ORIGINAL ARTICLE

Clinical Profile of Fibrocalculous Pancreatic Diabetes Cases: A Diabetes Entity Unique to Tropics

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ABSTRACT

Background: Fibrocalculous pancreatic diabetes (FCPD) is a unique form of diabetes reported from tropical countries. Though classically described in young, lean and malnourished people from tropical countries with a low socioeconomic background, recent evidences suggest that this classical presentation of FCPD is changing. ***Objective:*** The present study aims to explore detail clinical presentations of encountered FCPD cases in a tertiary hospital in Eastern India. ***Methods:*** A prospective observational study included cases fulfilling the diagnostic criteria of FCPD. Each included patient was interviewed for their basic demographic profile, body mass index, family history and duration of diabetes mellitus. Clinical, biochemical and radiological investigations were done. ***Results:*** A total of 11 patients were studied. Mean age observed was 26.18 years, with majority having their disease diagnosed before the age of 30years. The classical triad of pain abdomen, steatorrhea and DM was present in only 3 cases. On clinical examination, only 1 patient was found to be hypertensive. All patients had HbA1c more than 7% with 5 of them having HbA1c >=8%. Neuropathy was the most common complication detected, followed by nephropathy and retinopathy. Straight X-ray Abdomen after proper bowel preparation showed presence of diffuse calcification involving the head, body and tail region in all the 11 cases, thus confirming the diagnosis. All the cases were managed medically with injectable insulin. ***Conclusion:*** Although insights have been gained into its natural history, the etiopathogenesis continues to be elusive. Despite the low prevalence of the disease, clinicians practicing in tropical countries should always keep in mind FCPD as a differential diagnosis during evaluation of a young diabetic patient, especially if patient is lean and there is a history of abdominal pain or steatorrhea with absence of ketosis.

Keywords: Fibrocalculous pancreatic diabetes, diabetes mellitus, clinical presentation

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INTRODUCTION

Fibrocalculous pancreatic diabetes (FCPD) is an exclusive form of diabetes reported from tropical countries like India. This form of diabetes is unique because it typically occurs in young people with low body mass index (BMI) and associated with pancreatic damage and presence of calculi in the pancreas.[1] Abdominal pain followed by diabetes and steatorrhea is the common presentation. Diabetes is typically ketosis resistant.[2] Before the onset of diabetes, there is a pre-diabetic phase of pancreatic damage in these subjects, which is referred to as tropical chronic pancreatitis (TCP). People with FCPD are at a higher risk of developing pancreatic cancer.[3] Recent studies have shown that a proportion of the cases may have genetic factors and gene mutations that confer the risk of developing the disease.[1]

The exact pathogenesis of FCPD is however

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still unknown. Few hypotheses attributing the disease to protein-calorie malnutrition and cassava (tapioca) intake have been well probed. Presence of serum protease inhibitor Kazal type 1 (SPINK1), cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2), and chymotrypsinogen C in FCPD patients hints towards possible role of genetic predisposition.[4]

Though classically described in young, lean and malnourished people from tropical countries with a low socioeconomic background, recent evidence suggests that this classical presentation of FCPD is changing.[5] The usual age of occurrence is 10-30 years; however, FCPD is now often seen in younger as well as older individuals. Abdominal pain is the initial symptom, with diabetes presenting one to two decades after the onset of abdominal pain.[6]

Microvascular complications of diabetes are common in FCPD. In a study by Jyotsna et al.[7] neuropathy was seen in 43% of people with FCPD. Macrovascular diseases like stroke and peripheral vascular diseases have also been reported, probably due to longer survival.[1] Important causes of death in people with FCPD are pancreatic adenocarcinoma and diabetes-related nephropathy.

Worldwide, chronic pancreatitis is the major cause of pancreatic diabetes. Alcohol abuse is still the commonest cause for it and the condition is known as alcoholic chronic pancreatitis. In contrast, chronic calcific pancreatitis is a totally different distinct entity which is seen in only certain geographical areas of the world and presents with diabetes in adolescence or early adulthood, and not associated with alcohol intake.[1]

Diagnostic criteria for FCPD include:[8]

1. Occurrence in a tropical country
2. Diabetes by WHO criteria
3. Evidence of chronic pancreatitis: pancreatic calculi on X-ray or at least 3 of the following:
    a. Abnormal pancreatic morphology by sonography
    b. Chronic abdominal pain since childhood
    c. Steatorrhea
    d. Abnormal pancreatic function test
4. Absence of other causes of pancreatitis (alcoholism, hyperparathyroidism, hepatobiliary disease, gall stones, marked hypertriglyceridemia etc).

The present study aims to explore detail clinical presentations of FCPD cases as encountered in a tertiary centre in Eastern India over a period of one year.

METHODS

This prospective, observational study was undertaken in a tertiary care set-up in Eastern India. The study included only diagnosed cases of FCPD fulfilling the criteria as stated. [8] HIV seropositive cases were excluded. Each included patient was interviewed for their basic demographic profile, including socioeconomic variables like education, occupation and income. Modified Kuppuswamy scale was used to assess the socioeconomic profile. Patients' details like body mass index, family history and duration of diabetes mellitus (DM) were captured. Clinical, biochemical and radiological investigations were done. Biochemical investigations included Haemoglobin (Hb), Fasting Blood Glucose (FBG), Glycosylated haemoglobin (HbA1C), Low-density lipoprotein (LDL) cholesterol and urinary albumin test. Radiological investigation included abdominal X-Ray. Complications of DM in FCPD cases were noted. Data were represented using descriptive statistics including mean, standard deviation, frequency and percentages. Data was analysed using Microsoft Excel.

RESULTS

Of the 11 patients in our study, 6 were males and 5 females with sex ratio (male: female) being 1.2:1. The mean age of the patients was 26.18±5.64 years. 8 patients had their disease diagnosed before the age of 30 years, whereas the rest 3 cases presented after the age of 30. Out of the 11 patients, 5 were underweight of whom 4 were females, while rest patients had normal BMI. Family history of DM was present in one case only. All the patients belonged to lower middle or lower socioeconomic class as per modified Kuppuswamy scale. The mean duration of DM was 3.55±1.86 years.

The classical triad of pain abdomen, steatorrhea and DM was present in only 3 cases (27.3%). Abdominal pain was present in 8 cases (72.73%), chronic diarrhoea in 5 cases (45.46%) and osmotic symptoms including polyuria and polydipsia was

present in 3 cases (27.3%). History of diabetic ketoacidosis/ hyperglycaemic hyperosmolar non-ketotic diabetic coma was not noted in any cases.

On clinical examination, only 1 patient was found to be hypertensive (9.1%). All patients had HbA1c more than 7% with 5 of them having HbA1c >=8%. Biochemical parameters of the cases are shown in Table 1. Urinary albumin test was done in all cases. Macroalbuminuria was detected in 1 case and microalbuminuria was detected in 2 cases. Regarding the complications of DM, neuropathy was the most common complication detected in 5 out of 11 cases (45.45%), followed by nephropathy in 3 cases (27.3%) and retinopathy in 1 case (9.1%).

Straight x-ray of abdomen after proper bowel preparation showed presence of diffuse calcification involving the head, body and tail region in all the 11 cases, thus confirming the diagnosis (Figure 1 & 2).

All the cases were managed medically with injectable Insulin. Pancreatic enzyme supplementation and correction of micronutrient deficiencies were done. All cases were followed up at monthly intervals for up to 1year, during which they did not develop any complications.

Table 1: Biochemical parameters of study participants (N=11)

Biochemical parameters	Mean ± SD (95% CI)
Haemoglobin (g/dl)	11.28 ± 0.73 (10.78, 11.77)
FBS (mg/dl)	158.45 ± 20.93 (144.39,172.52)
HbA1c (%)	7.9 ± 0.62 (7.48, 8.32)
LDL Cholesterol (mg/dl)	110.45 ± 7.74 (105.26, 115.65)

DISCUSSION

Zuidema et al.[9] reported 45 patients with diabetes from Indonesia in the early 1959.These patients were from low socio-economic status, had protein-energy malnourishment and had features of chronic pancreatitis with no history of alcohol intake. In our case series we report 11 patients, all from lower middle or lower socioeconomic class. Majority of studies observed male predominance and age of presentation before 30 years.[10-12] In our study, 6 were males, 5 females and 8 out of 11 patients had disease onset before 30 years. Though most FCPD patients present with low BMI[1], we

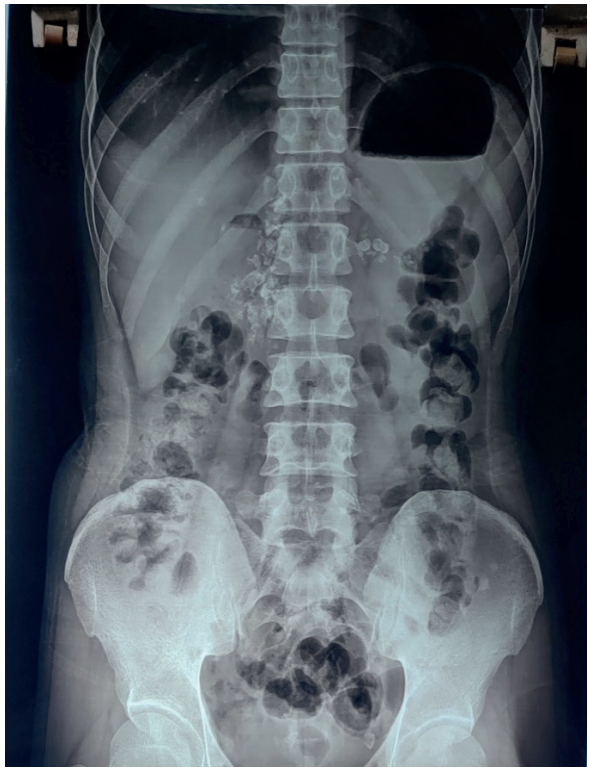

Figure 1. X-ray of abdomen of a male patient showing generalised pancreatic calcification involving head, body and tail of pancreas.

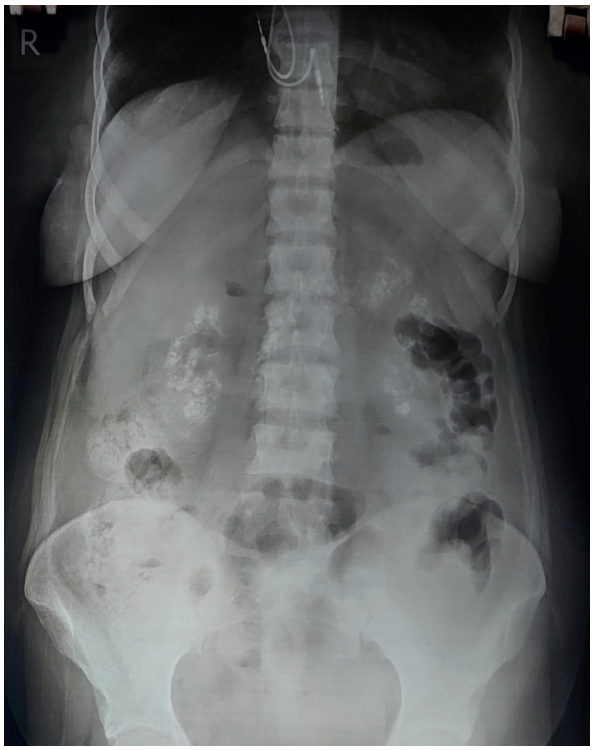

Figure 2. X-ray of abdomen of a female patient showing generalised pancreatic calcification involving head, body and tail of pancreas.

noticed almost equal number of underweight and normal weight patients. This changing trend in presentation of the disease is also reported from an Indian study.[10]

The classical triad of pain abdomen, steatorrhea and diabetes was not present in majority of the patients (8 out of 11), which is similar to the findings of Yajnik & Shelgikar,[13] who followed up the FCPD patients for 7 years. The glycaemic control was poor in all the patients with 5 out of 11 patients having HbA1c>=8%. This is comparable to the study findings of Bhat et al.[10]

None of the patients from our study presented with ketosis. There exist various factors contributing to 'ketosis resistance' in FCPD.[2] The prime reasons include decreased glucagon reserve due to destruction of the alpha cells of Islets of Langerhans, and partial preservation of beta cell function so as to secrete insulin sufficient to prevent ketogenesis but not to maintain euglycemia. Reduced availability of non-esterified fatty acids (NEFA) – substrate for ketogenesis, due to lack of subcutaneous fat, also contributes to 'ketosis resistance' in FCPD.

Neuropathy was the commonest complication seen in almost 50% of the cases. A study from Northeast India reported peripheral neuropathy in 43.5% cases.[7] However, we did not observe macrovascular complications in any of the cases, which may be due to young age, lack of obesity and absence of significant dyslipidaemia.

The first presenting symptom was usually abdominal pain which can start even in childhood. The pain is usually episodic, severe, localized to upper abdomen with radiation to the back and relieved by lying prone or stooping forward. There is usually a decrease in the frequency and severity of pain with time, and in most cases, it disappears by the time diabetes develops. Insufficiency of the exocrine part of pancreas leads to maldigestion and malabsorption of fat resulting in passage of bulky, oily and frothy stools which is difficult to flush away. Frank steatorrhea, however, is uncommon as the diet of these patients is usually low in fat. Diabetes usually develops 10–20 years after the first episode of abdominal pain. While few patients present with the classical triad of polyuria, polydipsia and polyphagia, most are asymptomatic and are detected incidentally. Rarely, patient may present in a state of impaired glucose tolerance (otherwise termed FCP-IGT), but it rapidly and inevitably progresses to frank diabetes.[1,14]

Diabetes in FCPD is mainly due to loss of cells of islets of Langerhans and subsequent insulin deficiency, some studies have reported that insulin resistance have role also in the pathogenesis of FCPD. Mohan et al.[15] performed insulin tolerance tests in 12 patients with FCPD and reported comparable insulin resistance between patients with FCPD and type 2 diabetes. A more recent study has also shown the presence of insulin resistance, measured by the homeostasis model assessment (HOMA-IR) in patients with FCPD.[16]

Patients with FCPD may develop complications as a result of the pancreatic pathology itself. the most dangerous complication of FCPD is pancreatic carcinoma. Studies done at Chennai indicate that the risk of malignancy in FCPD is increased up to 100-fold.[3] In contrast to the de novo ductal pancreatic cancer, malignancy in FCPD can arise from the body and tail of the gland, as well as the head. Diagnosis of malignancy in such cases is often difficult. Development of obstructive jaundice is an early sign. Unexplained weight loss or sudden worsening of pain in a patient with FCPD whose glucose levels are well controlled should always prompt the physician to search for malignancy. CA 19-9 is a useful tumour marker, but false-positive and false-negative results limit its utility. Other complications are that it may occur are pseudocysts, pseudoaneurysms, venous thrombosis, common bile duct obstruction, pancreatic fistulae and ascites. Patients may also develop deficiency of fat-soluble vitamins (A, D, E and K) and essential fatty acids as a result of fat malabsorption.[1]

Insulin remains the cornerstone of therapy. The anabolic effects of insulin are desirable especially in these low BMI patients. Also, a low-fat diet can help to reduce the incidence of steatorrhea. Adequate supplementation of fat-soluble vitamins is necessary. Pancreatic enzyme supplements may help to decrease steatorrhea and improve the quality of life in these patients. These supplements have also been shown to improve the control of diabetes, by enabling patients comply better with dietary restrictions.

CONCLUSION

The prognosis of FCPD cases has improved significantly in the last two to three decades.

Although insights have been gained into its natural history, the etiopathogenesis continues to be elusive. Despite the low prevalence of the disease, clinicians practicing in tropical countries should always keep in mind FCPD as a differential diagnosis during evaluation of a young diabetic patient, especially if patient is lean and there is a history of abdominal pain or steatorrhea with absence of ketosis.

Conflicts of Interest: None declared by the authors.

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Ethical Clearance: The study was approved by the Research Ethics Committee of the AARC, Kolkata, West Bengal, India (Approval No: HREC-AARC/30).

Authors' Contribution: Conception, study design, and data collection were performed by RC and PH. Data analysis was performed by SM. The first draft of the manuscript was written by SM and RC. Critical inputs were provided by BS. All authors contributed to the final version of the manuscript.

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