Chronic Pancreatitis

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ABSTRACT

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Chronic pancreatitis is a term that reflects the end- stage pathology of inflammation associated pancreatic diseases. Tropical pancreatitis is an entity first described in the 1950s and predominantly reported in Kerala. 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 especially in Kerala. An increase in alcoholic pancreatitis reflects an increase in alcoholism. Recent series report rarer causes including autoimmune pancreatitis.

Keywords: Chronic pancreatitis, Tropical pancreatitis

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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 initial classic studies involved a comparison of clinical features with pathological changes in the pancreas at autopsy with the X-ray abdomen being the sole imaging tool available. Over the years, the disease was further characterized by studies by many researchers. 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.[2] 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.[3] 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".[4] Thus TCP was a disease that had exceptionally distinctive features at the time it was described.[5]

PREVALENCE

Prevalence of CP in western countries ranges from 10–15 per 100,000 population. In Japan, reported prevalence is 45 per 100,000 population. The commonest cause of chronic pancreatitis in the Western world and in Japan is abuse of alcohol. The Asia–Pacific survey (2004) showed a prevalence of 114–200 per 100,000 population in India.[5,6] 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.[7] This study also showed a female predominance (M:F ratio, 1:1.8) unlike hospital-based data.

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

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pancreatic intraductal calculi, development of diabetes and steatorrhea, malnutrition, and a high rate of development of pancreatic cancer.[8] A prediabetic phase clearly exists.

Recent reports suggest that the presentation is changing.[9] 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.[10]

The Indian Pancreatitis Study group (IPANS) conducted an online nationwide study encompassing 32 centers with AIMS, Kochi as the lead centre.[11]

Etiopathogenesis

Alcoholic chronic pancreatitis

Usually, drinking 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. We have reported differences in drinking patterns in patients with ACP as compared to those with alcoholic liver cirrhosis.[12] 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

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. TCP is now increasingly observed in the affluent and well nourished and rarely even in the obese. 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 which is well known to be implicated in pathogenesis of CP.
2. Dietary toxins: Manihot esculenta (cassava, tapioca) is a tuber which contains varying amounts of cyanogen glycosides. Cassava cultivation was introduced in Travancore 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 Geeverghese hypothesis indicated an association between dietary cyanide and TCP.[13] 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.[14] Cyanide toxicity however, still remains a suspect.
3. Genetic factors: Initial attempts to unravel genetic basis of familial clustering was in the form of HLA studies in Kerala.[15] 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" only16. Mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene could be important in TCP.[17] Cathepsin B, anionic trypsinogen, CTRC, and CASR genes are other genes studied18-20. Genome-wide association studies are needed to have a clear picture of the exact role of genetic factors.[21]
4. Oxidative stress: Cassava toxicity as well as malnutrition produces an ideal setting for free radical injury.

Oxidative stress and antioxidant depletion, however, appears to be a common pathogenetic mechanism in chronic tissue inflammation and injury; convincing pancreas specific effects in TCP remain unclear.

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

CLINICAL FEATURES

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.[22]

The most characteristic symptom is epigastric pain, which has the typical characteristics of pancreatic pain. The initial presentation is as 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. Often episodes of pain seem to be precipitated by dietary indiscretions e.g. following fatty meal. In many patients during the initial episodes of pain, conventional imaging like USG or CT may not reveal evidence of CP; on follow-up characteristic changes may be seen. ERCP or EUS may detect early changes of CP in these patients.

Malabsorption typically presents as steatorrhea; however overt steatorrhea may be lacking as many patients restrict fat in diet. Some patients may give history of passage of oil droplets.

Diabetes in TCP has been termed fibrocalcific pancreatic diabetes (FCPD) and is usually ketosis-resistant.[23-26] Most patients eventually need insulin although initially, glycemic controls can be achieved by dietary measures and/or oral agents. The 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.

Natural History

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.[27,28] 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.[29] Phenotypic differences within families is have been reported by us.[30]

Pancreatic Function Tests

Over the years a number of tests have been used to study pancreatic function in TCP.[31-36] Serum immunoreactive trypsin measurements have shown a spectrum of pancreatic involvement. In advanced stages, there is marked reduction of trypsin level while in early stages, it may be subnormal or even elevated due to acute pancreatitis. When Lundh meal test were performed, 93% of TCP patients with calcification had low tryptic activity as compared to 27% of the non- calcific variety.[31] Secretin pancreatozymin 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 in a study reported by the senior author.[35] There are several reports using fecal chymotrypsin as a screening test for evaluating exocrine function. Recently the role of fecal elastase 1 estimation in TCP has been demonstrated in a study by our group;[36] 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 Chari et al as well as other workers suggest that there are striking differences in radiological appearances in ACP and TCP.[37] 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.[38] Subsequent studies suggest that usual findings in TCP include large pancreatic calculi predominantly in head region causing maximal dilatation of MPD.[39] 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 early CP with patients often presenting as recurrent acute pancreatitis (RAP). It is also useful in evaluation and management of complications like pseudocysts.

Pathology

Pancreatic changes of CP have been described in an animal model.[40] 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 have been characterized.[41]

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. Dietary counseling can be effective alternative to use of expensive replacements.[42] The concerns of those with diabetes need extra consideration. We have shown recently that zinc[43] and folic acid deficiency[44,45] exist in CP.

Medical: As in other forms of chronic pancreatitis, medical management consists of analgesics and enzyme supplements for pain relief and exocrine insufficiency, respectively. Pain can be managed with analgesics including opioids using the WHO analgesic ladder. High protease pancreatic enzymes and to a lesser extent octreotide can be useful in management of pain. Fat maldigestion 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.[46] Antioxidant therapy has been shown to be beneficial.[47]

Endoscopic Treatment

Reddy et al first presented their experience with endoscopic stenting of pancreatic duct in TCP. Sphincterotomy and short-term stenting after dilatation of strictures and removal of calculi can improve the CP patients from a structural and potentially functional standpoint48. The patients with a dilated pancreatic duct due to a downstream obstruction by a stone, stricture or both are likely to benefit from endotherapy. Endotherapy does not benefit patients who have predominant involvement of the side branches. The pancreatic sphincter is widened with a pancreatic sphincterotomy; strictures in pancreatic duct, if any are dilated; and stones are extracted with a wire basket. Larg calculi can be pulverized with ESWL and the fragments are extracted during ERCP. Apart from its use as adjunct to endotherapy ESWL has also been used as a primary modality to a lesser extent.[49] Pancereatoscopy using SpyGlass is a new tool for facilitating endotherapy.[50]

Nerve ablation procedures like celiac plexus block or neurolysis, and splanchinctomy have also been used. EUS-guided celiac plexus block has been shown to be superior in an RCT recently.[51]

Surgical Management

Surgical treatment remains the gold standard for the management of intractable pain and treatment of complications.[52-54] 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, pseudocysts, pancreatic fistula and left-sided portal hypertension

Surgical procedures commonly used include **lateral pancreaticojejunostomy** or **Partington- Rochelle modification of Peustow procedure,** localized resection of head of pancreas by **Frey procedure** or **Beger operation**, and in cases of suspected pancreatic malignancy, **Whipple's operation**. 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.

Unlike ACP, the special problems involved in surgery in TCP include management of diabetes and association of malignancy at a young age.[53] While wide ductotomy, stone clearance and drainage give good symptomatic results in benign disease, the overall results are usually poor in patients with cancer.

ROLE OF A PANCREAS CLINIC

A multidisciplinary pancreas clinic with dedicated personnel that are capable of offering comprehensive care, patient education, regular follow-up and documentation including physician (s), and a clinic coordinator, social worker, and dietician who work in close collaboration with pancreatic surgeon and diabetologist, is a key concept. Our evaluations revealed that this has bestowed substantial improvement in symptoms, lifestyle and subjective perceptions of patients with chronic pancreatitis. There was significant improvement in HRQoL assessed using the SF 36. Furthermore, we have been able to achieve a substantial rate of cessation of alcohol and smoking among CP patients, through repeated 3–6 monthly counseling.[55]

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.[56-58] 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. There is no evidence that stone clearance and duct drainage procedures (endoscopic or surgical) can protect from malignancy in TCP. There are anecdotal reports of pancreatic cancer occurring several years after a pancreatic drainage procedure.

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 marker59. 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, pseudoaneurysms, venous thrombosis, CBD obstruction, and pancreatic fistulae and ascites.

Autoimmune Pancreatitis

This form of chronic pancreatitis is characterized by the presence of auto antibodies, 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 may be accompanied by other autoimmune manifestations like primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, and Sjögren's syndrome. Tissue IgG4 staining is a useful adjunct to serological diagnosis. 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. Very few cases have been reported from India till date.[60]

Idiopathic Chronic Pancreatitis

Idiopathic chronic pancreatitis (ICP) accounts for 40–60% of CP in India, as compared to 10–30% in the West. There are some differences in clinical spectrum of ICP in South India as compared to North India.[61,62] 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.[63-65] Etiological search for viruses (e.g. viral serology) is not a part of current diagnostic work-up for ICP.[66]

CONCLUSION

Classical forms of TCP are less often seen now. Presently ACP constitutes about one-third of CP patients. Autoimmune pancreatitis and other rare causes like hyperparathyroidism are now increasingly

reported. However ICP remains a dominant cause of CP in India.[67] Advances in the understanding of the role of genetic factors as well as environmental factors will help in clarifying the exact etiopathogenesis.

END NOTE

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Editorial Comments

Tropical Pancreatitis is typically seen in the southern and central Kerala. The valuable experience gained in managing this disease is being shared.

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