Chronic hereditary pancreatitis with N29I mutation in a Turkish child

Makbule Eren, Figen Gürakan, Nurten Koçak

Section of Gastroenterology, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Eren M, Gürakan F, Koçak N. Chronic hereditary pancreatitis with N29I mutation in a Turkish child. Turk J Pediatr 2005; 47: 173-175.

Hereditary pancreatitis, an autosomal dominant disease, is the second most common cause of pancreatitis in children. Here we report a child with recurrent pancreatitis attacks and N29I mutation. Due to the increased risk of pancreatic cancer, taking a detailed past and family history and early diagnosis are important.

Key words: hereditary pancreatitis, N29I mutation, endoscopic retrograde cholangiopancreatography.

Hereditary pancreatitis (HP) is an autosomal dominant disorder characterized by recurrent episodes of acute pancreatitis during childhood. It is the second most common cause of chronic pancreatitis in children[1]. Recurrent attacks frequently progress to chronic pancreatitis and subsequent pancreatic ductal adenocarcinoma in time. Since the incidence of pancreatic ancer is 53-fold increased over the general population diagnosis and differentiation of HP gain importance[2]. However patients are very commonly undiagnosed for many years. Recurrent episodes of acute attacks and prolonged inflammation are supposedly responsible for the increased incidence of cancer[2]. Since clinical presentation is similar to other pancreatitis cases, both presence of family history and detection of the defective gene are very important in differentiation. Here we present a patient who had recurrent pancreatitis attacks clinically indistinguishable from other causes of pancreatitis, with N29I mutation. The father also had chronic pancreatitis. We emphasize the importance of family history and mutation analysis to avoid diagnostic delay.

Case Report

An 11-year-old boy was referred to our clinic with the provisional diagnosis of chronic pancreatitis. He complained of recurrent fever, abdominal pain, nausea and vomiting attacks since three years of age. Frequency of attacks was 3-4 episodes per year and a pseudocyst was detected on abdominal ultrasound and tomography at the referring hospital. A careful past history revealed that his father also complained of several similar attacks since his childhood. Physical examination was normal except for tenderness at epigastric region. Laboratory investigation revealed a normal complete blood count and liver function tests, and trigyceride (69 mg/dl), cholesterol (148 mg/dl), very low density lipoprotein (VLDL: 14 mg/dl), low density lipoprotein (LDL: 90.2 mg/dl), high density lipoprotein (HDL: 14 mg/dl), serum calcium level (9.8 mg/dl), serum amylase level (100 IU/L) and sweat chloride test (10 mEq/L). Abdominal ultrasonography detected cyst formation at the tail of the pancreas measuring 4x8.6x5.5 cm, compatible with pseudocyst. Magnetic resonance cholangiopancreaticography demonstrated dilatation and irregularity of Wirsung's canal in addition to the cyst formation. Endoscopic retrograde cholangiopancreatograhy (ERCP) revealed stricture of the pancreatic channel at the head region of the pancreas, multiple stones inside this strictural part and dilatation of the distal segment. Balloon dilatation, stone extraction and stent implantation to the strictural part were performed. Along with these investigations, mutation analysis detected a single copy of the N29I mutation and the patient was found to be consistent with a diagnosis of HP. His pseudocyst formation regressed and stent was removed after seven months with healing of the stenotic part.

Discussion

Hereditary pancreatitis is defined as recurrent episodes of pancreatitis in two or more members of one family. It has autosomal dominant inheritance with 80% penetrance[2]. The cause of incomplete panetrance remains unknown. Age of onset may range from infancy to the 30's. It has been suggested that genetic and environmental factors contribute to the expression and age of onset. Studies with twins showed 43% phenotypic discordance[3]. Genetic defect of the disease has been mapped on the long arm of chromosome 7[1-4]. Usually, point mutations at exon 3 or 2 of the gene protease serine 1 (PRSS1), which encodes cationic typsinogen, are responsible for the disease. Two main causative mutations have been detected thus far, R122H and N29I[2,4]. The mutation in exon 2 (N29I), which was found in our patient, alters asparagine to isoleucine. The effect of this mutation is unclear, however, enhancement of trypsinogen autoactivation, alteration of the binding of pancreatic secretory trypsin inhibitor (PSTI) or alteration of the initial hydrolysis site are the proposed mechanisms[2].

Apart from earlier onset and high prevalence of pseudocyst formation, the natural history of HP is similar to that of other causes of chronic pancreatitis[4]. The past history is the most important point in the diagnosis of HP. In our case, the symptoms of the patient started as early as three years of age. Although pancreatic duct stenosis and pancreaticolithiasis on ERCP could be implicated in the etiology of pancreatitis, earlier onset of the disease and presence of family history forced us to do further mutation analysis in our patient.

Recurrent attacks frequently end in chronic pancreatitis and subsequent pancreatic cancer. The incidence of pancreatic ductal adenocarcinoma is increased 53-fold compared to the normal population. At the age of 70, cumulative risk has been determined as 40%[1-4].

The effect of the mutation to create differences in clinical presentation and prognosis has been studied in a few trials. The clinical presentation and results of radiological diagnostic procedures were similar to those seen in other acute pancreatitis cases. According to reports comparing patients with R122H mutation to those having N29I mutation the mean age of onset is lower, exocrine failure is prevalent and more surgical interventions are needed in the R122H group[4]. In terms of endocrine dysfunction, no difference was found between these two common mutations[4]. However, the severity of chronic pancreatitis and symptoms were found to be similar for both mutations[5]. In our patient, pseudocyst regressed with insertion of stent and to date, no surgical intervention has been required.

According to EURPAC, attacks of acute pancreatitis occur at a rate of 2.0 per year; this was 3-4/year in our patient. Drainage of the pancreatic ductal system relieves pain and reduces the number of attacks[6]. Therapeutic ERCP with stent implantation was performed in our patient. Whether or not this results in a reduction in the number of attacks will be observed in the future.

Acute attacks need the same interventions as in other causes, i.e. rehydration and pain relief. Here the important issue is to define preventive strategies before irreversible changes occur during these ongoing attacks. Will this probable intervention prevent chronic pancreatitis and the subsequent cancer? Does the cancer develop as the end point of prolonged inflammation and chronic pancreatitis, since patients with chronic pancreatitis have also been found to have increased risk of pancreatic cancer, or does the mutation per se increase the risk of adenocarcinoma? If so, which mutation has the highest risk? Although therapies with antioxidants for pain control and drainage of the pancreatic ductal system by endoscopic procedures to reduce the number of acute attacks were found to be effective in HP, these issues need to be further investigated[6,7].

In conclusion, we advise taking a careful family history in early onset and recurrent acute pancreatitis cases and performing mutation analysis to avoid a possible diagnostic delay.

Symptomatic relatives also need to be investigated for the possible mutation and may be followed up for cancer, as proposed[1,4].

Acknowledgement

We thank the Gastroenterology Section of Yüksek İhtisas Hospital for performing ERCP and stent implantation, and Mr. David Bourn, clinical scientist of Merseyside and Cheshire Regional Molecular Genetics Laboratory, U.K., for mutation analysis.

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