over 75% of patients have abnormal stool fat excretion. Fecal chymotrypsin levels show a 87%-96% reduction as compared to controls. The bentonite test (N-benzoyl-L-tyrosyl-p-aminobenzoic acid) is a useful method of assessing the exocrine function. However, Gagee and Mohan reported that the recovery of PABA from Indian patients was lower than that in English patients.

Jaundice may occur due to biliary stricture secondary to inflammation of the pancreatic head or may reflect obstruction by a superimposed malignancy.

In 1956, Mohan Rau reported complete disappearance of calcification in a patient who had extensive calcification and who had undergone laparotomy. While stones may pass into the duodenum or jejunum following a pancreatico-enteric anastomosis, there is no convincing evidence of a "burn out" resulting in pain relief and regression of calcification similar to that described among patients with alcoholic pancreatitis.

Malignancy

Many retrospective and prospective studies have reported a high association between TP and carcinoma of the pancreas. In most cases calculi have existed for several years prior to the development of malignancy. Presence of changes of chronic pancreatitis in the ductal system downstream from the tumor establishes that these cases do not have tumor-induced obstructive pancreatitis. Carcinoma of the pancreas is rare in southern India, according to tumor registries.

Patients with TP who develop pancreatic cancer differ from those in whom cancer occurs de novo in the presence of extensive calculi, higher frequency of diabetes mellitus, and presentation with abdominal pain rather than jaundice. Unlike de novo cancer, which has a predilection for the pancreatic head, TP cancers occur more frequently in the body and tail. About 60% of tumors appear to arise from an area in the body of the pancreas close to the neck. Once carcinoma supervenes, survival is short (median 11 months) despite resection of the tumor and chemotheraphy.

Preoperative identification of cancer may be difficult in many cases. The occurrence of weight loss, appearance of constant upper abdominal pain, and deterioration in diabetic control should raise a suspicion of malignancy. Fine-needle aspiration cytology/biopsy may have a low yield because the malignant cells within an organ affected by fibrosis may not be easily aspirated. Tissue or intraoperative biopsies may also be inconclusive. In our experience, weight loss, short-duration symptoms, evidence of ductal block on endoscopic retrograde pancreatography (ERP), and high serum bilirubin levels (in head tumors) correlated with the presence of malignancy.

Diagnosis

There are no specific criteria to diagnose TP. The disease can however be diagnosed with reasonable certainty especially in a geographic area of high incidence if the patient does not consume alcohol and if two of the following three criteria are present: 1. pancreatic calculi on abdominal X-ray; 2. ultrasoundographic evidence of dilatation of the main pancreatic duct; and 3. ERP evidence of changes of chronic pancreatitis. The latter two criteria allow patients with acalculous disease and those with normal sized ducts to be diagnosed.

Management

Steatorrhea is usually not troublesome (because of low dietary fat intake) and can be controlled with pancreatic enzymes. Between two-thirds and three-fourths of patients have diabetes; a third are controlled by diet alone, another third by oral hypoglycemic drugs, and the remaining by insulin. Vascular complications need to be identified and treated promptly.

Pain is the most distressing symptom, leading to absence from work and other problems such as addiction to narcotics and/or alcohol. Many patients have pain relief for long periods with the use of antispasmodics and analgesics. In others, pain is not relieved even after the use of narcotic analgesics. The role of pancreatic enzymes in relieving pain due to TP has not been adequately studied.

Lateral pancreaticojejunostomy (LPJ) is the most commonly performed operation in patients with TP. It permits drainage of the entire pancreatic duct and also allows drainage of cysts either separately or in continuity. Several reports have emphasized the good results with this procedure. Pancreaticogastrostomy, on the other hand, is not suitable for patients in whom a wide ductotomy has been performed; anastomosis of the duct to fundus to duodenum may be difficult. Should leakage occur, a combined gastro-pancreatic fistula results. Use of transduodenal pancreatic sphincteroplasty is confined to the rare situation of a solitary stricture at the ampulla; however, it may be used as an adjunct to LPJ in clearing stones in the pancreatic head.

Pancreatic resection is indicated when the disease predominantly affects one portion of the gland, in cases where effective drainage cannot be achieved (especially in the head), and in patients with normal sized ducts or recurrent pain following LPJ. The benefits of resection must be weighed against the problems due to exocrine and endocrine deficiency which occur invariably. Total pancreatectomy is also not a satisfactory option. Results from a few unpublished reports have been poor because of problems in managing the apocrine state.

There have been only two reports of nerve interruption procedures in TP. In 1976, Bahuleyan reported excellent early results following splanchicectomy in 12 patients. However, long-term follow-up is not available. In another report, Venkatesh Rao reported good or fair results in 11 of 15 patients undergoing postcellae neurectomy; this operation was
combined with a pancreatecogastrostomy.4

Clearance of calculi and achievement of satisfactory drainage in the head region is often unsatisfactory owing to the presence of numerous side branches, and also because the main duct dips deep into the parenchyma, making ductotomy difficult. Coring out of the head is a satisfactory option as it provides excellent drainage and avoids major pancreatic resection.5 Drainage of the pancreatic and bile ducts into an isolated loop of jejunum, which is then anastomosed to the duodenum, has been described. This has several advantages: the bile and pancreatic secretions are returned to the duodenum and there is no pancreato-enteral asynchrony; the risk of duodenal ulceration is also minimized.6

Results of surgery
Owing to improvements in the perioperative management of diabetes and its associated metabolic problems, mortality rates have decreased from around 15% in the early 1980s to less than 5% today. A review of our own experience revealed a 7% mortality in the first 100 cases, which dropped to 2% over the next 100 cases. Over a median follow-up of 60 months (longest 12 years), pain relief was observed in approximately 90% of cases. Reoperations were required in 5%. Most failures reported within 48 months after operation. Poor results were seen in patients with malignancy, and in benign cases where stone clearance or ductotomy was incomplete. Our present policy is therefore to perform a wide ductotomy extending from the pancreatic tail to within 0.5 cm to 1 cm of the medial border of the duodenum and to achieve complete clearance of stones from the main pancreatic duct. This permits free drainage of side branches into the main ducts and intestine. Where necessary, a head-coring operation may be used to achieve better drainage; resection may be necessary only in patients with severe involvement of the head, those with multiple pseudocysts or with biliary and duodenal obstruction, where resection may be easier than multiple anastomoses.5

Role of nonoperative methods
In 1971, Reddy presented his initial experience with endoscopic pancreatic stenting in 29 patients with TP and proximal strictures.6 His experience now extends to 137 patients (personal communication), 67 of whom underwent pancreatic stenting whereas the rest underwent only a sphincterotomy. Extracorporeal shock wave lithotripsy (ESWL) and irrigation of pancreatic duct through previously placed nasopancreatic stents was used in some cases. Early results were excellent but long-term results are not available yet. However, there were no controls, nor was this modality compared with surgery. Over a third of the patients had acalculous disease with uniform ductal dilatation. Calculi greater than 1 cm were rare.

Most reports from south and south-west India describe a disease distinct from those treated by Reddy in Hyderabad. In our experience, calculi are invariably present, are larger in size, are present throughout the ductal system, and many of these have dumb-bell-shaped extensions into the side branches and are difficult to extract even after a wide ductotomy. There are multiple strictures; 'proximal strictures' are rare.

Geographic variations
TP has been reported from various parts of India including Delhi, Chandigarh, Bihar, Uttar Pradesh, Mumbai, Manipal, Hyderabad, and some centers in Tamil Nadu, besides Kerala where the disease is endemic.6 Owing to lack of uniform documentation, the data from various centers do not allow easy comparisons. While the disease did affect young nonalcoholic individuals in all these reports, some notable distinctive features were: presence of calculi in only 15 of 121 cases in Chandigarh; a mild form of disease with lower frequency of diabetes mellitus in Mumbai; severe pancreatic fibrosis without calculi in Calcutta; and fibrocalsisocal pancreatic diabetes, malnutrition, but virtually no abdominal pain or cancer in Orissa. The experience from Delhi has shown great similarity to the Kerala experience: a high incidence of diabetes and abdominal pain, reports of cancer, and lasting relief of pain following ductal drainage operations.6 It thus appears that TP is a disease of many clinical facets, and its clinical presentation varies from one center to another.

Controversies
Many aspects of the disease are still not well understood. Although there is some suggestion for a genetic predisposition, the disease may well be a result of multiple factors which have not been identified. Although most (97%) patients have calculi at presentation, it is clear that a precalculous stage does exist. The disease has a long latent period and the first symptom may be due to a complication. It is now clear that TP is premalignant, but the natural history of its development remains to be unraveled. The predisposition to carcinoma may be genetically predetermined and not dependent on chronic inflammation or stasis. In that event, surgical operations aimed at clearance of stones and wide duct drainage may not protect the patient from cancer.

The future goals in TP lie in efforts at disease prevention which requires more precise identification of causative factors, improved methods of exterine and endocrine substitution therapy, judicious use of nonoperative or operative modalities in relief of pain, and prevention or at the very least early identification of life-threatening complications such as carcinoma.

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