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PANCREATITIS AND CYSTIC FIBROSIS

Pancreatitis, either recurrent acute or chronic, is an infrequent occurrence in CF, yet CF is the most frequent cause of pancreatitis in childhood.¹ Knowledge describing the relationship of genotype and phenotype to CF pancreatitis is leading to a better understanding of the complication. This issue of The CF Supplement reviews pancreatitis and CF.

FEATURED PAPERS

Symptomatic pancreatitis in patients with cystic fibrosis.

Gooding I, et al. Am J Gastroenterol 2009;104:1519-23. **Objective:** To identify characteristics associated with pancreatitis in CF. **Methods:** All patients at one adult CF center with symptomatic pancreatitis were identified through a search of the center's database. The database was maintained since 1965 and contained 1,154 patients. Clinical details were extracted from medical records and compared to age- and sex-matched pancreatic sufficient (PS) controls. **Results:** 1.6% (16) of patients had symptomatic pancreatitis. Mean age of diagnosis with CF was 18.7 years and 28.8 years for the first presentation of pancreatitis. PS patients who experienced pancreatitis were more likely to become pancreatic insufficient (PI) when compared to PS patients who did not develop pancreatitis.

Conclusions: Mild CF transmembrane conductance regulator (CFTR) mutations and R117H were found more often in patients with pancreatitis. Also, afterwards they were more likely to develop PI status compared to PS patients without pancreatitis.

The changing face of the exocrine pancreas in cystic fibrosis: the correlation between pancreatic status, pancreatitis and cystic fibrosis genotype.

Augarten A, et al. Eur J Gastroenterol Hepatol 2008;20:164-8. **Objectives:** To determine the pancreatic status of the CF population of Israel; to analyze the clinical characteristics of those with PS; and to characterize the correlation between pancreatic status, pancreatitis, and CF genotype. **Methods:** The Israeli CF database was searched for: age at diagnosis, presenting symptoms, sweat chloride

concentration, pancreatitis, diabetes, and liver disease. CF mutations were recorded. **Results:** 27.5% (139) were PS. None had two mutations associated with severe disease. 34% of the 139 PS patients had normal or borderline sweat tests; 14.3% (20) had pancreatitis. Four of the 20 patients became PI following bouts of pancreatitis. None of the 366 PI patients had pancreatitis. **Conclusions:** CF patients who were PS carried at least one mild mutation. Pancreatitis occurred only in CF patients who were PS; and they were at risk for becoming PI.

Increased risk of idiopathic chronic pancreatitis in cystic fibrosis carriers.

Cohn JA, et al. Human Mutation 2005;26:303-7. **Objective:** To determine if the risk for idiopathic pancreatitis (IP) is increased in CF carriers who have one CF-causing mutation plus one normal allele. **Methods:** 52 cases of IP were identified. DNA was tested for CFTR mutations. **Results:** 15 subjects had a total of 18 pathogenic CFTR alleles with 8 having common CF-causing mutations. **Conclusions:** IP differed from other established CFTR-related conditions in that IP risk was increased in CF carriers with one documented normal CFTR allele. While having two CFTR mutations imparted a higher risk of developing pancreatitis, having only one mutation also placed a person at risk.

SPECIAL POINTS OF INTEREST:

- *Pancreatitis is an infrequent occurrence in CF, yet the most frequent cause of pancreatitis in childhood.*
- *Persons who are CF carriers may be at risk for pancreatitis.*
- *Pancreatitis should be considered for CF patients with episodes of unexplained abdominal pain, nausea, and vomiting.*

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REVIEW

Pancreatitis is the inflammation of the pancreas, during which enzymes become activated in the pancreas instead of the duodenum.² Pancreatitis can be either acute or chronic: refer to reference 2 for a concise review of pancreatitis in the general population. Annually in the United States, about 210,000 people are admitted to the hospital with acute pancreatitis.² Etiology is varied with the most common being long-standing excessive alcohol consumption or gallstones.³ Other possibilities include metabolic, traumatic, operative, infectious, and pharmacologic causes. Malnutrition and deficiency of micronutrients may contribute to pancreatitis.⁴ About 20% of the cases of pancreatitis in the non-CF population are described as idiopathic (IP), or without clear cause. Since the 1990's much has been learned about the role of genetic mutations and pancreatitis in the general population. Work by Cohn, et al. suggested that up to 37% of patients with IP have mutations of CFTR.⁵ Two other mutations associated with IP are serine protease inhibitor Kazal 1 (SPINK 1) and cationic trypsinogen (PRSS1). In a study of 381 patients with IP, 49% had one or more mutations associated with hereditary pancreatitis; 32% had CFTR abnormalities; 6% had SPINK1 mutations, and 8.9% had PRSS1 mutations.⁶ Interestingly, 5.5% had both CFTR and SPINK1 mutations and 1.8% had mutations of CFTR and PRSS1. Persons who are CF carriers may be at particular risk for developing IP. Cohn et al.^{Featured paper} found that CF carriers with one documented normal CFTR allele had a fourfold risk for IP.

In CF, pancreatitis may reflect abnormal CFTR function. Normally, CFTR activity in the pancreas leads to the secretion of a bicarbonate-rich alkaline fluid within the acinar lumen thereby maintaining solubility of secreted enzymes.⁷ It has been suggested that in CF, the dysfunctional CFTR causes ductal obstruction and/or alteration in acinar function, which in turn initiates intracellular activation of pancreatic enzymes by an unknown process. The abnormal process may lead to highly concentrated secretions, resulting in obstruction and organ damage.^{8,9} In patients with 2 severe mutant alleles, pancreatic destruction of functional acinar tissue occurs in utero or in early infancy, therefore PI patients are free of symptoms of pancreatitis.⁷ PS patients have evidence of a defect of pancreatic electrolyte and fluid secretion,¹⁰ but still retain sufficient CFTR activity to preserve function to digest food and assimilate nutrients.⁷ A relatively small amount of CFTR function is sufficient to protect the pancreas from becoming PI. Normal enzyme activity can be maintained with as little as 2% of pancreatic function.^{5,9,11,12} It remains unclear as to why some PS patients develop pancreatitis and

why some of these patients become PI. The development of pancreatitis may be related to secondary modifying genetic factors unrelated to the CFTR gene or possibly an environmental event, such as exposure to medications or alcohol, which initiate the process.⁷ Based on the theoretical pathophysiological basis of pancreatitis in CF, it is reasonable to expect pancreatitis to occur only in individuals with pancreatic function.¹

As early as 30 years ago, cases of pancreatitis were reported in patients who have CF.¹³ Pancreatitis prevalence is low with rates varying reflecting the definition used to identify it. In CF researchers have defined pancreatitis as: 1) patients experiencing an acute episode of abdominal pain in association with elevated serum amylase level (at least 1.5 times greater than the upper limit of the reference range) provided the pain could not be attributed to another cause;⁷ or 2) the presence of typical pancreatic pain as assessed by a hepatopancreatobiliary specialist, and either significant rise in serum amylase (three times the upper limit of normal) or pancreatic imaging findings;^{Gooding, Featured paper} or 3) episodes of abdominal pain associated with elevation of serum amylase or serum lipase levels.^{Augarten, Featured paper} No specific definition was used when reporting pancreatitis in the CF Foundation registry data analyzed by Maisonneuve, et al.¹⁴ Authors did not differentiate between acute or chronic pancreatitis. For patients who have CF, Augarten, et al.^{Featured paper} suggested a

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REVIEW (CONT.)

classification system based on serum enzyme levels and genotype mutation.

Depending on the CF database evaluated, prevalence of pancreatitis ranged from 1.2% to 17.3%.^{7,14,15,}

^{Augarten, Featured paper} Pancreatitis in patients who were PI was a rare occurrence and may reflect the manner in which pancreatic status was classified (PI or PS) at the time of CF diagnosis.¹ The mean age at which patients experienced the first episode of pancreatitis was in the early twenties,^{7,15, Augarten, Featured paper} with pancreatitis being diagnosed prior to the diagnosis of CF in some.⁷ Diagnosis of pancreatitis preceding that of CF may reflect use of data collected prior to the routine availability of newborn screening. Specific genetic mutations could not be identified, but pancreatitis seemed to occur in CF patients described as class IV or V (in which CFTR activity is reduced but not completely inactive).^{Augarten, Featured paper} Patients carrying the R334 mutation were seen in Maisonneuve's population with 48% of the 79 with R334 being Hispanic, 13 living in Puerto Rico.¹⁴ In the group studied by Gooding,^{Featured paper} 14 of the 16 patients were delta F508 plus a mild CFTR mutation with R117H being found most often. Durno⁷ noted that the frequency of delta F508 plus a mild mutation was greater in the PS patients with pancreatitis. Not all PS patients experienced pancreatitis and not all of those who developed pancreatitis became PI.^{Gooding, Featured paper,} ⁷ Pancreatitis, especially with numerous bouts, may be an indicator of impending PI. Details regarding specific genotypes and pancreatic function are provided by a number of authors.^{5,7,16,17, Gooding, Featured paper, Augarten, Featured paper}

Trypsinogen is an inactive protein secreted by the acinar cells of the pancreas and is converted into trypsin by action of enteropeptidase from the duodenal mucosa. Elevated serum immunoreactive cationic trypsinogen (IRT) is the basis for newborn screening. The rationale is that duct obstruction develops in utero in the CF pancreas, leading to enzyme leakage into the blood.¹⁶ PS infants have enough pancreatic damage to have elevated IRT to be identified through newborn screening.¹⁸ IRT may be used to monitor the progression of pancreatic disease in CF.¹⁹ As acinar function declines, IRT levels decline.

CLINICAL APPLICATIONS

Pancreatitis may occur more often than recognized in PS patients and should be considered for patients with episodes of unexplained abdominal pain, nausea, or vomiting.⁷ Alcohol intake, diet, gallstones, or reaction to the post-endoscopic retrograde cholangiopancreatography (ERCP) procedure may be the immediate cause, yet PS patients may develop

CLINICAL APPLICATIONS (CONT.)

pancreatitis without these risk factors. Some patients may experience pancreatitis during vacations at which time they may consume a diet and alcohol different from their usual pattern. Pregnancy is a risk factor for pancreatitis in all women including those with CF who are PS.^{20,21} Because some PS patients who experience bouts of pancreatitis become PI, pancreatic function should be determined by either fecal elastase, or fecal fat study.¹

There is no nutrition management recommendation specific to CF for pancreatitis. The exocrine pancreas is involved in the digestion of food. Pancreatitis, of any origin, interferes with this role, causes pain, results in catabolic stress, and can result in malnutrition. Pain associated with pancreatitis is partially related to the secretory mechanisms of pancreatic enzymes and bile. To control discomfort, patients may limit food intake. The standard nutrition treatment for pancreatitis includes maintaining hydration and optimal intake such as of calories, fluids, minerals, and vitamins especially the fat-soluble vitamins. Since enteral feeding plays a role in maintaining gut immune system integrity, it is preferred over parenteral nutrition.²² Although patients may initially be kept NPO, evidence suggests that enteral feeding should be commenced as soon as possible.²³ Enteral products containing MCT may be useful. Jejunostomy is considered when pain is refractory. When food intake is initiated, six small daily feedings, including adequate vitamins and minerals, are indicated. To reduce discomfort and/or steatorrhea, pancreatic enzyme replacement therapy (PERT) is used. The RD is referred to current nutrition therapy references regarding management. DiMagno, et al.,³ Meier, et al.,²² and Escott-Stump²⁴ provide excellent details.

SUMMARY

In reviewing the limited data available about pancreatitis and CF, it appears that: 1) if newborn screening is not routinely available, pancreatitis may be recognized before the diagnosis of CF and patients who have pancreatitis may have been diagnosed with CF at an older age; 2) pancreatitis may lead a person with CF from the PS to PI state, but not always; 3) PS patients with pancreatitis carry at least one mild mutation, but specific mutations that make PS patients at risk for pancreatitis have not been identified. Nutrition management is indicated for both acute and chronic pancreatitis, and is that which is commonly practiced for persons with pancreatitis from any etiology. The RD needs to pay astute attention to the patient's pain threshold. PERT usually is necessary. The aim is to optimize the patient's weight and nutrient intake via the enteral route as soon as possible.

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