Liver disease in cystic fibrosis

Indra DM van Mourik

Abstract

Cystic fibrosis (CF) is a multiorgan disorder, caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, resulting in abnormal regulation of salt and water movement across membranes. In the liver this leads to hyperviscous bile accumulating in the biliary tree, causing cholangiocyte and hepatocyte injury and inflammation, stimulating focal fibrosis. With increased life expectancy CF related liver disease (CFLD) has become a leading cause of morbidity and mortality in patients with CF. Most patients with CFLD remain asymptomatic even though approximately 5–10% develop multilobular cirrhosis during the first decade of life. Most will develop signs of portal hypertension. Active screening for CFLD and introduction of non-invasive imaging techniques and novel biomarkers would identify individuals at risk for cirrhosis prior to its development in order to institute therapy to prevent or reduce disease progression, and can detect patients who have developed clinically silent cirrhosis to allow monitoring and interventions to reduce or mitigate complications. Liver transplant should be considered for those who develop hepatic dysfunction or advanced portal hypertension, although deteriorating pulmonary function and quality of life should also be taken into account. Current research in CFLD focuses on repairing the basic defect and reducing inflammation thus aiming to find treatment modalities that prevent development and/or progression of CLFD.

Keywords cirrhosis; cystic fibrosis; liver disease; oesophageal varices; portal hypertension; transplantation

Introduction

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disease in Caucasians with an incidence of approximately one in every 3000 live births worldwide. Median life expectancy in the UK is currently around 50 years for those born in 2000 and thereafter.

CF is a multiorgan disease affecting the lungs, pancreas, intestine, liver, sweat glands, and in males the Wolffian ducts. It results from mutations within gene coding for the cystic fibrosis transmembrane conductance regulator (CFTR) protein, responsible for maintaining fluid balance across epithelial cells, and comprising almost 2000 different mutations. The resulting secretory defect determines inability to maintain luminal hydration of ducts, leading to physiochemical abnormalities of secretions and duct obstruction.

Advances in CF patient care have led to an increase life expectancy and as such cystic fibrosis related liver disease (CFLD), usually not presenting until puberty, has become one of the leading causes of morbidity in CF patients. After cardiorespiratory problems and transplantations complication, CFLD is the third leading cause of death accounting for 2.5% of overall CF mortality.

Indra DM van Mourik *MD MRCP FRCPCH, Consultant Paediatric Hepatologist with the Liver Unit, Birmingham Children's Hospital NHS Foundation Trust, Birmingham, UK. Conflict of interest: none declared.*

Prevalence

Prevalence figures of CFLD vary widely. This may be explained by differences in diagnostic criteria used and in populations studied. Some retrospective studies in a clinical setting reported prevalence figures between 4.2% and 17%, with higher figures (up to 38%) reported in cross sectional studies using biochemical and ultrasonographic assessment of liver disease. Prevalence increases through childhood (incidence of approximately 2.5 per 100 patient-years), reaches a peak in mid-adolescence, with no further increase thereafter. Approximately 5–10% of all CF patients will develop multilobular cirrhosis during the first decade of life. This suggests that the mechanism and risk factors for liver damage present in early childhood for those CF patients who develop liver disease.

Risk factors

Factors associated with development of CFLD include severe genotype (i.e. class I, II or III mutations on both alleles), male sex, history of meconium ileus and age at diagnosis of CF. No specific CFTR mutation has been associated with presence and severity of CFLD. There is some evidence that polymorphism in genes that upregulate inflammation, fibrosis or oxidative stress may increase susceptibility for developing liver disease. Research into the identification of such modifier genes is ongoing. To date only the *SERPINA*-1 gene has been reported to be a genetic modifier for CFLD. This means that CF patients who also carry the heterozygous Z-allele mutation of α1-antitrypsin are more likely to develop significant CFLD.

A few reports described a higher incidence of CFLD in patients with meconium ileus. Additional factors such as extensive bowel resection, prolonged parenteral nutrition, drug toxicity and poor nutrition in early life may contribute to development of CFLD.

A delay in diagnosing CF may predispose children to liver disease, most likely due to relatively poor nutritional status.

Pathophysiology

There is a wide spectrum of hepatobiliary disease in CF patients including specific alterations due to the underlying CFTR defect, iatrogenic lesions and effects of extra-hepatic disease (Table 1).

CFTR expression in the liver is restricted to the apical membrane of cholangiocytes and gall bladder epithelial cells. Defective CFTR protein here causes abnormal chloride transport and hydration, leading to increased bile viscosity and reduced alkalinity, resulting in plugging of intrahepatic bile ducts by inspissated secretions and progressive injury to biliary epithelium and hepatocytes. This process progresses slowly from simple bile plugging, to focal biliary fibrosis/cirrhosis, and multilobular cirrhosis. It is not entirely clear why initial distribution of hepatic lesions is focal, or why not all CF patients develop overt liver disease.

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Hepatobiliary manifestations in CF

Type of lesion	Clinical manifestation	Frequency (%)
Specific alterations directly caused by the CFTR defect	• Focal biliary cirrhosis	20–30
	• Multilobular biliary cirrhosis	10
	• Portal hypertension	2–5
	• Neonatal cholestasis	<10
	• Sclerosing cholangitis	Often silent
	• Microgallbladder	30
	• Cholelithiasis	15
Lesions of iatrogenic origin	• Hepatic steatosis	25–60
	• Drug hepatotoxicity	Undefined
Lesions reflecting effects of a disease that occurs outside the liver	• Hepatic congestion	Rare
	• Common bile duct stenosis	Rare

Table 1

Steatosis is a common finding in CF patients of all ages with between 23 and 67% affected. The exact pathogenesis is still unknown although it has been associated with selective nutritional deficiencies (e.g. essential fatty acids, carnithine, choline, trace elements, minerals) and altered phospholipid metabolism in CF. It can also develop as a consequence of long-term antibiotic therapy, raised circulating inflammatory cytokines and insulin resistance. Steatosis was initially thought to be a benign condition in CF. However, with more data now available reporting progression from simple steatosis to non-alcoholic steatohepatitis and cirrhosis, this may no longer be the case.

Identification of CF liver disease

CF is a rare cause of neonatal cholestasis caused by obstruction of extrahepatic bile ducts by inspissated bile. This can mimic biliary atresia. It usually resolves spontaneously over the first months of life and is not associated with a higher risk of developing cirrhosis.

CF liver disease is often asymptomatic, even when multilobular cirrhosis is present. The most common presentation is hepatomegaly found on routine physical examination. Peripheral signs of chronic liver disease (palmar erythema, spider naevi, jaundice, oedema, dilated abdominal wall veins) appear late when pathological changes are pronounced and cirrhosis and portal hypertension are advanced.

As some studies have suggested that early biliary lesions are potentially reversible it is important to identify CFLD at an early stage through active screening. Goals for screening are two-fold: 1) to identify individuals at risk for cirrhosis prior to its development in order to institute therapy to prevent or reduce disease progression, and 2) to detect patients who have developed clinically silent cirrhosis to allow monitoring and interventions to reduce or mitigate complications (e.g. surveillance endoscopy program).

Current CF Trust Standards of Clinical Care for Children and Adults with CF in the UK recommend that '*annual screening for liver disease should be carried out on all patients aged 5 years and above. This should include regular examination for hepatosplenomegaly, annual blood liver function and clotting tests, alternate year ultrasound liver for abnormal architecture and signs of splenomegaly in children. Routine ultrasound may not be necessary in adults with previous normal scans*'.

Common screening tools used are physical examination, liver biochemistry and prothrombin time, ultrasonography and liver biopsy.

Liver function tests

Biochemical abnormalities (AST, ALT, GGT and ALP) are frequently mild or only intermittently present, and have low sensitivity and specificity. It is not uncommon for patients with advanced cirrhosis to have completely normal liver function tests. They can also occur as a result of drug treatment, infection, or malnutrition and other causes for abnormal liver function tests should always be ruled out (see Table 2). Liver function tests and coagulation studies should be performed annually on all CF patients to screen for CFLD.

Ultrasonography

Ultrasonography of the hepatobiliary system is the most suitable initial method of investigation. It is relatively cheap, non-invasive and can detect focal biliary fibrosis, multinodular cirrhosis, steatosis and biliary abnormalities, as well as identify evidence of portal hypertension. Once CFLD has been identified, it can be used to monitor for progression to more advanced hepatobiliary changes and portal hypertension.

Liver biopsy

Histological assessment, the diagnostic gold standard in many chronic liver diseases, is not as useful in CF due to the patchy

Causes of acute or chronic liver disease in CF patients showing hepatic abnormalities

Disease	Investigations
Acute/chronic viral hepatitis	Serology for HAV, HBV, HCV, EBV, CMV, adenovirus, HHV6, parvovirus
α1 antitrypsin deficiency	Serum α1 antitrypsin level and phenotype
Autoimmune hepatitis	Autoantibody screen (SMA, anti-LKM1, LC1), immunoglobulin screen
Coeliac disease	Total IgA, IgA anti-tissue transglutaminase
Wilson disease	Ceruloplasmin & serum copper
Genetic haemochromatosis	Iron, ferritin, total iron binding capacity (TIBC)
Other causes of steatosis	Malnutrition, diabetes, obesity

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; EBV, Epstein–Barr virus; CMV, cytomegalovirus; HHV6, human herpes virus type 6; SMA; smooth muscle antibody; LKM1, liver kidney microsomal type 1; LC1, liver cytosol type 1.

Table 2

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