Fibrocalculous pancreatic diabetes-Part II

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Radiological features

Presence of pancreatic calculi is the hallmark of FCPD. The calculi are multiple, large, rounded, dense, discrete and almost always confined to larger ducts. They are usually seen to the right of the first or second lumbar vertebrae, and often the whole pancreas may be studded with calculi. We (Chari et al, 1991; 1992) and Geevarghese (1968) 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.

If pancreatic calculi are definitely present it is not necessary to use other imaging techniques as the diagnosis of chronic pancreatitis, and hence of FCPD, is obvious. However we have shown that while the sensititivity of pancreatic calculi is quite good with a plain abdonimal x-ray, the specificity improves if an imaging technique is also used eg. ultrasound (Suresh et al, 1988). Ultrasound and computerized tomography also help to confirm the location of calculi within the pancreatic duct and to document other features of chronic pancreatitis, eg. ductal dilatation. They also provide information regarding the structural changes in the gland particularly the ductal morphology. Ultrasound findings reported by Mohan et al (1985a) include shrinkage in size of the gland, increased echogenicity and ductal dilatation which is often very marked. CT scanning has allowed a closer look at pancreatic morphology during life (Yajnik, 1992). The pancreatic mass is preserved in the "early" stages and swelling of the parenchyma is evident. In more advanced stages, the pancrease shows varying degree 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. Between ultrasound and CT the former is obviously the first choice because of the cost factor and also because in those who are very lean, ultrasound offers certain advantages. However the pancreatic imaging is far better with CT which also helps to pick up micro-calculi who could be missed on plain abdominal x-ray. Mass lesions (eg. carcinoma) are also better delineated on CT scan.

Endoscopic retrograde pancreatography (ERP) 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 (Balakrishnan et al, 1985). ERP is useful in patients in whom surgery is being planned as knowledge of the duct morphology can help to decide the type of surgery. This is also useful in suspected cases of pancreatic cancer occuring in FCPD patients. Finally ERP is often done as a therapeutic procedure whereby sphincterotomy with removal of stones near the head is done or where stents are placed.

Pathology of pancreas

The pathology of the pancreas in FCPD has been described in detail by Nagalotimath (1980) and Nair and Latha (1986). 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. Pitchumoni and colleagues have reported on the ultrastructure of pancreatic calculi in FCPD (Schultz et al, 1986).

Studies on the histopathology of the pancreas have been based on biopsy or autopsy specimens but in most studies, only patients with advanced stages of the disease have been studied. In the initial stages, inflammatory changes may be seen in the exocrine pancreas. These consist of infiltration by lym-

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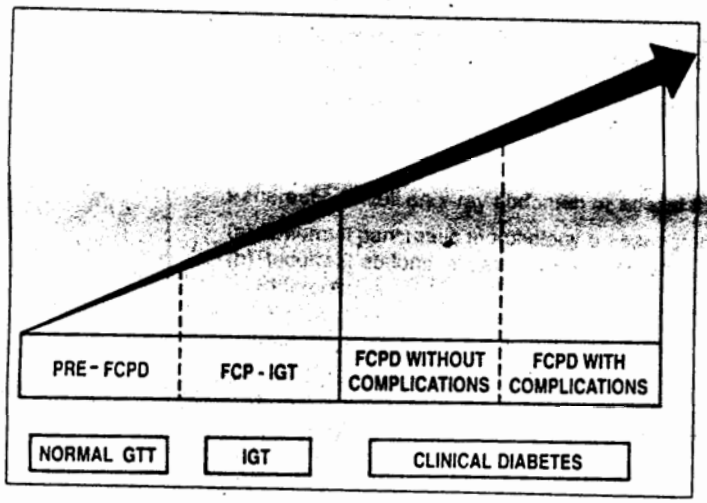
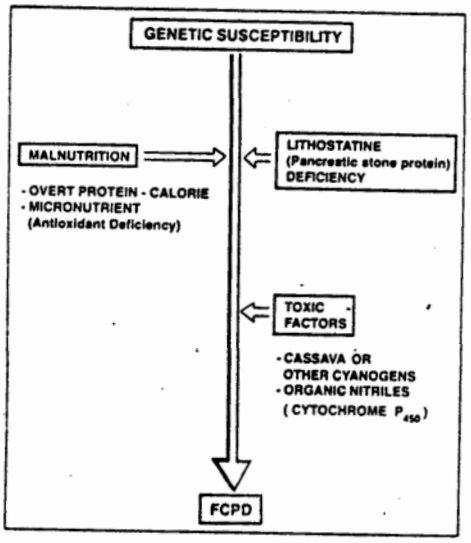


phocytes, plasma cells and eosinophilic cells. As the disease progresses, widespread destruction of acini occur and inflammatory cells may not be seen. Fibrosis starts early and classically leads to "cirrhosis of the pancreas". In some cases, extensive fat infiltration also occurs. Ducts and ductules 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 (Nagalotimath et al 1980).

The islets of Langerhans appear to be intact till fairly advanced stages of the disease. Nesidioblastosis has been described by Nair and Latha (1986). The islets are probably destroyed later due to surrounding fibrosis ('strangulation'), and possibly also by disruption of blood supply.



Exocrine pancreatic function

Several authors have reported on exocrine pancreatic function in FCP. Punnose et al (1987) reported on 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 (Balakrishnan et al. 1988) showed that the lactoferrin levels of the pancreatic juice was considerably higher in Indian controls and patients with chronic pancreatitis compared to their Euroepan counterparts.

Serum immunoreactive trypsin measurements show a spectrum of exocrine pancreatic involvement (Yajnik et al, 1989 and 1990). In early cases serum immunoreactive trypsin levels are subnormal only in a few subjects, while in some it was markedly elevated suggesting active pancreatitis. In advanced cases serum immunoreactive trypsin level was subnormal in most cases. Faecal chymotrypsin (FCT) measurements (Yajnik et al, 1988; Mohan et al, 1989b) and pancreatic isoamylase (Yajnik et al, 1989; Wiyono 1988) have also been used to assess exocrine pancreatic insufficiency in FCPD patients. In our experience, faecal chymotrypsin test is a simple and inexpensive method for screening for exocrine pancreatic insufficiency in FCPD patients with a high specificity although the sensitivity is not satisfactory, particularly to pick-up early stages of the disease (Mohan et al, 1989b).

Criteria for diagnosis and variability of FCPD

Despite excellent clinical descriptions of the disease, till recently no criteria had been laid down as yet for the diagnosis of FCPD. Mohan et al (1994; 1985) were the first to propose a set of criteria for the diagnosis of FCPD, based on an extensive review of the literature and these criteria have been fairly widely accepted (Yajnik 1992). Table 1 lists Mohan's criteria for FCPD.

Tabel 1. Mohan's criteria for Fibrocalculous Pancreatic Diabetes (FCPD) (Mohan et al, 1988)

1. A patient should originate from a "tropical" country.
2. "Diabetes" should be present according to WHO Study Group (1985) criteria..
3. Evidence of chronic pancreatitis must be present:
   Pancreatic calculi on x-ray abdomen or atleast three of the following:
   (a) Abnormal pancreatic morphology on sonography/CT Scan.
   (b) Recurrent abdominal pain since childhood.
   (c) Steatorrhoea
   (d) Abnormal pancreatic function test.
4. Absence of other causes of chronic pancreatitis i.e. alcoholism, hepato-biliary disease, primary hyperparathyroidism, etc.

All the above studies highlight the fact that fibrocalculous pancreatitis is a highly variable (heterogenous) condition. in contrast to the earlier descriptions of the disease modes three decades ago. Table 2 summarizes the variability with respect to the clinical, biochemical, ERP and histopathological features of FCP.

Complications

It was earlier believed that being a secondary form of diabetes, microvascular complications are rarely seen in FCPD. Our studies (Mohan et al, 1985; 1988; Ramachandran et al 1985; 1987) and that of Geevarghese (1985) have shown that microangiopathy occurs as frequently in FCPD as in primary forms of diabetes like NIDDM and IDDM. We (Rema and Mohan 1989; Pitchumoni et al 1992) have shown than 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 (Mohan et al 1985; 1988: Mohan and Premalatha 1995; Ramachandran et al 1985; 1987). Recently Govindan and Das (1993) have reported on the occurrence of autonomic neuropathy in FCPD patients. We have also recently shown that the prevalence of autonomic neuropathy in FCPD is similar to NIDDM patients (Mohan et al, 1996).

In contrast, macrovascular complications were less common in FCPD, but we have reported on the occasional occurrence of ischaemic heart disease and peripheral vascular disease (Mohan et al 1989). The low frequency of macrovascular complications may be due to the relative youth of the patients, leanness and the low cholesterol levels (Mohan et al 1985b). The occurence of complications in FCPD has recently been reviewed (Shelgikar et al 1995).

Complications due to chron[illegible]atitis include pseudocysts, pancreatic abscess and ascites. Patients may present with obstructive jaundice, which can either be due to stenosis of the common bile duct or a stone obstructing the passage or due to associated carrcinoma of pancreas. Recent studies from our group (Chari et al 1993) and by Augustine (1992) and Balakrishnan (1987) suggest that FCPD could be a premalignant condition as several patients with FCPD were noted to develop carcinoma of the pancreas on long term follow-up. Current evidence (Chari et al, 1993) suggests that the risk for developing carcinoma in FCP is higher than in termperate zone although the reasons for this are not clear.

Long term survival and causes of mortality

Few studies have reported on long term mortality and survival data in FCPD. We have noted that long term survival of patients with FCPD is quite good with several patients surviving over 25 to 30 years after onset of diabetes. The majority of deaths were related to diabetes related causes especially diabetic nephropathy. Severe infections, pancreatic cancer and other chronic pancreatitis related causes accounted for the remaining deaths Yajnik and Shelgikar (1993) have also observed that chronic infections and diabetes related causes contribute to mortality in FCPD.

Tabel 2. Variability in Fibrocalculous Pancreatic Diabetes (Mohan and Premalatha 1995)	
1. Symptoms	Asymptomatic, marked symptoms
2. Carbohydrate intolerance	Normal GTT, IGT Overt diabetes
3. B-cell reserve	Good Poor Neglegible
4. Response to therapy	Diet alone Oral agents Insulin
5. Proneness to ketosis	Ketosis-resistant Ketosis-prone
6. Exocrine dysfunction	Only after provocative tests Clinical steatorhoea
7. ERCP	Absent to mild ductal changes Marked ductual changes (more common)
8. Histopathology	Mild changes: calculi absent or small (less common) Marked changes: (more common) extensive fibrosis ductal dilatation multiple calculi

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. The role of surgery in FCPD has been recently reviewed (Mohan and Chari, 1994; Thomas et al. 1990). Sphincterotomy, side-to-side pancreatico-jejunostomy (Puestow's procedure) and end to side pancreatico-jejunostomy (Duval's procedure) have been tried with fairly good results. Many of these procedures are beneficial with respect to alleviation of pain. Some patients however have recurrence of pain. Tripathy and Samal (1987) 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. However it is likely that these changes are transient and the diabetic status appears to be largely unaffected by surgery.

Conclusion

Fibrocalculous Pancreatic Diabetes (FCPD) is a unique form of diabetes secondary to chronic pancreatitis seen in developing countries of the world associated with either overt protein calorie malnutrition or more likely with a deficiency of certain micrountrients. FCPD affects young individuals and has an aggressive course to reach the end points of diabetes, pancreatic calculi and exocrine pancreatic dysfunction in the majority of cases. There are characteristic features of FCPD 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 is emerging as a possible etiological or predisposing factors. The contribution of genetic factors and environmental toxins eg. cyanogenic glycosides or other nutritional or toxic factors could lead to improved understanding of other forms of diabetes as well and merits further study.

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