ABSTRACT

We report a case of 40 year old Caucasian gentleman, who presented with recurrent episodes acute pancreatitis over a year and a half.

He was found to be positive for ΔF508 mutation (Heterozygote) on Cystic fibrosis carrier screen CDSL 0412721.

In spite, of the repeated attacks of acute pancreatitis he did not develop any chronic complications to it nor was any aetiological agent implicated, making them most likely due to defective cystic fibrosis transmembrane receptor (CFTR) gene status.

CASE SUMMARY:

A 40 year old Caucasian gentleman presented with episodes of acute abdomen over a period of a year and a half which were diagnosed to be acute pancreatitis. All the attack had similar presentation of acute epigastric and central abdominal pain which radiated to the back. In all there were five episodes.

He did lose a considerable amount weight after first episode (five kilograms in 2 months). During the first attack, amylase levels were 1600 units, and during rest of the four attacks it was between 1000-2400 units. An ultrasound of abdomen revealed two stones in the gall bladder, with no common bile duct dilatation. There were diffuse fatty liver changes. Rest of the scan did not reveal any abnormality. After the second attack of acute pancreatitis, he underwent a laparoscopic cholecystectomy. A MRI scan of abdomen failed to reveal any pathology. There is no history of alcohol intake. Liver enzymes were within normal limits (including AST: ALT ratio and GGT).

The patient had a history of being a carrier for ΔF508 mutation (Heterozygote) on Cystic fibrosis carrier screen CDSL 0412721 in June 2004.
He had been investigated for infertility and as a result we found out that he has fibrosis of vas deferens. His vitamin D levels were quite low (26 nmol/L). He did not have any fat malabsorption, diabetes mellitus or recurrent respiratory infections.

He is a known case of gastro oesophageal reflux disease (GORD) and a recent upper GI endoscopy revealed small hiatus hernia and reactive gastropathy.

He also has dyslipidemia with high serum cholesterol and LDL levels. (Serum cholesterol 6 and LDL 3.90)

DISCUSSION

Cystic fibrosis an autosomal recessive disease, the most common genetic defect of the white population, seen in about 1 in 2500 to 1 in 3500 live births.(1,2) Although, cystic fibrosis affect a number of organs but our patient surprisingly had only pancreatic manifestations due to CFTR gene mutation and not respiratory complications. CFTR gene is the most important molecule for regulating the pancreatic duct cell function- generating the bicarbonate rich pancreatic juice that helps to neutralize the acidic chime coming from stomach and flushing digestive enzymes out of the pancreas.(2) Thus CFTR molecule is relevant to the pancreatic disease when either its function or regulation of its function is altered by various gene mutations.

The overall clinical picture in an individual case depends on the nature of combined CFTR mutation, genetic background in which the defective genes operate and environmental factors.(3) About 70% of white patients with cystic fibrosis have a three base pair deletion of phenylalanine coding codon 508 (∆F508), although more than 1300 mutation have been reported.(2) Sometimes in patients with cystic fibrosis may not have any pancreatic complications. This is due to the reason that mutations such as R117 markedly reduce the chloride conductance without affecting the bicarbonate secretion.(4) On the other hand, like in our patient mutation affecting the bicarbonate transport can put patient at risk to recurrent pancreatitis without affecting the chloride dependent organs (respiratory features).(5)

The functional consequence of CFTR mutations depends on the combined effects of both CFTR alleles, and the severity of the phenotype depending on the mildest mutation.(6)

Recurrent acute pancreatitis requires, at minimum, a partially functioning pancreas and is therefore seen in some cases of cystic fibrosis with pancreatic sufficiency and atypical cystic fibrosis. Many of these features of cystic fibrosis cannot be explained by variations in CFTR sequence. Instead this features are caused by specific environmental factors (bacterial colonization, tobacco smoke and nutritional status) or modifier genes.(3,7) In 1998 two groups demonstrated that CFTR mutations were very common in idiopathic and alcoholic chronic pancreatitis thus some of the more than 1300
known CFTR gene sequence variant can cause milder disease (atypical cystic fibrosis) or pancreas specific injury or can be a part of a more complex trait.(8,9,10) In early onset idiopathic pancreatitis, this factor may be a heterozygous SPINK1 mutation but stronger environmental factors such as alcoholism and smoking may be causative.(5)

In adult population, presenting symptoms of cystic fibrosis include pulmonary disease, nasal polyps, liver disease, recurrent pancreatitis and chronic pancreatitis. Although the prevalence of CFTR mutation in patients with these common disorders is much lower than in those presenting with pancreatic insufficiency or meconium ileus.(2) Acute recurrent pancreatitis is a rare complication in CFTR mutation (around 1% have it) and much rarer to be a presenting feature which are both there in our patient.(2,11)

The pathogenesis of these episodes is not entirely clear. It is thought that as a result of dysfunction of the chloride channel mediated by the cAMP protein (CFTR), alters the composition of pancreatic juice, and decrease the concentrations of chloride and bicarbonate and volume of water.(12) In these conditions, with an acid and pancreatic juice hyper concentrated, favours the precipitation of protein content and pancreatic ductal obstruction. These patients, therefore, may be particularly susceptible to certain environmental factors such as fatty foods, alcohol and viral infections. (13)

In the course of the disease, the patients with acute pancreatitis secondary to cystic fibrosis, after several episodes, can progress to chronic pancreatitis with duct dilatation.(14) Although the management of acute pancreatitis secondary to cystic fibrosis does not differ, the importance of diagnosis lies in the possibility of genetic counselling. Hence all young patients with recurrent acute pancreatitis due to unknown causes must be ruled out.

CF-related liver disease (CFLD) occurs in up to 30% of people with CF. (15) However, it is only a significant clinical problem in a minority of individuals. For most there is an abnormality of liver function tests and in some of these, some fatty changes in the liver. In a minority of patients,
cirrhosis develops with secondary pulmonary portal hypertension.(15) The pathophysiology of the condition is related to obstruction of small biliary calculi and it is likely that modifier genes in addition to CFTR dysfunction play an important part in this process. Screening for liver disease is taken in most CF centres with annual assessment of liver transaminases, gamma glutamyl transferase (γ GT), and alkaline phosphatase. (16)

Fat-soluble vitamin deficiency is common in people with CF.(17) Vitamin deficiency rarely causes clinical deficiency syndromes though eye problems have been demonstrated in individuals with low vitamin A concentrations.(18) Neurological complications with peripheral neuropathy have also been demonstrated in vitamin E deficient patients.(19)

CF-related bone disease (CFRBD) is an important systemic complication. CFRBD is very similar to osteoporosis with low bone mass and micro architectural deterioration of bone tissue.(20) This leads to an increase in bone fragility and increases the susceptibility to fracture. In general the prevalence of CF-related bone disease is reported as at around 30 to 35% of adults.(21)

The pathophysiology of low BMD in people with CF has not been entirely determined but there is evidence of increased bone absorption and decreased bone formation.(22) Osteoclasts express CFTR, and several recent studies suggest that CFTR dysfunction contributes to the development of CFRBD.(23) It is difficult to determine the relative importance of many of these risk factors, but evidence increasingly points to systemic inflammation as being one of the most important drivers of low BMD. Proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumour necrosis factor-α stimulate Osteoclasts numbers.(24) Several interventions are likely to be very beneficial in preventing the development of CFRBD.

In a large study of 38,000 persons with cystic fibrosis there was a significant risk of increase in tumours of the digestive tract but not an increase in the risk of cancer in relation to the general population for all types of cancer.(25) These cancers tend to occur in the third decade of life and involved the tumours of the small and large intestine, stomach, liver, biliary tract, pancreas and the rectum. Their pathogenesis is uncertain and pancreatic cancer can be due to chronic inflammation as observed with other cases of chronic pancreatitis. These risks are important to keep in mind due to increasing life expectancy on patients with cystic fibrosis.

CONCLUSION

The case report illustrates the need to rule out cystic fibrosis in the patients with recurrent acute pancreatitis in whom aetiology is unknown.

The life expectancy in people with cystic fibrosis is improving, and hence it is vital to bear in mind the complications like related carcinoma and other complications.
REFERENCES

[5] Schneider A, Barmada MM, Lamb J; CFTR and SPINK1 mutations can cause early onset of idiopathic chronic pancreatitis; Nat Genet 2005
[7] Zielenski J; Genotype and phenotype in cystic fibrosis; Respiration 67: 117, 200


