Cystic Fibrosis Liver Disease

Definition

Cystic Fibrosis (CF) is an autosomal recessive disorder that is the most common genetic disorder of Caucasian individuals with a prevalence of about 1 in 3000 individuals of European descent and is estimated to affect 30,000 individuals in the United States (1). The disease is due to a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) (2-5). While the lungs and pancreas are the pathognomonic target organs in CF, many other organs are affected. These include, but are not limited to, the sweat gland, small and large intestine, vas deferens, sinuses, biliary tree and liver. With the increased survival of individuals with CF due to advances in care, liver disease has become an increasingly recognized problem. In 2011, liver disease accounted for 2.7% of deaths the preceding year (6). However, despite significant advances in our knowledge of CF, there have been minimal advances in our understanding of liver disease in CF. The discovery of the gene for CF in 1989, has led to a greater understanding of the pathophysiology of CF (3). There are over 1,900 mutations described in CFTR (7). The mutations are classified into 5 categories with class 1,2 and 3 mutations classified as severe and class 4 and 5 as moderate to mild (2). In the US, the most common mutation is ?F508, which leads to expression of small amounts of dysfunctional CFTR at the cell surface and is classified as a severe class 2 mutation (8). Despite a substantial amount of information linking certain CFTR genotypes to the clinical phenotype of the individual patient for pulmonary, pancreatic and intestinal disease, this is not true for liver disease in CF.

Pulmonary Disease: Lung disease in patients with CF results from inflammation, infection, and obstruction (9). Airways inflammation can be seen starting early in life. Airways become colonized with a variety of bacteria, most notably pseudomonas aeruginosa, among others (10). Mucus becomes thick as a result of dehydration of airway mucus, the presence of free DNA from lysed cells and the products of the inflammatory response. Patients are treated with physical methods to clear airway mucus (11), drugs to hydrate mucus, lyse DNA and control inflammation, and antibiotics when needed (12). Lung disease is progressive and is the cause of death in most patients with CF; measures to prevent decline and intervene early when there are pulmonary exacerbations are thus the mainstay of CF care.

Pancreatic Disease: Pancreatic insufficiency is a hallmark of CF. The therapy is directed at pancreatic enzyme replacement therapy, supplements of fat soluble vitamins, and acid blocking agents and bowel hydration if needed. Determination of pancreatic status can be accomplished by pancreatic stimulation test, 72 hour fecal fat collection or determination of fecal elastase (13). Ninety percent of individuals with CF have pancreatic insufficiency. The pathology of the pancreas is one of ductular obstruction with fibrosis and loss of acinar cells. Pancreatic insufficiency is almost uniform in individuals with severe mutations. Pancreatic insufficiency is present at birth in about 70% of patients and in ~90% by one year
of age. Pancreatic sufficiency, seen in about 15% of CF patients at birth, is associated with heterozygosity or homozygosity for milder CFTR mutations (classes 4 and 5). Patients with pancreatic sufficiency have an increased risk of acute, recurrent acute and chronic pancreatitis (14). For both pancreatic sufficient and insufficient CF, as the injury to the pancreas progresses, pancreatic endocrine insufficiency increases with diabetes becoming more common in the second and third decades of life.

Liver Disease

The most significant form of liver disease in CF is multilobular biliary cirrhosis often with portal hypertension in up to 7% of individuals with CF (15-19). The reported frequency of the various manifestations of hepatobiliary involvement is shown in the following table.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>5-10%</td>
</tr>
<tr>
<td>Hepatic Steatosis</td>
<td>20-60%</td>
</tr>
<tr>
<td>Elevated AST, ALT or GGT</td>
<td>50-80%</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>5-10%</td>
</tr>
<tr>
<td>Microgallbladder</td>
<td>20-30%</td>
</tr>
<tr>
<td>Biliary strictures</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>1-2%</td>
</tr>
</tbody>
</table>

With the protean manifestations of liver involvement in CF, there is a need for uniform criteria for the definition of liver disease/involvement in CF. The majority of studies of liver involvement in CF have combined several of the various manifestations of liver involvement of CF under one global term Cystic Fibrosis Liver Disease (CFLD). There are many drawbacks to this approach as it does not allow comparison of natural history, diagnostic accuracy or treatment studies in CFLD. In 2007, the CF Foundation convened a group of international experts in CF related liver disease. This group has proposed the following classification for CF related Liver Disease to guide research in the field. It is
recommended that all future studies utilize a uniform classification and definition of CFLD. This proposed classification is shown in the following table.

1. CFLD with cirrhosis/portal hypertension
   i. Clinical evidence of portal hypertension
   ii. Evidence of cirrhosis by histology, imaging or laparoscopy

2. Liver Involvement without cirrhosis/portal hypertension (patients could have more than one: i.e. II a,c.)
   i. Biochemical abnormalities
      a. Persistent AST, ALT, GGT >1.5 or 2 X ULN
      b. Intermittent
   ii. Steatosis by liver biopsy, possibly radiologic imaging
   iii. Fibrosis by liver biopsy
   iv. Cholangiopathy (documented by abnormalities of the biliary tree on US, MRCP, CT, or ERCP)
   v. Ultrasound abnormalities that are not diagnostic of cirrhosis
      a. Abnormal echogenicity

Clinical Features

The typical presenting clinical features of the severe forms of CFLD (cirrhosis) are signs of portal hypertension including splenomegaly and GI bleeding from esophageal or gastric varices.

Elevated AST, ALT or GGTP: Abnormal values for AST and ALT are common in CF with a reported frequency of abnormal values of up to 80% during 8 years of follow up (20) (17) and abnormal GGTP in 10% by 10 years of age (21). However persistently abnormal values greater than two times the upper limit of normal are infrequent (21, 22). There is no data to suggest that abnormal values for AST, ALT or GGTP are predictive for the development of cirrhosis and portal hypertension.

Multipulbular biliary cirrhosis with or without portal hypertension is the complication with the most significant impact on outcome and affects between 5 and 10% of patients with CF. Several studies have demonstrated that cirrhosis is an early event, with the median age of recognition by 10 years (15, 17, 23, 24). Risk factors for cirrhosis have included male sex, Hispanic ethnicity and pancreatic insufficiency (15) (23). There is no identified genotype phenotype correlation with CFTR other than the observation that portal hypertension is seen primarily in individuals who have class I or II mutations (15) (23). The major complications in patients with portal hypertension are variceal hemorrhage and hypersplenism, sometimes massive in patients with CF. Hepatocellular failure is rare and patients can maintain normal hepatic synthetic function for years and even decades. Similarly, the impact of cirrhosis on the clinical course of CF is unclear.
Other manifestations of liver involvement:

*Neonatal cholestasis* occurs in 1-2% of infants with CF. However, CF is a rare cause of neonatal cholestasis accounting for <1% of the diagnoses of infants with cholestasis (25).

*Hepatic steatosis* has been reported to occur in 20-60% of patients with CF (26). In many cases this was reported in association with malnutrition related to CF. However, hepatic steatosis has been reported in well nourished children and adults with CF. It is unclear if hepatic steatosis progresses to cirrhosis.

*Focal Biliary Cirrhosis* is considered the characteristic hepatic disorder of CF. It is characterized by focal areas of fibrosis and regenerative nodules and areas of normal liver. The prevalence has been reported between 10 and 70% depending on the method of detection and the era (26). The highest frequency for this disorder comes from autopsy reports that predate current therapies. If and at what frequency this pathologic entity progresses to multilobular biliary cirrhosis and portal hypertension is unknown.

*Microgallbladder* is the most common abnormality reported to occur in up to 30% of patients.

*Cholelithiasis* is reported in 1-10% of patients with CF.

**Diagnosis**

CF is diagnosed by an elevated sweat chloride (>60 meq/L), performed by a certified lab. The demonstration of 2 disease causing mutations in the setting of end organ involvement (e.g. pulmonary, sinus, absences of the vas deferens, pancreatic insufficiency, meconium ileus, cirrhosis) is also sufficient for the diagnosis. With the ability to perform genetic testing, there are patients with mutations who do not have evidence of end organ involvement or abnormal sweat chloride who do not meet the current classification of CF (27).

CF liver disease with cirrhosis is diagnosed by the findings of cirrhosis by imaging, histology or laparoscopy. The disorder may be suspected in the setting of a hard nodular liver with or without the findings of portal hypertension (splenomegaly, esophageal or gastric varices, ascites, hypersplenism). If histology is sought, the focal nature of the disease requires a large biopsy for confirmation.

Histology: The histology of CF cirrhosis is one of focal biliary fibrosis. Inspissated eosinophilic material in the bile ducts is seen commonly and may be present to some extent in all individuals with CF. There is expansion of the portal tracts with fibrosis and minimal inflammation with subsequent micro and macronodular cirrhosis. Exclusion of other causes of liver disease (including alpha-1-antitrypsin deficiency, Wilson’s disease, chronic viral hepatitis, autoimmune hepatitis and biliary tract abnormalities) is important.
Treatment

To date, there has been no treatment that has been shown to reverse established cirrhosis in CF. The treatment of CF cirrhosis includes attention to good nutrition, avoidance of hepatotoxins, maintenance of appropriate fat soluble vitamin status, zinc status and treatment of complications of portal hypertension. Patients should be vaccinated against hepatitis A and B and should avoid NSAIDS and alcohol. Ursodeoxycholic acid has been shown to decrease AST and ALT and perhaps decrease biliary plugging. There have been no randomized trials of ursodeoxycholic acid in CF cirrhosis. Liver transplantation in well selected individuals has been shown to have excellent outcomes. However, management of the complications of portal hypertension also has been shown to be associated with excellent survival.

Prognosis

The prognosis for children with CF and cirrhosis has not been well characterized. Current data suggests that portal hypertension is the most common complication in individuals with CF and cirrhosis, but that poor haptic synthetic function is a late finding.

ChiLDReN Network studies that include patients with CF Liver Disease

Yes. The ChiLDReN Network currently has three studies that include patients with CFLD.

The PUSH, MRE and ELASTIC studies are all natural history studies that include patients with CFLD. A natural history study is aimed at acquiring information and data that will provide a better understanding of rare conditions. Participants will be asked to do such things as allow study personnel to obtain information from medical records and an interview, and to collect blood, urine, and tissue samples when clinically indicated, in order to understand the cause of this disease and to improve the diagnosis and treatment of children with this disease. All of the information obtained in these studies is confidential and no names or identifying information are used in the studies.

PUSH: A longitudinal study of the risk of hepatic cirrhosis in Cystic Fibrosis.

Eligibility: Children ages 3 through 12 years of age with Cystic Fibrosis and pancreatic insufficiency who are enrolled in the CFF or Toronto CF registry studies. This study is closed to enrollment.

ClinicalTrials.gov Study NCT01144507

MRE: Study to assess the feasibility of using MRI based liver stiffness determination in children with CF.

Eligibility: Children with Cystic Fibrosis and pancreatic insufficiency who are enrolled in the PUSH Study at one of the participating clinical centers.

ClinicalTrials.gov Study NCT02979340
ELASTIC: A study to determine if liver stiffness as measured by transient elastography (TE), when combined with ultrasound (US) pattern characterization can improve the identification of children with cystic fibrosis and liver disease.

*Eligibility:* Children with Cystic Fibrosis and pancreatic insufficiency who are enrolled in the PUSH Study at one of the participating clinical centers.

ClinicalTrials.gov Study NCT03001388

**Organizations or foundations that help families dealing with CFLD**

The ChiLDReN Network works with numerous groups that support patients and families who are dealing with rare liver diseases. Please click here to go to that page on our website (Information for Families). You will see the list of groups and information about them.

**References**


