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Hereditary Pancreatitis Associated with a Cationic Trypsinogen Mutation

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Abstract

Introduction: Hereditary pancreatitis is a very rare form of early pancreatitis with autosomal dominant pattern of inheritance. Follow-up is very important due to a markedly increased risk of pancreatic cancer.

Case Presentation: We report a case of a 22-year-old man with several episodes of acute recurrent pancreatitis, initially labeled as alcoholic related versus idiopathic but finally diagnosed of hereditary pancreatitis due a mutation in cationic trypsinogen gene.

Conclusion: Genetic testing should be considered in patients with unexplained recurrent pancreatitis at early age and family history of pancreatitis due to a markedly increased risk of pancreatic cancer. This rare case emphasizes upon considering this entity in the differential diagnosis of recurrent pancreatitis especially in young adult, genetic diagnosis and counselling during follow-up.

Hereditary pancreatitis is a very rare form of early pancreatitis with autosomal dominant pattern of inheritance. Follow up is very important due to a markedly increased risk of pancreatic cancer. We report a case of a young man with episodes of acute recurrent pancreatitis, initially labeled as alcoholic related versus idiopathic but finally diagnosed of hereditary pancreatitis due a mutation in cationic trypsinogen gene.

Keywords: PRSS1; Hereditary pancreatitis; Cationic trypsinogen; Genetic susceptibility; Recurrent acute pancreatitis

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Introduction

Hereditary pancreatitis is a rare disorder that causes chronic pancreatitis in both children and adults with high penetrance in the relatives. There are different gene mutations and inheritance patterns related with recurrent acute pancreatitis in early adolescence, chronic pancreatitis in late adolescence or adulthood and a markedly increased risk of pancreatic cancer. Treatment of hereditary pancreatitis is similar to acute and chronic episodes and pancreatectomy could be an option in selected patients with severe pain due to chronic pancreatitis, especially in young adults. Here we report the case of a young man with recurrent acute pancreatitis with familial history of this pathology and a genetic base with hereditary pattern.

Case Presentation

A 22-year-old man was admitted to our Internal Medicine Service because of abdominal pain radiating to the back, without fever, nausea or vomiting. He was first diagnosed with pancreatitis at the age of 19. Since then, he was admitted twice with acute pancreatitis episodes, related with heavy alcohol consumptions.

The day before admission he felt well and denied alcohol use. On examination of the patient, vital signs were normal and liver was not palpable but patient referred intense epigastric and hypochondrial pain during abdominal palpation. Laboratory findings showed white-cell, red-cell and platelet count normal, total bilirubin level of 1.3 mg/dL (normal value <1.2), alkaline phosphatase level of 58 U/l (normal value <150), gamma-glutamyl transpeptidase of 14U/l (normal value <78), aspartate aminotransferase of 24 U/l (normal value <45) and alanine aminotransferase of 24 U/l (normal value <72), amylase of 1586 U/l (normal range 30-110 U/l) and lipase of 2927 U/l (normal range 8-78 U/l). Erythrocyte sedimentation rate, serum C-reactive protein, albumin level, serum triglyceride, IgA antibodies and IgG4 subtype level were within normal range. Antinuclear

antibody and antineutrophil cytoplasmic antibodies were negative. Abdominal computed tomography (CT) revealed an enlarged and edematous pancreas with fat inflammation but without collections, necrosis areas or other complications supporting an acute pancreatitis not complicated with no evident cause. A moderate amount of free fluid was found in pelvis. There were no gallstones. Conventional treatments with intravenous fluids, analgesia for pain control and bowel rest were applied. Our patient improved in few days and he was discharged being asymptomatic.

A diagnosis of acute recurrent pancreatitis at an early age with no evident cause was made so, to complete the study, a family medical history was collected. We found that his father was diagnosed with chronic pancreatitis at age 36 years with multiple acute episodes. With the suspicion of hereditary pancreatitis (HP) due to two members having clinically pancreatitis, we performed mutation analysis for serine protease 1 cationic trypsinogen gene (PRSS1). We identified p.Arg122Cys mutations in exon 3 of PRSS1 gene, which is a pathogenic variant related with autosomal dominant hereditary pancreatitis.

With the diagnosis of HP we strongly recommended avoiding smoking, alcoholic drinks, fatty foods, and physical and emotional stresses. Our patient doesn't need multivitamins or pancreatic enzyme replacement therapy.

During the subsequent months after the diagnosis was made, the patient developed two more episodes of acute pancreatitis not complicated, without evident cause. Since then, he has remained asymptomatic avoiding environmental triggers. Nowadays, our patient keeps rigorous follow-up in order to provide genetic counselling and prevent pancreatic cancer.

Discussion

Hereditary pancreatitis (HP) is a rare condition defined as two or more individuals with pancreatitis in two or more generations of a family, with different pattern of inheritance [1]. Several gene mutations have been described since first described in 1952 [2]. Incidence of chronic pancreatitis is about 3.5-10 per 100000 inhabitants and year but incidence of HP still remains unknown. Clinical findings in patients with HP area similar to that non-genetic based, except for the age of disease onset. HP manifest at an earlier age than alcoholic or biliary pancreatitis and recurrent attacks of acute pancreatitis, chronic inflammation, fibrosis, chronic pain and an increased risk of pancreatic cancer are characteristics of this disorder [3,4]. Diagnosis is suspected by clinical findings and medical and family history and confirmed by molecular genetic testing. HP is associated with mutation in cationic trypsinogen gene (PRSS1), serine protease inhibitor Kazal type 1 gene (SPINK1) chymotrypsinogen C gene (CTRC) and cystic fibrosis transmembrane conductance regulator (CFTR) [4,5].

Autosomal dominant HP is most often related with mutations in PRSS1 with, at least, 80% of penetrance. PRSS1 locates on chromosome 7q35 and encodes trypsin-1 which is the most abundant isoform of trypsinogen in human pancreatic juice [3,5,6]. PRSS1 pathogenic variants are found in 60%-100% of families with HP [3,6,7]. Different mutation and variants in PRSS1 have been described being R122H the most common. R122 is the primary autolysis site and constitutes a defensive mechanism against premature trypsin activation within the pancreas. R122H variant is determined by a G>A transition (c.365G>A) causing a missense substitution of histidine for arginine in position 122 on exon 3 [3,6-8]. Simon et al. [9] describes that HP is caused by either a gain or a loss of trypsin function determined by the activation of recombinant Cys-122 mutant which alters stability of calcium binding loop and lead to an altered catalytic activity and an imbalance between protease-antiprotease equilibrium.

A high risk of pancreatic cancer has been described in HP patients above 40 years old with an estimated ratio of cancer of 40 to 60 compared with the general population, higher in smoking population [3,5,10]. Genetic counseling to cancer prevention and early identification of advance precursor lesions using endoscopic ultrasonography associated to tomography is essential for the management of patients with HP [10]. Treatment of HP (acute and chronic episodes) is similar to that non-genetic based. Pancreatectomy has been performed as a last resort to improve the quality of life in those with uncontrolled pain, particularly young adults and children and could be consider as a preventive technique associated to islet autotransplantation for selected patients at high risk of cancer. Finally, survival for HP patients is similar to general population when patients do not develop pancreatic cancer.

Conclusions

Autosomal dominant hereditary pancreatitis is a rare, complex disease associated with genetic risk factors. Mutations of the cationic trypsinogen are the most common defects related to this entity and should be suspected in young people with unexplained recurrent-acute or chronic pancreatitis, especially if familial history of pancreatic disease exits, like in our case. Genetic counselling and early diagnose of pancreatic cancer are essential in the management and follow-upof these patients due to markedly increased risk of pancreatic cancer.

Learning Points

- Autosomal dominant hereditary pancreatitis is a rare disorder caused by mutations in cationic trypsinogen gene.
- Genetic testing should be considered in patients with unexplained recurrent-acute or chronic pancreatitis at early age and family history of pancreatitis.
- Hereditary pancreatitis patients have a markedly increased risk of pancreatic cancer so prevention and early diagnosis is essential during follow-up.

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