Fibrocalculous Pancreatic Diabetes

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1. Introduction

In developing countries, peculiar forms of diabetes associated with undernutrition have been reported since the beginning of the century. Conflicting criteria and varied clinical presentations of the disease led to confusion in proper characterization of these forms of diabetes. In 1985, thanks largely to the work of Bajaj[1], the WHO study group report on diabetes[2] included Malnutrition Related Diabetes Mellitus (MRDM) as a form of diabetes distinct from Insulin Dependent Diabetes Mellitus (IDDM) and Non-Insulin Dependent Diabetes Mellitus (NIDDM). Under MRDM two subgroups are recognized: Fibrocalculous Pancreatic Diabetes (FCPD) and Protein Deficient Diabetes Mellitus (PDDM). FCPD is a type of diabetes secondary to a unique form of chronic pancreatitis seen in developing countries. PDDM is distinguished from IDDM in that despite severe insulin requiring diabetes, patients do not develop ketosis if insulin injections are withdrawn. This article will only deal with FCPD.

2. Terminology

Several terms have been proposed for this syndrome including Tropical Calcific Pancreatitis, Tropical Chronic Pancreatit-is, Tropical Pancreatic Diabetes, Nutri-tional Pancreatitis, Endemic Pancreatic Syndrome etc. For sake of uniformity and international agreement in description of the disease it is advisable to adopt the WHO study group report term - Fibrocalculous Pancreatic Diabetes (FCPD). We and several other groups had earlier used the term ‘tropical’ to describe this disease. However, due to migration of patients from tropical to temperate zones, the disease is occasionally reported from developed countries[3,4] in migrants from tropical countries. Hence the term ‘tropical’ is best avoided. We propose that the term Fibrocalculous Pancreatitis (FCP) be used when one refers to the pancreatitis and Fibrocalculous Pancreatic Diabetes (FCPD) when one refers to the diabetes secondary to FCP.

FCP differs from alcoholic chronic pancreatitis seen in the western world in several respects: the age at onset is younger, the disease has a more accelerated course, the prevalence of diabetes and pancreatic calculi is considerably higher and finally alcoholism is absent (by definition). The differences between FCP and alcoholic chronic pancreatitis have been reported by us earlier[5,6] and they are summarized in Table 1.

3. Historical background & prevalence

In 1959, Zuidema[7] from Indonesia was the first to describe diabetes associated with pancreatic calculi and protein calorie malnutrition. Reports from several tropical parts of the world including Uganda, Nigeria, Brazil and several countries in Asia including Thailand, Bangladesh and Sri Lanka subsequently confirmed the existence of this syndrome.[8-12] In India the frequency of FCPD is higher in the South than the North. Geevarghese[9] one of the pioneers in the field has reported on over 1700 cases from the state of Kerala in south western India which in fact has the highest known prevalence of FCPD in the world. Large series have also been reported from Kerala[10], Tamil Nadu[11,12], Orissa[13], Karnataka[14] and other parts of India.

In Kerala, in the 1960's, FCPD constituted 29.3% of the total diabetic cases admitted as inpatients at the Kottayam Medical College[9]. However, this figure came down to 0.009% in 1980. This might however reflect a change in priorities for admission to the hospital as most diabetic patients would now be treated on an out-patient basis. There is only one population based study on the prevalence of fibrocalculous pancreatitis. Balaji[15] made a systematic survey of 6079 families in Quilon district, Kerala. A population of 28,507 was studied by clinical history, ultra-sonography and Para-amino-benzoic acid (PABA) tests. Twenty-eight cases (1:1000) had chronic calcific pancreatitis. At the M.V.Diabetes Specialities Centre (MVDSC) at Madras, a large referral centre for diabetes, about 50 patients with FCPD are registered annually which constitutes 1% of all diabetics and 4% of "young" diabetics (defined as onset below 30 years of age) seen at our centre. Figure 1 shows the distribution of FCPD in relation to other types of diabetes seen at MVDSC, Madras.

For the last few years a " pancreatitis " registry has been set up at our centre. The current status of patients in this registry is shown in Table 2. It can be seen that FCPD and Pre-FCPD together comprise 393/484 patients (81.2%) of chronic pancreatitis. Thus FCP is the commonest form of chronic pancreatitis seen at our centre and Alcoholic Chronic Pancreatitis is the next common type (16.7%).

4. Clinical features

FCPD patients present with several distinct clinical features. Patients are invariably poor and present with extreme emaciation, protein energy malnutrition, bilateral parotid enlargement, distension of the abdomen and rarely, a cyanotic hue of the lips. Recently there appears to be a change in the clinical features of FCPD patients because of improved nutritional status. In our series[16] overt malnutrition was observed only in 25% of patients, although 70% were lean. Many FCPD patients are from the middle and a few from the upper strata of society. While leanness continues to be a feature, extreme degrees of undernutrition and emaciation are less common. A body mass index (BMI) of less than 19, often taken as a criterion for undernutrition, is seen in about 50% of our patients while the rest have BMI varying from 19-25. In the majority of patients the diagnosis of diabetes is made between the ages of 20 and 40, but onset in childhood[17], in infancy[18] and in older age groups[19] is not uncommon.

5. Natural History of FCPD

The cardinal triad of FCPD is abdominal pain, pancreatic calculi and diabetes.

In the natural history of FCPD the first symptom to manifest is usually abdominal pain. After periods varying from a few months to several decades, pancreatic calculi may be diagnosed by routine abdominal radiography. At this time the patient may still have normal glucose tolerance and no evidence of exocrine pancreatic dysfunction. After some months to years, glucose intolerance and/or exocrine pancreatic dysfunction may set in as shown in Fig 2.

Although this is the classical natural history, sometimes the first sign of the disease may be pancreatic calculi, diabetes or steatorrhoea

5a. Pain Abdomen

FCPD patients usually have a history of recurrent abdominal pain from childhood. However, we[19] have seen that in the older cases (above 60 years) the pain may start in the 4th or 5th decade of life. It is usually very severe, epigastric in location, may radiate to the back and is relieved by stooping forward or lying in a prone position. It is characterized by periods of remission and exacerbation and usually abates by the time diabetes sets in. Hence the frequency of pain is always higher in a gastroenterologist's series than in a diabetologist's series. Due to the intensity of the pain, many patients become addicted to powerful narcotic analgesic drugs.

5b. Steatorrhoea

Overt steatorrhoea is seen in about a third of patients. However in others it may be subclinical and is diagnosed by exocrine pancreatic function tests. The low frequency of steatorrhoea is attributed to the low fat content of the diet. When the fat content of the diet was experimentally increased, steatorrhoea was found to occur in over 90% of patients.[10]

5c. Nature of Diabetes

Diabetes is usually severe and occurs a decade or two after the first episode of abdominal pain. Despite requiring insulin for control of hyperglycaemia, FCPD patients rarely develop ketoacidosis on withdrawal of insulin. This may be due to several factors. Our studies[21] as well as that of others[20,22-24] have shown that the pancreatic beta cell function is partly preserved in patients with FCPD. This residual b -cell reserve may be sufficient to protect against ketoacidosis. Other explanations for the resistance to ketosis include: a low glucagon reserve, decreased adipose tissue mass and carnitine deficiency.[20]

Contrary to earlier reports, insulin requirement is not very high and the mean daily insulin dose in our patients is 40± 12 units especially if sulphonylureas are also used. The latter are in fact often combined with insulins as they help to reduce the cost of treatment as insulin is expensive. Thus insulin resistance is not a feature of FCPD. On the contrary

many patients may be sensitive to insulin and hypoglycaemia may occur more often. This could be explained by the absence of glucagon.

We[11] have shown that there is a wide spectrum with respect to the clinical severity of FCPD. While most patients require insulin injections, about 10-20% of patients may respond to oral hypoglycaemic agents at least for the first 5-10 years and in some cases for much longer periods of time. While the majority of the insulin requiring patients are ketosis resistant, a few may be prone to ketosis. The response to therapy appears to correlate with the pancreatic b -cell function, as assessed by serum C-peptide levels.[15,16] Although most patients ultimately develop overt diabetes, we have seen patients in the stage of Impaired Glucose Tolerance (IGT) and at a still earlier stage, the glucose tolerance can be normal. We propose that the terms Pre-FCPD be used to denote the stage of Normal Glucose Tolerance, FCP-IGT to denote the IGT phase and FCPD after overt diabetes has set in.

6. Radiological features

Presence of pancreatic calculi is the hallmark of FCPD. The calculi are multiple, large, rounded, dense, discrete and always confined to larger ducts. They are usually seen to the right of the first or second lumbar vertebrae, but may occasionally overlap the spine. In some patients the whole pancreas may be studded with calculi. We[6] and Geevarghese[9] have shown that in FCPD, unlike in Alcoholic Pancreatitis, calculi are very rarely seen to the left of verterbrae i.e. in the tail region of the pancreas, as they tend to start in the larger ducts, i.e. in the head region and then proceed tailward. The opposite appears to be the case in alcoholic pancreatitis.

Ultrasound and CT scan help to confirm the location of calculi within the pancreatic duct and to document other features of chronic pancreatitis, e.g. ductal dilatation. They also provide information regarding the structural changes in the gland particularly the ductal morphology. Ultrasound findings reported by us[25] include shrinkage in size of the gland, increased echogenicity and ductal dilatation which is often very marked. CT scaning has allowed a closer look at pancreatic morphology during life[20]. The pancreatic mass is preserved in the " early " stages and swelling of the parenchyma is evident. In more advanced stages, the pancreas shows varying degrees of atrophy and finally there may be very little pancreatic parenchyma, its place being taken by a "bag of stones". In some cases, fat infiltration is prominent. The pancreatic duct appears irregularly dilated with stones in the lumen.

Endoscopic retrograde cholangio- pancreatography (ERCP) is rarely required to diagnose FCPD. However it is sometimes useful to diagnose "non calcific FCPD" where the ductal abnormalities help to diagnose this condition[26].

7. Pathology

The pathology of the pancreas in FCPD has been described in detail by Nagalotimath.[27] Macroscopically the pancreas of FCPD patients is usually small, atrophic and fibrosed.

The ducts are dilated with multiple calculi in the major ducts or its tributaries. Mucinous, putty - like material which are protein plugs, form the initial nidus on which calcium deposition takes place. The calculi are composed of carbonates, with traces of phosphates, oxalates, magnesium and proteins.

Studies on the histopathology of the pancreas have been based on biopsy or autopsy specimens. In most studies patients with advanced stages of the disease have been studied. Excellent reviews by Nagalotimath[27] and Nair[28] have described the pathological lesions in FCPD.

In the initial stages, inflammatory changes may be seen in the exocrine pancreas. These consist of infiltration by lymphocytes, plasma cells and eosinophilic cells. As the disease progresses, widespread destruction of acini occur and inflammatory cells may not be seen.

Fibrosis starts early and classically leads to "cirrhosis of the pancreas". In some cases, extensive fat infiltration also occurs. Ducts and ductules show degenerative changes, and the lining epithelium may show squamous cell metaplasia. Ductules crowd together due to loss of intervening acinar tissue and also show true proliferation. In some patients pathological changes suggest "localised and arrested" disease[27].

The islets of Langerhans appear to be intact till fairly advanced stages of the disease. There is no "insulitis". Hypertrophy as well as atrophy are seen. Nesidioblastosis is a well described feature. The islets are probably destroyed later due to surrounding fibrosis (‘strangulation’), and possibly also by disruption of blood supply. There are no studies of islet numbers in FCPD but presumably they must be severely diminished with progression of the disease.

8. Exocrine pancreatic function

Several authors have reported on exocrine pancreatic function in FCP. Punnose et al[29] reported the usefulness of the Lundh Meal test. Using a cut-off point of 21 u/ml, 93% of the calcific FCP cases compared with 27% of the non-calcific variety had low tryptic activity.

Secretin-pancreozymin tests done by Balakrishnan’s group[30] in collaboration with the Marseille group showed that the lactoferrin level of the pancreatic juice was considerably higher in Indian patients and controls than in their European counterparts. This suggests that the pancreatic acinar cells could be hyperactive, perhaps in response to a pancreatic insult.

Serum immunoreactive trypsin measurements showed a spectrum of exocrine pancreatic involvement.[31-34] In early cases (normal glucose tolerance and IGT) serum immunoreactive trypsin was subnormal only in a few subjects, while in some it was markedly elevated suggesting active pancreatitis. The exocrine reserve appeared relatively well preserved till a late stage. In advanced cases (FCPD), serum

immunoreactive trypsin was subnormal in most cases and severely diminished in over two thirds. Faecal chymotrypsin measurements showed similar results[31,33] as did pancreatic isoamylase.[31,34] In our experience faecal chymotrypsin test is a simple and inexpensive method for screening for exocrine pancreatic insufficiency in FCPD patients.

9. Variability of FCP

Recent studies mentioned above highlight the variable nature of the FCP.

Table 3 summarizes the variability with respect to the clinical, biochemical, ERCP and histopathological features of FCP.

10. Criteria for FCPD

Despite excellent clinical descriptions of the disease, no definite criteria have been laid down as yet for the diagnosis of FCPD. Mohan et al[8,11] have proposed the following criteria for the diagnosis of FCPD, based on their own studies and an extensive review of the literature (Table 4).

11. Specific diabetic complications

It was earlier believed that being a secondary form of diabetes, microvascular complications are rarely seen in FCPD. Our studies[16,35] and that of Geevarghese[36] have shown that microangiopathy occurs as frequently in FCPD as in primary forms of diabetes like NIDDM and IDDM. We[35] have shown that sight-threatening forms of retinopathy i.e. both maculopathy and proliferative retinopathy do occur in FCPD patients. Neuropathy, nephropathy and left ventricular dysfunction, also occur in our patients[16]. Recently Govindan and Das[37] have reported on the occurrence of autonomic neuropathy in FCPD patients.

In contrast, macrovascular complications were less common in FCPD, but we have seen occasional occurrence of ischaemic heart disease and peripheral vascular disease[38]. The low frequency of macrovascular complications may be due to the relative young age of the patients, leanness and the low cholesterol levels[16].

12. Complications due to chronic pancreatitis

Complications due to chronic pancreatitis include pseudocysts, pancreatic abscess obstructive jaundice, which can either be due to stenosis of the common bile duct or a stone obstructing the passage or due to associated carcinoma of the pancreas. Recent studies from our group,[39] Augustine[40] and Balakrishnan[10] suggest that FCPD could be a premalignant condition as several patients with FCPD were noted to develop carcinoma of the pancreas on follow-up. Current evidence[39] suggests that the risk for developing carcinoma in FCP is higher than in temperate zone pancreatitis al-though the reasons for this are not clear.

13. Management of chronic pancreatitis

Pancreatic enzymes help to reduce steatorrhoea and may indeed, alleviate pancreatic pain in some cases. More often however, pain is severe and intractable and is not relieved even by powerful analgesics. At this stage, surgical intervention may benefit. Sphincterotomy, side-to-side pancreatico- jejunostomy (Puestow's procedure) and end-to-side pancreatico-jejunostomy (Duval's procedure) have been tried. Many of these procedures are beneficial with respect to alleviation of pain. Some patients however have recurrence of pain and these procedures rarely alter the diabetic status of the patient. Tripathy and Samal[41] reported that after surgery the mean daily insulin requirement fell from 46 units to 34 units and that the basal serum insulin improved from a mean of 4.3 to 10.2 micro units/ml in patients. However it is likely that these changes are usually transient and the diabetic status appears to be largely unaffected by surgery.

14. Aetiology and pathogenesis

The etiopathogenic mechanisms for FCPD are still unclear. Malnutrition and cyanogenic alkaloids (derived from cassava or other food items) have often been incriminated as etiological factors. Recently, 'oxidant stress' has been proposed as a mechanism in pancreatic damage.

14a. Malnutrition

Severe clinical malnutrition at the time of diagnosis in several FCPD patients suggested to many workers a causative role for nutritional deficiencies.[8,10,42-45] However, a past history of severe malnutrition (kwashiorkor) is usually absent. Moreover, malnutrition at presentation may well be secondary to severe exocrine and/or endocrine pancreatic deficiency. A proportion of FCPD patients do not show undernutrition by the BMI criteria.[16,46] Recent work suggests that micronutrient deficiency rather than overt protein and calorie deprivation, may predispose to FCPD (see below).

14b. Cyanogenic alkaloids

McMillan and Geevarghese[47] observed the geographical occurrence of FCP in areas where the tuber cassava (tapioca, manihot) is consumed as a staple food and suggested a causative role for cassava in the aetiology of this condition. They suggested that dietary deficiency of sulphur amino acids (methionine, cystine) could hamper detoxification of cyanide to thiocyanate and lead to high levels of 'free' cyanide which might be toxic to b -cells. Studies in rats have shown that cyanide administration can lead to transient hyperglycaemia but not to permanent diabetes.[9,16] The relevance of these observations to the clinical situation is still unclear, especially the role of cyanide in causing pancreatic damage. Recent studies in Africa[48] failed to find FCPD in areas where cassava is eaten as a staple food but this again could be related to differences in processing/cooking of the tuber. The role of other foodstuffs which may contain cyanogenic glycosides merits further study.

14c. Genetic, familial and immunological factors

Familial clustering of FCP, sometimes in successive generations has been described.[10,36,49,50] In our series[50] 12% of parents and 21% of siblings of FCPD patients showed evidence of exocrine pancreatic involvement, and 21% of parents and 11% of siblings had previously undiagnosed NIDDM. In the absence of a specific genetic marker, it is difficult to say if these results reflect a genetic transmission or a shared environmental factor. We[51] also recently reported that about 40% of FCPD patients shared the HLA-DQ-B haplotype which is usually associated with IDDM. Another 40% of FCPD patients showed an association with the class 3 allele of the insulin gene which is similar to the association seen in our NIDDM patients. Obviously more work is needed, but these studies provide evidence for the first time, for a genetic susceptibility to FCPD.

14d. Oxidant stress and anti-oxidant deficiency

Braganza[52] has suggested that chronic pancreatitis in the U.K. is a result of heightened but unmitigated oxidative detoxification reactions in the pancreas and liver, coupled with exposure to xenobiotics biotransformed by cytochrome P-450 enzyme systems and a relative deficiency of anti-oxidants. She has now extended the hypothesis to include FCP[53]. In preliminary collaborative studies, we[54] found evidence of increased exposure to xenobiotics, especially polycyclic aromatic hydrocarbons (cigarette, kerosene and firewood smoke and vehicular fumes) in patients of FCP compared to controls. This was associated with elevated theophylline clearance (a marker for heightened cytochrome P-450 activity)[55].

Further studies[56] have shown evidence of anti-oxidant deficiency, particularly of Vitamin C and Beta Carotene in the Madras FCP patients and control subjects compared to the Manchester subjects. The levels of selenium and Vitamin E were not significantly different between the two groups. More studies are needed on the micronutrient status of FCP patients to confirm these findings.

Conclusion

Fibrocalculous Pancreatitis is a unique form of chronic pancreatitis seen in developing countries associated with either overt protein calorie malnutrition or more likely with a deficiency of certain micronutrients. Compared to temperate zone pancreatitis, FCP affects younger individuals and has a more aggressive and accelerated course to reach the end points of diabetes, pancreatic calculi and exocrine pancreatic dysfunction. There are characteristic features of FCP radiologically, ultrasonographically, on ERCP and on histopathology. Although a secondary form of diabetes, specific diabetes related complications do occur in FCPD. There appears to be a high risk of developing pancreatic carcinoma. Although the etiology of FCPD is still unclear, the role of micronutrient deficiency merits further study. The contribution of genetic factors and environmental toxins e.g. cyanogenic glycosides still remains unclear.

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