Cystic fibrosis : an unusual cause of chronic pancreatitis

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Abstract

Chronic pancreatitis is most frequently associated with alcohol abuse.

This should however not always automatically be accepted as the presumed cause. When the history is doubtful, uncommon etiologies must be considered as is illustrated by the present case. A 38 years old man was in the past 20 years treated for chronic pancreatitis ascribed to ethylisme although he always denied this. When the diagnosis was eventually questioned, new investigations showed slightly elevated sweat electrolyte concentrations and a △ F508/R117H genotype compatible with cystic fibrosis (CF). Demonstration of mild respiratory abnormalities, obstructive azoospermia and CF in his brother supported this diagnosis.

Although rarely, pancreatitis typically develops in the kind of CF patients with milder genotypes and less severe symptoms. Systematic analysis for genetic mutations in patients with idiopathic chronic pancreatitis (ICP) revealed however that this mild form of CF is a less exceptional cause than thought. As CF patients increasingly survive into adulthood this disease should be considered as a possible etiology in the differential diagnosis of pancreatitis at all ages. (Acta gastroenterol. belg., **2003**, 66, **260-262**).

Key words : cystic fibrosis, pancreatitis, △ F508, R117H, obstructive azoospermia, sweat test, alcohol.

Introduction

Chronic pancreatitis is an inflammatory condition that results in permanent structural changes in the pancreas, which lead to impairment of exocrine and endocrine function (1). Alcohol abuse is the principal cause of chronic pancreatitis. It accounts for 70-80% of all cases. The risk increases with the duration and the amount of alcohol consumed (2). The differential diagnosis of this type of pancreatitis is usually not difficult when a long history of alcohol abuse is present. Stigmata of chronic liver disease may also be detectable.

Other causes of chronic pancreatitis are : heredity, ductal obstruction (secondary to tumor, trauma), tropical pancreatitis (malnutrition, cassava fruit) and systemic disease such as systemic lupus erythematosus, hyperparathyroidism and auto-immune pancreatitis.

In some cases no cause for the pancreatitis can be found (10-20%). Concealed alcohol ingestion, hypersensitivity to small amounts of alcohol and unreported trauma can lead to the misdiagnosis of idiopathic pancreatitis. But it is also possible that a distinct entity is not identified. Mutations of the cystic fibrosis gene and the trypsinogen gene have been found to be associated with ICP (3,4,5).

The aim of this article is to draw attention to the fact that chronic pancreatitis can be a presentation of cystic fibrosis. Therefore it is important that every physician should consider this possibility when confronted with a chronic pancreatitis and take the necessary diagnostic steps.

Case

A 38-year-old man presented with the following remarkable history.

Except for abdominal pain after eating certain foods in late childhood no complaints were mentioned. At the age of 19 complaints of dyspnoe and wheezing led to the diagnosis of asthma. Four years later, attacks of severe abdominal pain started to occur, localised in the epigastrium and left hypochondrium. The pain radiated to the back, prevented him from moving and was only controlled by high doses of analgesics. The patient experienced 6 of these attacks over a period of 12 years. During these attacks, amylase and lipase were highly elevated and abdominal ultrasonography showed an oedematous pancreas. Based upon these findings chronic pancreatitis was diagnosed and attributed to chronic alcohol abuse, although the patient always denied this. Exocrine pancreatic function was never determined.

Remarkably cystic fibrosis was considered twice. A sweat test was performed but although the chloride content was elevated (72 meq/l and 86 meq/l), there was no change in etiological diagnosis.

In 1998, 12 years after the onset of the disease, the patient suffered from a new episode of pancreatitis. CT scan showed a large pseudocyst in the pancreas with mass-effect on the splenic vein and local portal hypertension. Because of these findings and the recurrent attacks of pain, irresponsive to analgesics, the patient eventually underwent a subtotal pancreatectomy. The pathological examination of the pancreas showed chronic fibrous pancreatitis. After the operation pain subsided but the patient developed pancreatic insufficiency and diabetes for which he needed insulin. Further investigations showed azoospermia as well.

Only a few months later a blood sample was taken to perform molecular testing for cystic fibrosis. The patient was screened for 30 common mutations. Two mutations

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in the CFTR-gene were found : △ F508 and R117H, confirming that he had cystic fibrosis.

The findings in this patient did suspect the same diagnosis of cystic fibrosis in his two-year younger brother who had mild chronic diarrhoea, vague abdominal pain and difficult weight gain. Investigations for infertility had revealed azoospermia. His sweat test was also positive and the same DNA mutations were found. Mutation screening on the children of the patient's sister was negative.

Discussion

Cystic fibrosis is the most common autosomal recessive disease among Caucasian populations, with a frequency of one in 2000 to 3000 live births (6). It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, coding for a chloride channel found in all exocrine tissues (7). Deranged chloride transport leads to thick, viscous secretions in the lung, pancreas, liver, intestine, and reproductive tract, and to increased salt content in sweat gland secretions. The usual presenting symptoms are persistent pulmonary infections and exocrine pancreatic insufficiency (6).

In the classic form of CF the pancreas is already severely damaged at birth (8), which results in early pancreatic insufficiency and symptoms of maldigestion. 15% of patients initially preserve sufficient pancreatic output (9). It is in this pancreatic sufficient group that recurrent attacks of pancreatitis have been described. Exceptionally this pancreatitis can even be the first and unique manifestation of the disease (10).

In a retrospective study on 2000 patients with cystic fibrosis, only 10 (0.5%) presented this complication. The mean age of the patients at the time of the first attack of pancreatitis was 17.6 years (range 7-25 year) (10).

The reason why pancreatitis only occurs in pancreatic sufficient patients, can be explained by the following mechanism : CFTR protein is present at high levels in intralobular and proximal ductular epithelia (11). Although there is still some residual exocrine acinar function, the dysfunction of the chloride channels results in reduced intraluminar fluid and bicarbonate secretion. Under these chemical conditions the pancreatic enzymes will precipitate and obstruct the pancreatic ducts, leading to recurrent attacks of pancreatitis (12). In the classic form of cystic fibrosis, the absence of functional acinar cells prevents the occurrence of pancreatitis.

The reported patient is a typical example of this manifestation. Between the age of 23 and 35, he repeatedly suffered from clinically and biochemically obvious bouts of pancreatitis, eventually treated by subtotal pancreatectomy. Before this operation, pancreatic exocrine function was never tested. But normal growth, weight gain and absence of signs of malassimilation suggested pancreas sufficiency. At that time, the diagnosis of cystic fibrosis was not considered. At present however criteria for the diagnosis (13,14) are undoubtedly met : azoospermia and elevated sweat chloride levels were demonstrated, he developed respiratory abnormalities and the diagnosis of CF is also confirmed in his brother. DNA mutational analysis demonstrated two mutations at the CFTR gene locus : △ F508 and R117H. He thus is compound heterozygous for one severe (△ F508) and one mild allele (R117h), after the classification on the basis of the association between genotype and phenotype (15,16,17).

Several studies showed that there is a strong association between CFTR mutations and ICP (3,4,18-22). Cohn and Sharer both found that in a group of patients with idiopathic chronic pancreatitis, the frequency of CFTR mutations was higher than expected (3,4). None of the patients in both studies had clinical evidence of sinopulmonary disease and the sweat chloride levels were not diagnostic for cystic fibrosis.

More recent data even indicate that the frequency of CFTR gene mutations is significantly increased both in ICP and alcoholic chronic pancreatitis (23) Consequently this finding suggests that looking for CF mutations should not only be restricted to cases of ICP without a history of alcohol abuse.

Making the diagnosis of CF will not change the treatment of the pancreatitis, but is of paramount importance for the future therapeutic strategy of other potential manifestations. It also provides important information for genetic analysis both in siblings and remote family members.

Conclusion

Cystic fibrosis is no longer exclusively a disease of children. Thanks to therapeutic improvements an increasing group of patients reaches adulthood.

This implies that no longer only paediatricians will be confronted with CF patients, but that these patients progressively will be a part of the patient population of internal medical specialists. Therefore it is important that every physician and internist in particular knows what cystic fibrosis is about and realises that chronic pancreatitis can be a complication or an initial presentation of the disease at all ages. It is useful to search for CF mutations to include cystic fibrosis in the etiological approach of a case of chronic pancreatitis, especially when the history of alcohol abuse is doubtful.

Although the treatment of pancreatitis due to CF is not different from that by any other cause, the diagnosis of CF is paramount in order to treat other potential manifestations and to provide important information for genetic counseling in siblings and remote family members.

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