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EDITORIAL

Fibrocalculous pancreatic diabetes—current scenario in developing countries

G. Praveen [1] · V. Mohan [1]

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Fibrocalculous pancreatitis diabetes (FCPD), a secondary form of diabetes due to tropical chronic pancreatitis (TCP), is seen exclusively in developing countries of the tropical world. From a worldwide perspective, alcoholism is the most common cause of chronic pancreatitis. However, in many tropical countries like India and Bangladesh, the commonest cause of chronic pancreatitis is TCP [1].

TCP is characterised by recurrent attacks of pain abdomen usually in the first or second decade of life along with steatorrhea and diabetes which usually sets in by the third decade. Some of its distinctive features are presence of large intraductal calculi, accelerated course of the disease and high susceptibility to pancreatic cancer [2].

Geevarghese, one of the pioneers in the field, documented one of the largest series of FCPD cases in the world from Kerala state [3]. Indeed, in Kerala in the 1960s, FCPD constituted 29.3% of the total diabetes registered at a medical college [4]. However, this figure dramatically reduced during subsequent years and a prevalence of 0.36% was reported during the periods 2001–03 and 0.2% in the periods 2006–10 in one hospital-based series [5].

Balakrishnan et al. [6], in a nation-wide prospective study in India on chronic pancreatitis based on clinical and radiological criteria, reported a prevalence of 3.2% for FCPD, 38.7% for alcoholic pancreatitis and 60.2% for 'idiopathic pancreatitis', although the latter could include TCP as well.

✉ V. Mohan
drmohans@diabetes.ind.in

[1] Dr.Mohan's Diabetes Specialities Centre & Madras Diabetes Research Foundation, WHO Collaborating Centre for Noncommunicable Diseases Prevention and Control, IDF Centre of Excellence in Diabetes Care & ICMR Centre for Advanced Research on Diabetes, No 4, Conran Smith Road, Gopalapuram, Chennai, Tamil Nadu 600086, India

Changing disease spectrum

Over the last two decades, the prevalence and clinical spectrum of FCPD and TCP have been showing a subtle change, perhaps due to changes in nutritional status and lifestyle changes. The disease now occurs in older age groups, with the mean age at presentation being nearly a decade later, than in the previous reports. The presentation of the disease has also become more heterogeneous, with only about 10–15% of patients presenting with the classical picture of FCPD. While the frequency of classical TCP is decreasing, pancreatitis due to alcohol and probably other environmental toxins is on the rise [7, 8].

The etiopathogenesis of FCPD is still poorly understood. Earlier hypotheses attributed the disease to protein calorie, malnutrition and cassava (tapioca) intake [9]. However, these hypotheses have never been proven either in well-designed case control studies or in experimental models [10].

Familial clustering of FCPD has been described by several authors and the role of genetic predisposition has been actively pursued. Recent studies have shown serum protease inhibitor Kazal type 1 (SPINK1), cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2) and chymotrypsinogen C to be associated with FCPD [10]. The N34S mutation of the SPINK-1 has been reported to be strongly associated with idiopathic and familial pancreatitis [11].

Recently, Mahurkar et al. [12] have proposed a two hit model for the pathogenesis of diabetes in TCP. The first hit includes the mutation of one or more genes, resulting in the formation of supertrypsin in the acinar cell of the pancreas. The second hit probably involves certain unidentified genes which may lead to one or more phenotypes such as stone formation, fibrosis and/or diabetes mellitus.

Patients with FCPD are known to have severe diabetes but there is a wide spectrum of clinical presentation, with some patients initially requiring only oral antidiabetic drugs but progressing to insulin requirement in the later stages, along with pancreatic supplements for the exocrine insufficiency. A

conspicuous clinical feature of FCPD is the absence of ketosis, in spite of high plasma glucose levels. This is due to partial preservation of pancreatic beta cell function [13] and possibly other mechanisms involved in ketone body synthesis and counter regulatory hormones [14]. Although insulin secretory defect is the major cause of diabetes, growing evidence for a possible role for insulin resistance, role of glucagon and body composition abnormalities, has added new dimensions to the pathogenesis of FCPD [15, 16].

Complications in FCPD can be due to long-standing diabetes which can cause both microvascular as well as macrovascular complications. Advanced retinopathy has been reported in FCPD patients [17]. Nephropathy, peripheral neuropathy and autonomic neuropathy also have been reported, but overall, macrovascular complications are less common in FCPD patients [18]. Pancreatic cancer is the most sinister complication of chronic pancreatitis and several prospective and retrospective studies have described FCPD as a premalignant condition. FCPD patients should therefore be monitored with CA-19.9 measurements and imaging (USG or CT scan) for the early diagnosis of pancreatic cancer. They should also be regularly monitored for all fat soluble vitamins especially vitamin D, whose deficiency can cause pancreatic osteodystrophy.

In this issue of IJDDC, Zabeen et al. [19] report a series of FCPD patients among Bangladesh children and adolescents. They report that 106 (25%) of a series of 429 children and adolescents with diabetes diagnosed below 18 years of age had FCPD. They report clinical features which have been frequently associated with FCPD. For example, compared to type 1 diabetes (T1D), FCPD patients had older age at onset, less common DKA and atypical symptoms at presentation.

Interestingly, 9% of FCPD patients and 3% of T1D had cataract. While cataract has been described earlier in children with both disorders, this high prevalence of cataract is rather surprising. The high A1c levels at diagnosis suggest a long period of uncontrolled diabetes leading to sorbitol-induced changes in the lens [20]. The authors are to be congratulated for picking up so many cases of FCPD among children. This is, thanks to routine screening with abdominal X-rays and ultrasound abdomen to rule out FCPD, something which is not commonly done nowadays, in most diabetes clinics.

The prognosis of FCPD patients has improved in the last two to three decades and of its natural history is also better understood but its etiopathogenesis continues to be elusive. Despite its relatively low prevalence, a differential diagnosis of FCPD must be borne in mind during evaluation of a young diabetic patient in a tropical country, especially if patient is lean and there is a history of abdominal pain or steatorrhea or if there is absence of ketosis.

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