



THE CF SUPPLEMENT

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THE LIVER AND CYSTIC FIBROSIS

The liver is a complex organ with a diverse number of functions including: metabolizing nutrients, synthesizing bile, activating hormones, filtering foreign particulates, and detoxifying compounds. Any harm to the liver is detrimental to health. CF-related liver abnormalities (CFLA) are common, although overt CF-related liver disease (CFLD) is rare. The causes are multifactorial, reflecting a unique constellation of factors. Methods to detect and manage CFLA and CFLD are limited. [1] This newsletter reviews CFLA and CFLD, with special emphasis for the nutritionist.

FEATURED PAPERS

Hepatobiliary abnormalities and disease in cystic fibrosis: Epidemiology and outcomes through adulthood.

Bhardwaj S, et al. J Clin Gastroenterol. 2009;Jun 11. **Objectives:** To determine the: 1) prevalence of; 2) risk factors for; and 3) factors which predict CFLD. **Methods:** Retrospective chart review of all patients at one CF center over a 32 year period. Mean time of follow-up: 8 yrs. **Subjects:** 283 patients; mean age 17 yrs (2 months to 63 yrs). **Results:** 65% of the 283 patients had CFLA; 84% of which were <18 yrs of age; 25% went on to develop CFLD. 15% of the 283 patients had CFLD with 93% <18 yrs of age. **Conclusions:** Abnormal liver chemistries without clinical evidence of CFLD were common; risk of liver involvement decreased with age, falling by 5% per year. Initial development of CFLD appeared to be rare after 18 yrs of age.

Hepatobiliary disease in patients with cystic fibrosis.

Moyer K, et al. Curr Opin Gastroenterol. 2009;25:272-8. **Objective:** To review advances in CFLD knowledge. **Findings:** Liver abnormalities were varied and ranged from defects related to the underlying CF genetic defect to those related to systemic disease and malnutrition. Focal biliary cirrhosis and progression to multilobular cirrhosis with portal hypertension and end-stage liver disease were the most clinically relevant problems. Liver transplant may not improve survival in CF patients with portal hypertension. **Summary:** Hepatobiliary disease was a common finding. Of those identified with CFLD early in life, CFLD may impact quality of life and survival.

Is significant cystic fibrosis-related liver disease a risk factor in the development of bone mineralization abnormalities?

Alex G, et al. Pediatr Pulmonol. 2006;41:338-44. **Objective:** To assess the effects of CFLD on bone health. **Methods:** Matched-control study. All subjects received: DEXA, assessment of fat-soluble vitamins, liver function, and pulmonary function. **Subjects:** 13 patients with CFLD; age range: 10-19 yrs; and 13 CF

patients without CFLD matched for gender, age, and size.

Results: Patients with CFLD had slightly lower FEV1 and significantly higher ALT. Measures of bone density and measures of fat-soluble vitamins were not different between patients with CFLD and CF alone. **Conclusions:** CFLD did not appear to result in additional risk for development of bone mineralization abnormalities.

REVIEW

Pathogenesis

Liver abnormalities seen in persons who have CF are numerous and reflect: 1) CFTR defects; 2) the CF disease process occurring outside of the liver; and 3) CF treatment side effects. [2] Examples include: focal biliary cirrhosis, multilobular cirrhosis, portal hypertension, neonatal cholestasis, sclerosing cholangitis, microgallbladder, cholestasis, hepatic congestion, common bile duct stenosis, and drug hepatotoxicity. [3] Also seen in CF is steatosis which may be related to malnutrition and/or deficiencies of fatty acids, choline, and carnitine, although the exact cause is unknown. [4] Steatosis does not seem to be correlated with CF outcome or to the development of the more serious focal or multilobular cirrhosis.

CFLA and CFLD are unpredictable and difficult to detect. They develop slowly and progress slowly. [3] Lack of clear definition and classification of CFLA/CFLD is a challenge in indentifying the true incidence. To better define CFLA/CFLD the following classification system has been proposed: 1) CFLD: Portal hypertension or cirrhosis (based on histology, imaging, or laparoscopy); 2) CFLA: Liver involvement without portal hypertension or cirrhosis: persistent or

SPECIAL POINTS OF INTEREST:

- *Cystic fibrosis liver abnormalities and cystic fibrosis liver disease are unpredictable and difficult to detect.*
- *Specific gene mutations appear not to be associated with the risk of developing liver disease.*
- *Mild liver abnormalities can be undiagnosed, yet subtly impact nutritional status.*

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REVIEW (CONT.)

intermittently elevated AST, ALT, GGT, steatosis, fibrosis, cholangiopathy, and/or abnormal ultrasound; and 3) Preclinical: No evidence of liver disease with normal clinical examination, normal imaging, and normal biochemistry. [5] Traditional methods to identify CFLA, such as ultrasound and biopsy, may not be sufficiently sensitive to diagnosis CFLA or CFLD. [6] Liver biopsy, considered the gold standard, may miss the early focal lesion of cirrhosis.

CFTR is expressed at the apical membrane of cholangiocytes and gallbladder epithelial cells, but not in hepatocytes. [7] CFTR regulates the fluid and electrolyte content of bile, thus bile formation and flow. [8] The cause of CFLA and CFLD is speculative. The hypothesis is: Impaired secretory function of the biliary epithelium results in thickened, inspissated secretions in the bile ductules throughout the liver, causing bile duct plugging which may lead to release of inflammatory mediators, stellate cell activation, collagen deposition, fibrosis, and ultimately cirrhosis. [Bhardwaj, featured] [9] In addition, impaired bile flow can lead to an accumulation of toxic hydrophobic bile acids resulting in hepatocyte injury, leading to fibrosis and cirrhosis. [Bhardwaj, featured] Focal biliary cirrhosis, (FBC) with cirrhosis of only some areas of the liver, is unique to CF. FBC is difficult to diagnose because it easily can be missed by biopsy. FBC can progress to multilobular biliary cirrhosis (MBC). MBC can be asymptomatic, yet be quite serious, leading to portal hypertension. In a study of 1108 CF patients, 17 had CFLD. The duration of the CFLD did not impact the progression of liver complications and patients survived many years, with the greatest challenge being the management of portal hypertension. Hypoalbuminemia, persistent coagulopathy, and mild hyperbilirubinemia were harbingers of hepatocellular failure. Lung function in the CFLD group did not differ from patients with CF alone. [10]

In families with more than one child who has CF, not all develop CFLD. Unlike pancreatic function in which specific gene mutations are associated with severity of pancreatic function, the same is not the case for CFLD. Specific mutations do not appear to predict liver disease, but patients who have CFLD do have at least one severe mutation. Work is ongoing to determine if patients who develop CFLD also may be heterozygote carriers of other chromosomal mutations for liver disease, such as alpha 1-antitrypsin [11] that make them more susceptible to liver injury in the presence of abnormal CFTR function. In animal models, abnormal intestinal bacteria were associated with the development of fibrosis. [12] Could abnormal intestinal microflora seen in CF contribute to CFLD? [13] Additional factors, yet to be determined in CF, are the roles of malnutrition, nutrient deficiencies, and medications on liver health. A greater incidence of CF-related diabetes (CFRD) in patients with CFLD has been reported. [14] It has been suggested that patients with CFLA be screened for CFRD regardless of age. [15]

Prevalence

Many CF patients have some degree of CFLA. [4] Five to 10% of patients who have CF develop CFLD and it accounts for about 2.5% of all CF deaths. [4] Twenty to 50% of

patients have been reported to have elevated liver enzymes, with over 80% of patients having elevated levels at some time, including newborns identified through newborn screening. [16] Liver enzyme blood tests (LFTs) may not identify CFLA or CFLD. Patients with transient elevated LFTs may not go on to develop CFLA or CFLD; conversely patients with CFLD may have normal LFTs. [17] [18] [19] Hepatomegaly or splenomegaly in an otherwise asymptomatic patient may be the initial clinical presentation. [9] In autopsy studies, CFLA was identified in 10% of infants and 72% of adults, often first presenting at or around puberty. [20] There is evidence that CFLD peaks during adolescence, with a subsequent decrease following adolescence. The chance of developing CFLD after 20 years of age is unusual and those who do may experience a milder course. [17] [21] CFLA and CFLD risk factors include: male, pancreatic insufficiency, less than 20 years of age, severe genotypes, history of meconium ileus, later CF diagnosis, and of Hispanic origin. [17] [22] [23] For a better understanding of liver anatomy and function, the reader is directed to a comprehensive medical text. Besides the featured paper by Moyer, a number of review papers provide greater detail regarding pathogenesis and prevalence of CFLD. [3][4][8][9][20][24]

Treatment

Treatment consists of closely monitoring the patient and medical or surgical interventions, including liver transplant. Ursodeoxycholic acid ("urso") is a choleric agent and is used with conditions related to bile flow abnormalities. This medication may result in transient improvement in LFTs, but its efficacy in preventing the progression of liver disease is unknown. [9][25] Surgical intervention is reserved for those patients with portal hypertension and variceal bleeding refractory to less invasive treatment. Liver transplant is limited to patients with progressive liver failure and/or life threatening portal hypertension with mild pulmonary involvement; it can improve nutritional status. [24][26]

ABOUT EURAND

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CLINICAL APPLICATIONS

The liver is both a “factory” to manufacture (synthetic function) and a “warehouse” to store. In nutrition, the liver has a role in metabolism of nearly all nutrients. The liver’s synthetic function not only includes nutrients, but other indicators of nutrition and health such as: albumin, C-reactive protein, coagulation factors, cholesterol, and the binding factors for vitamins A and D. Abnormal liver function challenges the RD in maintaining optimal nutritional status in persons who have CF. There is little published information describing specific nutrition needs. The RD takes into consideration the nutritional demands of both CF and liver disease. Mild liver abnormalities can be undiagnosed, yet subtly impact nutritional status through their effects on bile formation and flow. Changes in synthetic liver function or physical examination (hepatomegaly) may indicate active liver involvement requiring modification of nutrition recommendations. Additionally, other factors can cause liver complications including inadequate or excessive intake of nutrients or other diseases such as Wilson disease and should be included in the differential nutrition diagnosis. [9] [27]

All CF patients should receive an annual nutrition assessment. Laboratory studies to assess liver function and to determine synthetic function are indicated. Nutrient deficiency (EFA, choline, carnitine) or excess (retinol, calories, alcohol, copper) should be ruled out as the cause of liver abnormalities. The assessment should include a review of usual alcohol intake and use of over-the-counter products (medications, vitamins, minerals and herbs). Due to poor bile flow and altered micellar formation, patients who have CFLA or CFLD may have increased energy intake needs and supplementation with MCT oil-based formulas may be indicated. In addition to their usual vitamins and minerals, some patients require supplementation with single nutrients, such as individual fat-soluble vitamins, or minerals like zinc, iron, or magnesium. [9][28] [29] Vitamin E as alpha-tocopheryl polyethylene glycol succinate (TPGS) may improve serum tocopherol levels. [9] Infants who have CFLA may benefit from use of an infant formula containing MCT oil. [9] EFA should be supplemented in those patients found to be deficient. Preliminary research indicates that patients with CFLD have decreased docosahexaenoic acid (DHA) when compared to controls. [30] Patients with portal hypertension and esophageal varices are a unique challenge. Placement of NG or G-tubes and use of TPN may not be indicated, making reliance on oral intake necessary.

In summary, CFLA are common in patients who have CF, and may go unidentified until portal hypertension develops. The CF medical community is attempting to develop methods to prevent CFLD and until then, to identify and treat CFLA and CFLD as early as possible. The ability to recognize all factors leading to CFLA and CFLD is essential. Nutrition plays an important role in the care of the person who has CFLA or CFLD.

USEFUL TERMS

Biliary tract: Often described as a tree starting with small branches and ending in a main trunk. Bile canaliculi to bile ductules to intrahepatic ducts to left/right hepatic ducts which merge to the common hepatic duct which exits the liver to the cystic duct of the gallbladder to form the common bile duct which joins the pancreatic duct forming the ampulla Vater where it enters the small intestine.

Cirrhosis: Destruction of the biliary system (bile ducts).

Cholangiocytes: Epithelial cells of the bile ducts.

Cholestasis: Condition in which little or no bile is secreted or flow of bile into the digestive tract is obstructed, resulting in accumulation of bile in the liver.

Cholangitis: Inflammation of the bile ducts.

Cholangiopathy: Diseases of the cholangiocytes.

Cholecystitis: Inflammation of the gallbladder.

Cholelithiasis: Stones in the gallbladder or bile ducts.

Focal biliary cirrhosis: Scattered (focal) areas of liver fibrosis, cholestasis, and bile duct proliferation.

Multilobular biliary cirrhosis: Widespread areas of portal fibrosis, cholestasis, and bile duct proliferation.

Portal hypertension: High blood pressure in the portal vein, often caused by cirrhosis. Can result in splenomegaly, esophageal varices, gastric varices, and other medical complications.

Steatosis: Abnormal retention of fat within liver cells.

Stellate cell or Ito cell: Cells found in the space of Disse (between the sinusoid and hepatocytes). The lipid droplet in the cell stores retinol. With liver damage, the stellate cells are “activated;” produce collagen scar tissue, which damage the bile ductules; leads to cirrhosis; no longer contain retinol.

Liver enzyme blood tests (LFTs):

Bilirubin: Substance produced from the breakdown of hemoglobin. Direct or conjugated: Associated with dysfunction or blockage of the liver. Indirect or unconjugated: Associated with destruction of red blood cells or abnormalities of conjugating enzymes. Total: Total of both bilirubins.

ALT: Alanine aminotransferase: Enzyme normally produced by the liver. It reflects hepatocyte health. In liver damage blood levels increase.

AST: Aspartate transaminase: Enzyme produced by the liver and muscles and is released into circulation following cellular damage.

GGT: Gamma-glutamyltransferase: Enzyme used to determine bile duct damage. It is more sensitive than ALT and AST in detecting obstructive jaundice, cholangitis, and cholecystitis.

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