

Chapter 15

Tropical calcific pancreatitis and fibrocalculus pancreatic diabetes in Bangladesh

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Summary

Fibrocalculous pancreatic diabetes (FCPD) is recognized as a malnutrition related diabetes. It is a point of debate whether FCPD and tropical calcific pancreatitis (TCP) are two different diseases or different stages of the same disease. In this article the evidence is examined whether FCPD is a distinct disease entity, particularly in the light of the authors' clinical experience and studies on the genetic aspects of this disease.

Introduction

Tropical calcific pancreatitis (TCP) is a distinct form of chronic calcific pancreatitis prevalent almost exclusively in tropical countries of Asia and Africa. A substantial number of patients with TCP presents with a form of diabetes termed as Fibrocalculus Pancreatic Diabetes (FCPD). The etiothogenesis of both pancreatitis and diabetes in these cases are still unclear. In the present review we would present evidence for genetic and environmental contribution in both pancreatitis and diabetes in TCP and FCPD.

Tropical Calcific Pancreatitis (TCP)

The disease is not common, but neither rare, in gastroenterological practices in Bangladesh. The patients are typically young, presenting age usually below 30 years, and there is slight male preponderance which may be more apparent than real. Severe abdominal pain is the predominant presenting symptom; in addition, the patients present with various gastrointestinal disturbances.

Pancreatic morphology of the TCP patients has been assessed with plain X-ray, ultrasonography and ERCP. Pancreatic calcification and ductal dilatation- deformity were documented with these techniques. By Axon criteria in ERCP, the ductal damage has been graded as being severe in almost all cases (Rahman et al 2000). Assessment of pancreatic function by the secretin induced bicarbonate output (Rossi et al 2004) and by fecal elastase-1 (Ali et al 2001) echoes the findings of morphological investigations.

TCP patients, by definition, have normal blood glucose both in fasting and postprandial states, their insulin/C-peptide levels are also found to be comparable to control (Rahman et al 2000; Ali et al 2001).

One crucial issue is the differentiation of this group from the alcoholic pancreatitis seen in the western world. Much younger age group, characteristic feature of the stone (large intraductal calculi) ductal deformity (grossly enlarged pancreatic duct), and severity of pancreatic damage at an early stage in TCP is usually sufficient to distinguish it from alcoholic pancreatitis. A more confirmatory evidence would be the involvement of different genes in the respective diseases. It has been demonstrated that about 20% of TCP cases have SPINK1 N34S mutation (Schneider et al 2002) and this has not been found in alcoholic pancreatitis. This, not denying the possible involvement of other genes, conclusively shows that TCP is an entity distinct from alcoholic pancreatitis.

Fibrocalculus Pancreatic Diabetes (FCPD)

For the purpose of the present discussion FCPD is being treated as the diabetic counterpart of TCP, but their interrelation is still uncertain. The presenting age of FCPD is even younger than that of TCP and the patients mainly come to the physicians for diabetes related symptoms. Sometimes, the pancreatic stones are accidentally discovered on plain X-ray/UCG. The morphological feature of the pancreas are almost similar to those of TCP except in 10–20% cases (who are mostly early FCPD cases) in whom the pancreatic damage may be moderate rather than severe (Rahman et al 2000). Pancreatic function shows gross compromise in both the groups (Ali et al 2001).

In contrast to exocrine pancreatic function the endocrine function show dramatic differences in TCP and FCPD subjects. An FCPD patient has very low and, in many cases only residual, insulin/C-peptide in fasting plasma and even with such levels they normally remain nonketotic although their presenting blood glucose level may be quite high (fasting usually >16 mmol/l). The B cell function of these patients has been assessed by glucagon and arginine stimulation (Rossi et al 2004), the conclusion, however, remained the same. Again, exploration of the pancreatitis genes were important in such cases and SPINK1 N34S

mutation has been found in about 55% and 32% FCPD in two different studies (Schneider et al 2002; Hassan et al 2002). This indicates a genetic similarity of FCPD with TCP, however additional gene and environmental factors must be involved in case of FCPD.

Nature of diabetes is a crucial and controversial issue in FCPD. In 1985 the WHO Expert Committee grouped the FCPD as a subclass of malnutrition related diabetes mellitus (MRDM) (WHO 1985), but in the etiological classification of 1999 it was grouped as a disease of the exocrine pancreas (signifying that it is a secondary diabetes) under the major class of other specific types (WHO 1999): American Diabetes Association (ADA) also holds a similar opinion (ADA 1997). Younger age of onset in general and lack of straightforward correspondence between exocrine and endocrine pancreatic damage (Rahman et al 2000) do not support this view. Particularly the near normal plasma glucagon level and the persistence of arginine stimulated glucagon response in FCPD provide strong evidences that diabetes in FCPD is just not similar to a straightforward secondary diabetes like alcoholic pancreatitis where glucagon response is blunted.

Further exploration on the primary nature of diabetes in FCPD reveals a type 1 like feature in around 20% case as substantiated by anti-GAD and IA-2 positivity (Hassan et al 2005). INS VNTR typing did not show significant preferential allele transmission and HLA-DQB1 shows significant association, ie increased transmission of HLA-DQ0302 and decreased transmission of HLA-DQ0202 (Chowdhury et al 2002).

Conclusions

Exploration of gene-environment interaction seems to be the next obvious step to clarify both the nature of pancreatitis and diabetes in TCP and FCPD. While some progress has been made in the genetic aspects, almost no progress could be made to identify the environmental factors. A preliminary study in the western half of Bangladesh indicates a north-south gradient in the prevalence of FCPD and this may indicate a possible link with geographical and cultural factors (as the population is genetically homogeneous). However, large scale community based studies, using the genetic, biochemical and epidemiological instruments, are now needed in this area.

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