INTRODUCTION

Chronic pancreatitis (CP) is defined as a continuing inflammatory disease of the pancreas characterized by irreversible morphological changes typically causing pain and/or permanent loss of function. The first reported usage of the term in English medical literature was probably by Comfort in the 1940s. In most of the patients in Western series, the predominant etiology was alcohol.

It was Zuidema from Indonesia who first reported a series of 45 patients with pancreatic calcification with diabetes mellitus who were poor and consumed a protein- and calorie-deficient diet, and also had striking clinical features of malnutrition like emaciation, parotidomegaly, hair and skin changes not unlike that of Kwashiorkor. This was followed by a series of reports of similar patients from various tropical countries in Asia (India, Bangladesh, Sri Lanka), Africa (Uganda, Nigeria, Zambia, Madagascar), and South America (Brazil) following which tropical pancreatitis (TCP) came to be recognized as a distinct entity with unique clinical and epidemiological features different from that of alcoholic chronic pancreatitis (ACP). The first case of pancreatic calculi in India was reported in 1937 by Kini. The largest series was reported by Geevarghese from the south-western state of Kerala who immortalized the uniqueness of this entity by the aphorism that these patients typically had “pain in childhood, diabetes in adolescence and death during prime of life”. Thus TCP was a disease that had exceptionally distinctive features at the time it was described.

ALCOHOLIC CHRONIC PANCREATITIS

Usually, drinking alcohol for several years is necessary to produce ACP; however, there is no threshold value below which the disease does not occur. In most patients, at least 5 years of alcohol intake exceeding 80 g/day is required prior to the development of chronic pancreatitis. Only 5–15% of alcoholics develop chronic pancreatitis suggesting the role of some genetic factors or some associated cofactor(s). Potential cofactors that have been proposed include a diet high in fat and protein, a relative deficiency of antioxidants or trace elements, and smoking. Cessation of alcohol use after the onset of alcoholic pancreatitis appears to variably diminish the rate of progression to exocrine and endocrine insufficiency.

TROPICAL PANCREATITIS

Tropical pancreatitis may be defined as a form of idiopathic CP seen in tropical Asia and Africa, characterized by abdominal pain, intraductal calculi, and diabetes mellitus in young, non-alcoholic subjects.

TCP occurs usually in children or young adults and is characterized by recurrent abdominal pain, large pancreatic intraductal calculi, development of diabetes and steatorrhea, malnutrition, and a high rate of development of pancreatic cancer. Chari et al have reported that compared to the West, ACP patients in South India had a shorter duration of symptoms in spite of having advanced disease. TCP and ACP patients in this series had distinct clinical profiles. Diabetes in TCP has been termed fibrocalcific pancreatic diabetes (FCPD) and is usually ketosis-resistant. Most patients eventually need insulin although initially, glycemic controls can be achieved by dietary measures and/or oral agents.
development of diabetes mellitus in patients with TCP was shown to be related to the duration of pain and calcification, and not to the presence or absence of exocrine deficiency.

Abdominal pain is usually the first symptom in TCP. The generally held theory is that FCPD is the end point of TCP i.e. TCP is the pre-diabetic stage of FCPD. However in many patients, the first sign of the disease may be detection of calculi, diabetes and rarely steatorrhea. As disease progresses, the episodes and severity of pain may diminish suggesting a “burnout of the disease”. Familial aggregation in TCP has been described. Phenotypic differences within families is have been reported by us. Recent reports suggest that the presentation is changing. The age of onset is older and the disease course seems to be milder. Overt steatorrhea is unusual (except when exposed to dietary fat challenge). However, unique features remain the strong propensity to develop diabetes mellitus (well before exocrine failure, and marked calcifications in a grossly dilated main pancreatic duct. Better management of diabetes and its complications, and maldigestion have resulted in longer survival and better outcomes. Improvement in socioeconomic conditions, better healthcare facilities, improved nutrition and sanitation are other factors which could have impacted the disease characteristics.

**PREVALENCE**

Tropical pancreatitis is now reported from most parts of India. However a high prevalence in Kerala suggests that it is an endemic disease. A field survey in Kollam district in Kerala involving 28567 inhabitants (6079 families) suggested a prevalence of CP to be 1:793 subjects. This study also showed a female predominance (M:F ratio, 1:1.8) unlike hospital-based data. The Indian Pancreatitis Study group (IPANS) conducted an online nationwide study encompassing 32 centers with Amrita Institute of Medical Sciences, Kochi as the lead centre. This study revealed that ACP comprised about 1/3 of cases of CP all over India while nearly 2/3 was ICP and only 4% met strict criteria for identifying classical TCP.

**ETIOPATHOGENESIS OF TROPICAL PANCREATITIS**

There is still lack of a definite understanding of the etiopathogenesis of TCP. Several hypotheses are proposed:

1. **Malnutrition:** This was initially suspected to play a causal role. TCP was thought to occur more commonly in poor malnourished patients as this was indeed the characteristic epidemiological feature in most early reports. Pancreatic fibrosis was shown to develop in chronic protein-starved rats. However recent studies suggest that malnutrition appeared to be an effect rather than the cause. The possibility of micronutrient deficiency contributing the predominant role is still an attractive proposition. Micronutrient deficiency could impact pancreatic function as some of these do appear to play a vital though often not well characterized role in pancreatic function. Alternatively, micronutrient deficiency could be implicated in production of oxidative stress.

2. **Dietary toxins:** *Manihot esculenta* (cassava, tapioca) is a tuber which contains varying amounts of cyanogen glycosides. Cassava cultivation was introduced in Trancore in the 19th century from South America during a famine. Initial reports suggested an epidemiological association of cassava consumption and prevalence of TCP in Kerala. The McMillan and Geeveghese hypothesis indicated an association between dietary cyanide and TCP. The postulated mechanism essentially was that hydrocyanic acid, liberated from cyanogenic glycosides (linamarin and lotaustralin) of cassava or other foods by action of gastric HCl produced pancreatic damage. TCP is however reported from several parts of India and the world where cassava is not consumed; conversely TCP was found to be rare in many populations eating large quantities of cassava. The processing and preparation of cassava appears to play some modifying effects. A case control study has also shown a lack of association between cassava and TCP. In a recent study we showed that while these patients are at a high risk for defective detoxification for cyanogens, there were no differences between cassava consumers and non-consumers.

3. **Genetic factors:** Initial attempts to unravel genetic basis of familial clustering was in the form of HLA studies in Kerala. Mutations in a gene that regulates inactivation of excess trypsin produced by pancreatic acinar cells, by autolysis, the SPINK 1 (serine protease inhibitor, Kazal type 1) was the first gene associated with TCP. But present consensus is that this plays a “modifier role” only. Mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene could be important in TCP. Cathepsin B, anionic trypsinogen, CTRC, CASR genes are some other genes studied.

4. **Oxidative stress, antioxidant depletion, and free radical injury:** Studies have shown differences in oxidative status between ACP and TCP. Zinc deficiency appears to affect oxidative stress.

It is likely that multiple genetic and environmental factors interact to produce expression of the disease in a given individual.

**PANCREATIC FUNCTION TESTS**

Over the years a number of tests have been used to study pancreatic function in TCP. Secretin pancreozymin tests revealed gross reduction in volume, bicarbonate, trypsin, and lipase content of the pancreatic secretion. The
lactoferrin and calcium levels of pancreatic juice were found to be considerably higher in both normal controls and TCP patients from India (Kerala) compared with their French counterparts. Recently the role of fecal elastase 1 estimation in TCP has been demonstrated in a study by our group; and it is now probably the “gold standard” indirect pancreatic function test. The same study also showed the benefit of acid steatocrit estimation for fecal fat quantification in TCP.

### RADIOLOGICAL IMAGING

**Ultrasonogram/Computed Scan abdomen**

Studies by Charri et al. as well as other workers suggest that there are striking differences in radiological appearances in ACP and TCP. While TCP was characterized by frequent occurrence of large, discrete, dense calculi, patients with ACP had typically small, speckled calculi with irregular, hazy margins.

**Endoscopic Retrograde Cholangio-Pancreatography**

The first ERCP study by Balakrishnan et al. indicated that calcific TCP had greater degree of ductal derangement as compared to non-calcific variety. Presently most centres report large intraductal pancreatic calculi predominantly in head region causing maximal dilatation of MPD. Benign biliary strictures are rare as compared to ACP.

**Magnetic Resonance Cholangio Pancreatography**

This is a useful non-invasive test. Sensitivity is 70–80% as compared to ERCP. However, it is poor in characterizing subtle changes in side branches. Secretin stimulation (s-MRCP) increases sensitivity to 90%. There is better visualization of MPD (97% vs. 64%) and side branches (63% vs. 4%).

**Endoscopic Ultrasound**

The role of EUS is significant in diagnosis of early CP and for evaluation of mass lesions.

### PATHOLOGY

Pancreatic changes of CP have been described in an animal model. In humans on autopsy, the pancreas is usually shrunken and feels firm to hard due to fibrosis and ductal calculi. The parenchyma is often thin and atrophic and the pancreatic ducts are dilated; the dilatation 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. The ultrastructure of the stones has been characterized.

### MICROSCOPY

The earliest 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 often dilated and filled with mucus plugs. Ductalization of acini also occurs in some cases. Dysplastic changes are seen in long standing cases. The most striking changes are found in the islets of Langerhans which show extensive nesidioblastosis, i.e. regeneration and formation of new islets.

### TREATMENT

#### Dietary Measures

Usually the patients restrict fat in diet as it helps in reducing recurrences of pain or acute exacerbations. However it is essential to ensure good nutrition. Use of additional anthropometric measures in addition to BMI is helpful in assessment of nutritional status. The concerns of those with diabetes need extra consideration. We have shown recently that zinc and folic acid deficiency exist in CP.

#### Medical Management

Counseling for total abstinence from alcohol is important. Pain can be managed with analgesics including opioids using the WHO analgesic ladder. High protease pancreatic enzymes can be useful in management of pain. Fat malabsorption is usually controlled by oral enzymes with high lipase content typically 30,000 units with each meal. However, patients often do relatively well with smaller doses. Diabetes sometimes responds to diet (1/3 cases) or oral hypoglycemic agents (1/3 cases) initially; subsequently most are found to require insulin. Although microvascular complications are more common, macrovascular complications have also been reported. Antioxidant therapy has been shown to be beneficial. Usual antioxidant preparation would include 500-1000 vitamin C, 250-300 IU vitamin E, 500-800 mcg selenium, 2 g methionine, 9000-10000 IU β-carotene. Addition of folic acid or zinc to this antioxidant cocktail needs to be validated. Region or etiology specific tailoring of antioxidants is an area of ongoing research.

#### Endoscopic Treatment

Pancreatic sphincterotomy and short-term stenting of main pancreatic duct after dilatation of strictures and removal of calculi is the usual mode of endotherapy. The patients with a dilated pancreatic duct due to a downstream obstruction by a stone, stricture or both are likely to benefit from endotherapy.

**Extracorporeal Shock Wave Lithotripsy**

Recent reports suggest a greater role for ESWL, both as an adjunct to endotherapy and as a primary modality; the latter to a lesser extent. Nerve ablation procedures like celiac plexus block or neurolysis, and splanchnicectomy have also been used. EUS-guided celiac plexus block has been shown to be superior in an RCT recently.
Surgical Management

Surgical treatment remains the gold standard for the management of intractable pain and treatment of complications.48-50 Usual 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, pseudocysts, pancreatic fistula and left-side ed portal hypertension

Unlike ACP, the special problems involved in surgery in TCP include management of diabetes and association of malignancy at a young age.49 While wide ductotomy, stone clearance and drainage give good symptomatic results in benign disease, the overall results are usually poor in patients with cancer.

Complications

The lifetime risk of pancreatic cancer in patients with chronic pancreatitis has been considered to be around 4%. In a large prospective series of CP followed over 7 years, we have observed that cancer occurred in about 7%. Many retrospective and prospective studies have reported a high association between TCP and pancreatic cancer.51-53 The risk is generally believed to be higher in TCP as compared to ACP. Unlike de novo ductal cancer, which has a distinct predilection for the head, cancer in TCP can occur frequently in body and tail.

Timely recognition of malignancy in TCP can pose difficulty. Development of obstructive jaundice in a patient of TCP is highly suggestive of malignancy. Rapid weight loss and sudden worsening of pain in absence of other complications are indicative of malignancy. Elevated levels of serum CA 19-9, especially in the absence of jaundice are also a useful marker.54 Other helpful features are ERCP showing total blockage of pancreatic duct in the absence of a stone, and irregular bile duct strictures and a head mass on CT scan (which may be very difficult to distinguish from an inflammatory mass).

Other complications include pseudocysts, pseudo-aneurysms, venous thrombosis, CBD obstruction, and pancreatic fistulae and ascites.

Autoimmune Pancreatitis

This form of chronic pancreatitis is characterized by the presence of autoantibodies, elevated levels of immunoglobulins especially IgG4, enlargement of the pancreas (diffuse or focal), pancreatic duct strictures, and pathologic features of a dense lymphocytic infiltrate. A common presentation is that of a pancreatic mass mimicking cancer. It is steroid responsive, often dramatically so. Steroid response is one of the diagnostic criteria for autoimmune pancreatitis. Low dose steroids or immunomodulators may be needed to maintain remission.

Idiopathic Chronic Pancreatitis

Idiopathic chronic pancreatitis (ICP) accounts for 40–60% of CP in India, as compared to 10–30% in the West. Etiological work-up for this group is an area of future research. Possibility of viral infections as one of the etiological factors for CP has been reported but there are no large series.55-57 Etiological search for viruses (e.g. viral serology) is not a part of current diagnostic work-up for ICP.58

Summary

Tropical pancreatitis is an entity first described in the 1950s and was the dominant etiology in Kerala. Fibrocalculous pancreatic diabetes was the term preferentially used to highlight the secondary diabetic state in this entity. Though originally described in young malnourished patients from the tropics, the present clinical scenario shows some differences. Traditional risk factors included malnutrition, dietary toxins and environmental agents. Identification of genetic mutations causing pancreatitis has broadened the perspective. Improvements in health care and socioeconomic conditions have contributed to better outcomes. However the disease burden is still considerable. Advances in the understanding of the role of genetic factors as well as environmental factors will help in clarifying the exact etiopathogenesis of TCP. An increase in alcoholic pancreatitis reflects an increase in alcoholism. Presently ACP constitutes about one-third of CP patients. Autoimmune pancreatitis and other rare causes like hyperparathyroidism are now increasingly reported. There appears to be some differences in the spectrum and profile of disease in South India as compared to North India.

References

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