

## Tropical calcific pancreatitis

Tropical calcific pancreatitis (TCP) is a form of idiopathic chronic pancreatitis with distinct clinical and epidemiological characteristics. It was described in the 1960s as "pain in childhood, diabetes in adolescence and death during prime of life" [1]. Although the natural history and outcome has improved considerably in the last half-century, the pathogenesis of this crippling disease remains elusive.

Nearly exclusive to the tropics, the disease has been described in many countries including Uganda, Nigeria, Zambia, Madagascar, Sri Lanka, Malaysia, Thailand, Bangladesh and India. The disease occurs usually in children or young adults and is characterised by recurrent abdominal pain, large pancreatic intraductal calculi, development of diabetes and steatorrhoea, malnutrition and a high rate of pancreatic cancer [2]. Tropical pancreatitis is endemic in several developing countries including India. The prevalence varies from 10 to 126/100 000 population, the highest figure being reported from the southern Indian state of Kerala [3, 4].

Even after 50 years of investigation, the exact aetiology is still not clear and several hypotheses are proposed.

1. Malnutrition was initially suspected to play a causal role as pancreatic fibrosis developed in chronic protein-starved rats in the laboratory, and TCP was thought to occur more commonly in the socio-economically weaker section of society. In systematic studies malnutrition appeared to be an effect rather than the cause, and TCP is now increasingly observed in higher socio-economic groups [5].
2. Cassava: (*Manihot aesculenta*), tapioca. This tuber is a staple crop in several regions of the tropics and contains varying amounts of cyanogen glycosides. As cassava consumption and prevalence of TCP are both common in Kerala, it was hypothesised that hydrocyanic acid, liberated from cyanogenic glycosides of cassava by the action of gastric HCl produced pancreatic damage. TCP is however reported from several parts of India and the globe where cassava is not consumed. Cyanide toxicity however still remains a suspect since certain lentils consumed in other parts have been shown to contain cyanide and may cause the disease [6].
3. Genetic factors: Genes in chronic pancreatitis became popular after the landmark discovery that hereditary pancreatitis was caused by a mutation in the cationic trypsinogen gene (PRSS 1) [7]. The R 122 H mutation at the autolysis site of the PRSS 1 gene results in a "gain of function" mutation because prematurely activated trypsin cannot be inactivated by autolysis [8]. This genetic mutation was not found in patients of TCP [9]. The role of another gene that regulates inactivation of excess trypsin produced by pancreatic

acinar cells, by autolysis, the SPINK 1 (serine protease inhibitor, Kazal type 1) has been the subject of recent studies. We found 44% of TCP patients to carry the N 34S mutation in SPINK 1 gene [9] in our study compared to only 2.2% in controls ( $p < 0.001$ ). Experts believe that mutations in this "disease modifier gene" along with other genetic or environmental factors may precipitate pancreatic inflammation and fibrosis and lead to TCP. Several groups have reported mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene in TCP. We found common mutations in this large gene in only 11 % of our patients [10]. Cathepsin B, anionic trypsinogen and keratin are other candidate genes in TCP in which mutations have been studied [11].

4. Oxidative stress: This hypothesis attributes the heightened oxidative stress with the depletion of antioxidants as the factor causing pancreatic damage in TCP [12]. Cassava toxicity and malnutrition produce an ideal setting for free radical injury. Oxidative stress appears to be a common pathogenetic mechanism in chronic tissue inflammation and injury; hence its causal role in TCP remains to be established.

### Pathology

The pancreas is usually shrunken and feels firm or hard due to fibrosis and ductal calculi. The parenchyma is often thin and atrophic and the pancreatic ducts are dilated; the dilation may be so severe so as to form cystic spaces filled with stones. The stones are initially soft and later enlarge and calcify; they are made of calcium carbonate (calcite) deposited on a protein lattice, and vary in size from small sand particles to calculi that are up to 20 g or more. Some parts of the pancreas may feel hard and nodular, and the head may sometimes appear as a mass when enlarged with stones, inflammation and fibrosis, making it difficult to distinguish from malignancy.

The earliest microscopic changes are seen in acini which show patchy disruption, a characteristic feature of TCP. In later stages diffuse fibrosis of the pancreas is seen. Ductal changes occur later. While acini undergo regressive atrophic changes, ducts show proliferative and metaplastic changes and are often dilated and filled with mucus plugs. Ductalisation of acini also occurs in some cases. Dysplastic changes are seen in long standing cases. The most striking and constant changes are found in the islets of Langerhans which show extensive nesidioblastosis, ie. regeneration and formation of new islets.

### Clinical features

The most characteristic symptom is epigastric pain,

which has the typical characteristics of pancreatic pain. The initial presentation is with recurrent severe episodes separated over long periods, followed later by frequent milder episodes or chronic persistent pain. In some patients the pain seems to 'burn off' perhaps due to loss of most pancreatic parenchymal tissue. There are several mechanisms by which pain can occur in TCP; these include pancreatic inflammation, ischaemia, fibrosis and pseudocysts, increased pressure on ducts and tissue, and neuro-immune interactions.

Malabsorption typically presents as steatorrhea which manifests only after lipase secretion is reduced to <10%. Diabetes in TCP has been termed fibrocalcific pancreatic diabetes and is usually ketosis resistant. Studies have shown that the 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. In our pancreatic clinic there are 150 patients with TCP being followed up. The mean age at onset was 23.2±6.2 years [13]. Disease characteristics include pain (70%), low BMI (<18 kg/m<sup>2</sup>) (53%), diabetes (26%), steatorrhea (15%), pancreatic calcification (57%) and abnormally low faecal chymotrypsin (80%).

### Treatment

As in other forms of chronic pancreatitis, medical management consists of analgesics and enzyme supplements for pain relief and exocrine insufficiency. Diabetes sometimes responds to oral hypoglycaemic agents initially; subsequently most are found to require insulin (83% in our centre) [14]. High dose antioxidant therapy with methionine is often effective in pain relief.

Only a subgroup of patients benefit from endotherapy. The prerequisite is a dilated pancreatic duct due to a downstream obstruction by a stone, stricture or both. Endotherapy does not benefit patients who have predominant involvement of the side branch. The pancreatic sphincter is widened by sphincterotomy and stones are extracted with a wire basket; if they are large they are pulverised with extracorporeal shock-wave lithotripsy and the fragments are extracted by endoscopy. A plastic pancreatic stent may be required to facilitate drainage of pancreatic juice and prevent impaction by a stone or fragment.

Surgical treatment remains the gold standard for the management of intractable pain and treatment of complications. Currently, the indications are:

1. Intractable pain not alleviated by medical therapy with calculi in pancreatic ductal system.
2. Head mass with suspicion of malignancy.
3. Complications such as non-resolving biliary or duodenal obstruction, pseudo-cysts, pancreatic fistulae and left-sided portal hypertension.

Surgical procedures commonly used include lateral

pancreaticojejunostomy or Partington Rochelle modification of Peustow procedure, localised resection of head of pancreas by Frey procedure or Beger operation, and in cases of suspected pancreatic malignancy, Whipple's operation. Experience at our centre has shown that 76% patients are pain free whereas 16%, 1% and 5% have mild, moderate and severe pain on a mean follow up of 12.6 months. In patients with high pancreatic ductal pressure and dilated main duct, ductal decompression by surgery or endoscopic treatment provides marked relief in pain; the endocrine and exocrine dysfunction in these patients however do not improve significantly [15].

### Complications

The lifetime risk of pancreatic cancer in patients with chronic pancreatitis is 4%, but the figure varies widely, especially in areas endemic for TCP. Timely recognition of malignancy in TCP is difficult, but essential for patient management. Development of obstructive jaundice in a patient of TCP is highly suggestive of malignancy. Very high values of the serological marker CA 19-9, in excess of 1500, especially in the absence of jaundice, is also a useful predictor. Other helpful features are endoscopy showing total blockage of pancreatic duct in the absence of a stone (penetrating duct sign), and irregular bile duct strictures and a head mass on CT scan, which may be very difficult to distinguish from an inflammatory mass on imaging. Other complications seen in these patients include pseudo-cysts, pseudo-aneurysms, venous thrombosis, common bile duct obstruction, and pancreatic fistulae, that require management on usual lines.

### Conclusions

TCP is a distinct clinical entity, easy to recognise in the typical setting. Its pathogenesis is still unclear. It is likely that multiple genetic and environmental factors interact to produce expression of the disease in a given individual. The age of presentation seems to have increased. Most patients are able to live longer and productive lives, perhaps with better management of diabetes, its complications, and maldigestion. Decompression and drainage of dilated ducts and removal of calculi provide gratifying relief of pain for long periods. The risk of malignancy and its diagnosis remains a challenge in long survivors.

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**G Choudhuri, D Singh and C P Lakshmi**, Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226014, Uttar Pradesh, India.

Correspondence: GC, e-mail <gourdas@satyam.net.in> and <gc@sgpgi.ac.in>. Accepted 21 November 2007. Conflicts of interest: none declared.