Long-Term Outcomes of Total Pancreatectomy and Islet Auto Transplantation for Hereditary/Genetic Pancreatitis

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BACKGROUND: Chronic pancreatitis is a debilitating disease resulting from many causes. The subset with hereditary/genetic pancreatitis (HGP) not only has chronic pain, but also an increased risk for pancreatic cancer. Long-term outcomes of total pancreatectomy (TP) and islet autogeneic transplantation (IAT) for chronic pancreatitis due to HGP are not clear.

STUDY DESIGN: We reviewed a prospectively maintained database of 484 TP-IATs from 1977 to 2012 at a single center. The outcomes (eg, pain relief, narcotic use, β-cell function, health-related quality of life measures) of patients who received TP-IAT for HGP (protease trypsin 1, n = 38; serine protease inhibitor Kazal type 1, n = 9; cystic fibrosis transmembrane conductance regulator, n = 14; and familial, n = 19) were evaluated and compared with those with non−hereditary/nongenetic causes.

RESULTS: All 80 patients with HGP were narcotic dependent and failed endoscopic management or direct pancreatic surgery. Post TP-IAT, 90% of the patients were pancreatitis pain free with sustained pain relief; >65% had partial or full β-cell function. Compared with nonhereditary causes, HGP patients were younger (22 years old vs 38 years old; $p \leq 0.001$), had pancreatitis pain of longer duration (11.6 ± 1.1 years vs 9.0 ± 0.4 years; $p = 0.016$), had a higher pancreas fibrosis score (7 ± 0.2 vs 4.8 ± 0.1; $p \leq 0.001$), and trended toward lower islet yield (3,435 ± 361 islet cell equivalent vs 3,850 ± 128 islet cell equivalent; $p = 0.28$). Using multivariate logistic regression, patients with non-HGP causes ($p = 0.019$); lower severity of pancreas fibrosis ($p < 0.001$); shorter duration of years with pancreatitis ($p = 0.008$); and higher transplant islet cell equivalent per kilogram body weight ($p \leq 0.001$) were more likely to achieve insulin independence ($p < 0.001$). There was a significant improvement in health-related quality of life from baseline by RAND 36-Item Short Form Health Survey and in physical and mental component health-related quality of life scores ($p < 0.001$). None of the patients in the entire cohort had cancer of pancreatic origin in the liver or elsewhere develop during 2,936 person-years of follow-up.

CONCLUSIONS: Total pancreatectomy and IAT in patients with chronic pancreatitis due to HGP cause provide long-term pain relief (90%) and preservation of β-cell function. Patients with chronic painful pancreatitis due to HGP with a high lifetime risk of pancreatic cancer should be considered earlier for TP-IAT before pancreatic inflammation results in a higher degree of pancreatic fibrosis and islet cell function loss. (J Am Coll Surg 2014;218:530−545. © 2014 by the American College of Surgeons)

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Abbreviations and Acronyms

CFTR = cystic fibrosis transmembrane conductance regulator
CL = confidence limits
CP = chronic pancreatitis
HGP = hereditary/genetic pancreatitis
HRQoL = health-related quality of life
IAT = islet autogeneic transplantation
IEQ = islet cell equivalent
MCS = Mental Component Summary
OR = odds ratio
PCS = Physical Component Summary
PRSS1 = protease trypsin 1
SPINK1 = serine protease inhibitor Kazal type 1
TP = total pancreatectomy

Chronic pancreatitis (CP) is a disease resulting in debilitating pain, narcotic dependence, and diminished quality of life, with patients often seeking surgical options for relief of pain. Although there are many recognized anatomic and drug-induced causes of pancreatitis, often the cause is unknown or idiopathic. There is an increasing recognition that a gene predisposition, hereditary/genetic pancreatitis (HGP), is associated with CP. Le Bodic and colleagues in 1996 described a genetic mutation in a specific gene affecting 47 of 147 members across 4 generations of a French family from Vendee.[1] The first molecular definition of hereditary pancreatitis was a mutation on chromosome 7q35 locus (R122H) of the protease trypsin 1 ([PRSS1], cationic trypsinogen) gene.[1,2] Protease trypsin 1 gene mutations are autosomal dominant with an incomplete penetrance (80%).[2,3] Since 1996, >30 mutations have been found.[2,3] The 3 common mutations are R122H, N291, and A16V.[3] Other gene mutations implicated in hereditary pancreatitis include serine protease inhibitor Kazal type 1 ([SPINK 1], neither autosomal dominant nor recessive) and cystic fibrosis transmembrane conductance regulator ([CFTR], autosomal recessive) gene.[4-6] Both of these carry a 1% penetrance. First symptoms in patients with HGP typically begin in childhood, usually before 10 years of age. Main symptoms are pancreatic pain and acute pancreatitis (>70%).[7] The disease progresses with morphological changes of CP occurring in the pancreas gland by a median age of 22 to 25 years.[7] Exocrine and endocrine pancreatic insufficiency occurs in 34% and 26% at a median age of 29 and 38 years, respectively.[7] More importantly, a recent large series of patients with hereditary pancreatitis showed that there is a 44% cumulative risk of pancreatic cancer by 70 years after onset of symptoms.[8] In addition, pancreatic adenocarcinoma developed in 6% of the patients in the EUROPAC (The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer) study and in 3% of the International Hereditary Pancreatitis Study group (a 50 times higher risk than the general population).[3,8] However, the relative role of CFTR/SPINK1 mutations in carcinogenesis is not well established compared with PRSS1 mutations.[9] The former mutations are likely to serve as disease-modifying genes, although modern series have indirectly expanded the definition of hereditary pancreatitis to include all mutations of PRSS1, SPINK1, and CFTR.[9]

Hereditary/genetic pancreatitis should be an excellent indication for total pancreatectomy (TP), removing all tissue associated with the pain and decreasing risk for development of adenocarcinoma. Islet autogeneic transplantation (IAT) before the pancreas is irreparably fibrosed should offer therapeutic benefit with preserved glycemic control and better quality of life after total extirpation of the pancreas. Few reports have focused on outcomes of TP-IAT in HGP patients.[10] This study reviews the University of Minnesota's experience with TP-IAT in patients with HGP-related CP compared with those without a recognized genetic component.

METHODS

An institutional database has been maintained for all TP-IATs performed between 1977 and 2012 at the University of Minnesota. This was reviewed and 80 procedures were performed for HGP. Patients were categorized as hereditary pancreatitis if there was genetic confirmation (ie, PRSS1, SPINK1, and/or CFTR) or if they met the family history criteria, defined as the presence of recurrent acute pancreatitis or CP in 2 first-degree relatives or 3 or more second-degree relatives in at least 2 generations without any other cause of pancreatitis.[9] The criteria for selection of patients offered TP-IAT for CP has evolved during the years, but has been standardized for the last 5 years. Currently, to qualify for TP-IAT, the patient must have had abdominal pain of longer than 6 months duration with impaired quality of life (eg, inability to work, inability to participate in ordinary activities, repeated hospitalizations, or constant need for narcotics, each coupled with failure to respond to maximal medical treatment or endoscopic pancreatic duct drainage procedures). In addition, there must be objective findings of CP, including at least 1 of the following: pancreas calcifications on CT scan, abnormal ERCP, or ≥6 of 9 criteria on endoscopic ultrasound; or any 2 of following: ductal or parenchymal abnormalities on secretin-stimulated magnetic resonance cholangiopancreatography, endoscopic ultrasound of pancreas with 6 of 9 criteria positive, or abnormal pancreatic function tests with peak bicarbonate <80 mmol/L; or histopathologic-confirmed diagnosis of CP from previous operations; or hereditary pancreatitis