Chronic Calcific Pancreatitis In The Tropics

Despite repeated attempts at elucidation, chronic calcific pancreatitis (CCP) in the tropics continues to be a fascinating and enigmatic disease. Several distinctive features clearly set it apart from its counterpart in Western countries—(a) CCP in the tropics is a disease of adolescents and young adults; (b) history of alcoholism and evidence of gall bladder disease are virtually absent; (c) majority of the victims are malnourished; (d) diabetes mellitus is a common concomitant requiring massive doses of insulin for its control; and (e) complications as varied as nephropathy to pulmonary tuberculosis set in early and death follows by the second or third decade.

First report of the clinical combination of emaciation, diabetes mellitus and pancreatic calcification in young people came from Indonesia. The disease was directly attributed to malnutrition. Subsequent reports came from many countries in Africa and Asia and soon it became apparent that this conglomeration of symptoms was unique and different from the well recognized entity of chronic calcific pancreatitis due to alcoholism commonly encountered in the West. The large scale occurrence of this disease entity in India was first recognized by the work of Goveghare and colleagues who first reported on the endemic nature of this illness in the state of Kerala. Though many reports of small series of CCP have followed from different parts of the country, the high frequency of the disease seen in the state of Kerala has been unparallel. It has been estimated that 0.4-3 to 1-7% of all admissions and 7-5 to 16.3% of all diabetes admitted to two major teaching hospitals in the state were cases of CCP. Of interest is the observation that CCP secondary to alcoholism, often reported from Northern India, is rare in this Southern state despite the high prevalence of alcoholism and the consequent spectrum of liver damage seen here.

The clinical and biochemical profile of CCP in the tropics has been well brought out in many excellent publications. The characteristic features include insidious onset in the first or second decade of life, predilection for males, recurrent and sometimes intractable abdominal pain, high association with diabetes mellitus, accompanying malnutrition and stunted stature, and inexorable progression to complications and ultimate fatality by the second or third decade. In fact, physicians in Kerala are so familiar with the clinical picture of a malnourished and usually underdeveloped young person with enlarged parotids, cyanotic hue of the lips and potbelly, that CCP is often a matter of spot diagnosis; further demonstration of diabetes mellitus and pancreatic calculi on abdominal x-ray complete the picture.

Plain film of the abdomen reveals pancreatic calculi in 60 per cent of cases. It may be a solitary calculus, usually seen to the right of the first or second lumbar vertebra or the whole gland may be studded with calculi. Calculi may be of all sizes and shapes and are generally irregular. Fasting blood sugar levels range between 200 and 400 mg/dl in the average case. Serum lipids values are found to be reduced. Stool fat values on an enhanced fat

intake are abnormal in about forty per cent of patients. D-xylose absorption and jejunal morphology are in the normal range.

Secretin-pancreozymin tests have shown low volume, enzymes and bicarbonate levels. On Lundh meal test, a marked reduction in trypsin activity (mean normal 19 μeq/ml/min) with a clear division between the values in calcific (< 2 μeq/ml/min) and non-calcific (2-15 μeq/ ml/min) cases has been observed.

ERCP studies have shown changes reminiscent of CCP due to alcoholism, though in non-calcific cases the changes are minimal.

Pathology of tropical CCP present certain characteristic features. The pancreas is small, atrophic, fibrosed and may be calcified. There is extensive atrophy of the acini with replacement by broad sheets of fibrous tissue. The ducts and ductules are dilated with intervening strictures. Some of the dilated segments appear like cystic spaces and contain inspissated material, organic debris, desquamated cells and calculi. The ductular epithelium is desquamated and may exhibit stratification in areas. Inflammatory reaction is minimal. The islets of Langerhans may be normal or atrophic, but may be hyperplastic. The calcified are predominantly composed of carbonates, with traces of phosphates, oxalates, magnesium and proteins. The contingent preservation of islets in the face of extensive acinar destruction and the poverty of inflammatory changes are so arresting that some pathologists have even wondered whether the entity is an "acini" all. The parotids show hypertrophy of acini and later atrophy with periductal fibrosis. Fatty liver is common and occasionally cardiogenic changes are noticed.

A variety of complications punctuate the course of CCP. Urinary infections, nephropathy, Kimmelstiel-Wilson syndrome, pulmonary tuberculosis, retinopathy, cataracts and hypertension occur in various combinations. Angiopathy and neuropathy complicated a significant number of cases (60% and 70% respectively), far exceeding the reported incidence in the Western type of CCP. Ketonis and hyperglycemic episodes are commonly observed. Hepatic complications include fatty liver and less commonly, cirrhosis. Ischemia and gangrene of the limbs are rare but have been observed in a few instances.

There have not been many studies directed towards the etiopathogenesis of tropical CCP. Hypothesis abound where facts are few and tropical CCP is a typical example of this. The earliest hypothesis linked CCP with protein-caloric malnutrition. Zaidel observed that all his patients were on a low protein diet and were grossly emaciated and concluded that the pancreatic lesions were the end result of long continued protein-caloric malnutrition. Similar observations were made by Shaper from Uganda. Many other reports confirm the predominant occurrence of the disease in poorer communities with low levels of nutrition. As early as 1950 Veghelyi and colleagues had reported nutritional pancreopathy benefited by high protein diet.
ion in enzyme and bicarbonate output resulting from prolonged protein-calorie malnutrition with reversal to normal, following a high protein diet has also been reported. However, it is worth noting that the changes in the pancreas brought on by protein-calorie malnutrition are essentially reversible. Only a minority of cases of Kwashiorkor have irreversible pancreatic fibrosis and atrophy. There are no protein plugs or inflammatory changes in the pancreas in Kwashiorkor and no abdominal pain. Nor is diabetes mellitus observed. Further, there is no evidence that protein deficiency in childhood may be responsible for pancreatic lesion in adults. Adult biopsies of pancreas in endemic areas of protein-calorie malnutrition have been found to be normal.

The majority of our CCP patients come from low socio-economic strata and their protein intake is poor. The average protein and fat content of their diet is 36 g and 30 g per day respectively, with a calorie value of 1925. They are malnourished and stunted in growth at the time of presentation. They exhibit paradoxical enlargement and fatty liver, both accompaniments of malnutrition. Many of them show signs of specific nutritional deficiencies. The pathological changes of extreme atrophy and fibrosis of the pancreas with scanty inflammatory cell reaction are consistent with the changes of protein malnutrition.

However, it is an interesting observation that an occasional patient with CCP comes from an affluent background. Moreover, the disease does not uniformly manifest in all protein-deprived populations. The nutritional deficiency in the victims could also well be the result of the diabetes mellitus and the pancreatic exocrine deficiency. It may be possible that CCP malnutrition has a conditioning effect on the pancreas rendering it more vulnerable to dietary toxins, immunological mechanisms or bacterial or viral infections.

A certain amount of clustering of cases of CCP has been noted in the hilly terrain of Kerala where the tuber tapoe (Cassava, Manihot utilissima or Manihot esculenta) is richly cultivated and forms the staple diet. Tapoea has 9% starch but only 0.4% protein and contains cyanogenic glycosides, linamarin and methyl linamarin which are converted by the gastric hydrochloric acid into hydrocyanic acid (HCN). HCN is excreted as thiocyanates and sulphur containing amino-acids methionine and cystine are used up in this conversion. The resultant deficiency of these essential amino acids in a malnourished subject could lead to fatty change and fibrosis of the pancreas and the liver, two of the organs with a high protein turnover. However, feeding experiments with tapoea in rats maintained on a low protein diet, conducted by some of our colleagues, failed to produce pancreatitis. In another study, administration of cyanide in water to rats did not result in pancreatitis. Moreover, there are many patients with CCP in Kerala who have rarely consumed tapoea. Thus, tapoea does not seem to be directly responsible for CCP though an additive role along with malnutrition cannot be ruled out.

CCP as seen in Kerala is a familial disease. Many sibs are affected though vertical transmission has not been noticed. There are pairs of twins afflicted by the disease. However no specific pattern of inheritance has been observed. There are now many reports of a similar type of pancreatitis from other parts of India and even other tropical countries. This points to common environmental factors. We have not observed predominance of any blood groups and a study of dermatoxyphiles has shown some characteristic patterns. HLA studies, which are under way, promise to provide some insight into a possible genetic influence.

Infections are quite common in tropical countries. Infections by many viruses are known to cause acute pancreatitis. Viral infection has also been shown to attack the beta cells of the pancreas with resultant diabetes mellitus. However, the role of viral infections in causation of chronic pancreatitis is not clear. This aspect is currently being investigated in our department.

Though ductal anomalies have been proposed to explain the pathogenesis of tropical CCP, the available data based on a few autopsies and case studies of the duct system does not lend support to this view. The hypothesis advanced by Nwokolo and Ohi, namely sluggish flow of pancreatic secretion, gastointestinal leading to inspissation, mucus plug formation and still later calcification, seems too simplistic a concept.

Factors like hyperlipidaemia and hyperparathyroidism are not operative in tropical CCP.

Electron microscopic study of the pancreas and analysis of pure pancreatic juice for proteins including lactoferrin and stone protein, minerals and other constituents, have been initiated by us and expected to shed some light on the pathogenesis. Immunological studies conducted by our group have shown reduction in T-lymphocytes, an elevation of IgG and IgM, presence in a few patients of pancreatic hemagglutinating antibodies and no significant level of auto-antibodies. The immunological changes may vary well be secondary, but their role in perpetuation of an already existing injury deserves consideration.

The management of CCP of tropics can be a frustrating experience. The diabetes is severe and needs large doses of insulin. Ketosis and hypoglycemic episodes are common. Stomatitis, when present, can be reduced but not totally reversed by pancreatic extracts. Pain may be severe and intractable and may necessitate surgical intervention. A variety of surgical procedures have been employed reflecting the inadequacies of available techniques. Splenectomy is disappointing while the modified Person's procedure of side to side pancreatojejunostomy appears to offer some relief. Surgery does not affect the course of the disease nor the insulin requirement. Most patients return with pain at varying intervals. Complications set in by the second or third decade and very few survive to reach the fourth.

Tropical CCP may well prove to be the proverbial Indian elephant. Its pathogenesis is most possibly multifactorial, with malnutrition as the broad canvas on which are superimposed the influences of food toxins, viral infections and immunological factors. In unduly focusing on the individual factors while turning a blind eye to the others, we may indeed miss the elephant and end up with its tail.

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Incidence of Peptic Ulcer on Endoscopy

Nanivadekar et al have presented in this issue most interesting and highly controversial data that the ratio of duodenal: gastric ulcers as seen on endoscopy in patients from Bombay is 5:1 and not much higher as reported earlier. It would be important therefore to obtain data from other centres in our country (including a few from Bombay) on endoscopy and preferably also on double contrast barium meal study before accepting the conclusions of this study without any reservation.

Several points need considerations in this context. Endoscopic observations in the study were not confirmed by routine or double contrast radiological examination. While routine radiological study is less accurate than endoscopy, double contrast study of stomach and duodenum for detection of duodenal or gastric ulcer is nearly as accurate as endoscopy with experienced radiologists. Whereas the detection of duodenal or gastric ulcer on routine radiological examination is less accurate than endoscopy, the high ratio of duodenal: gastric ulcer may not be very inaccurate as it has not been demonstrated that gastric ulcers are more frequently missed than duodenal ulcers on routine radiological examination.

The definite superiority of endoscopy as compared to radiology reported in several studies has resulted from several factors; (i) double contrast barium meal study is not routinely performed in most centres; (ii) radiologist should not be compared with good endoscopist; (ii) an endoscopist usually performs an examination after the results of barium meal study are known to him and hence detects all the lesions already detected by a radiologist and a few more. If radiological examination does not precede the endoscopy, it is quite possible that an endoscopist may miss some of the ulcers detected by a radiologist (eg, benign gastric ulcer high up on lesser curvature with a forward viewing instrument) and (iii) when a lesion is detected by an endoscopist and not

by a radiologist, it is always presumed that the latter had missed the lesion. It is quite possible that an endoscopist might have detected a 'lesion' which in reality does not exist. For example, mucosal sticking between two gastric folds or a gastric erosion might have been occasionally misinterpreted as a gastric ulcer on first examination and as healed when not detected on a second examination a few weeks later.

The interobserver and intraobserver errors, have been well recognized in interpretation of X-ray chest, electrocardiogram, sigmoidoscopy etc. Hence, errors in interpretation of lesions on gastro-intestinal endoscopy are to be expected even with experienced gastroenterologists. The extent of the error will be determined by: (a) the experience of the endoscopist; (b) the enthusiasm of the endoscopist; (c) the cooperation of the unsedated patient; (d) the time spent on each examination and (e) the clarity of the vision available from a new or old endoscope etc.

Since one would not accept observations of a radiologist on fluoroscopy alone without X-rays as accurate, one should also consider observations of any experienced endoscopist, without photographic documentation, as only possibly correct. The difficulties of obtaining photographic documentation routinely are obvious.

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References