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Review

Liver Disease in Cystic Fibrosis

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EDUCATIONAL AIMS

- To provide an overview of liver disease in children with cystic fibrosis.
- To review the incidence, pathogenesis, diagnosis, risk factors, outcomes and management of Cystic Fibrosis-associated Liver Disease.
- To describe the controversies about Cystic Fibrosis-associated Liver Disease existing in the current literature.

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SUMMARY

The survival of patients with cystic fibrosis (CF) has progressively increased over recent decades, largely attributable to early diagnosis through newborn screening and advances in nutritional and respiratory care. As the life expectancy of patients with CF has improved, non-respiratory complications such as liver disease have become increasingly recognized.

Biochemical derangements of liver enzymes in CF are common and may be attributed to a number of specific hepatobiliary abnormalities. Among them, Cystic Fibrosis-associated Liver Disease (CFLD) is clinically the most significant hepatic complication and is believed to have a significant impact on morbidity and mortality. However, there remains much conjecture about the extent of the adverse prognostic implications that a diagnosis of CFLD has on clinical outcomes. The purpose of this review is to give an overview of the current knowledge regarding liver disease in children with CF.

INTRODUCTION

Survival of CF patients has progressively improved since the introduction of the diagnostic sweat test in the 1950s. The median survival age of CF patients now ranges from 37.4 years in the United States and Germany[1] to even 48.1 years in Canada,[2] whereas in 1970 median survival was only 16 years. This change is largely attributable to advances in nutritional and respiratory care,[3] as well as early diagnosis by newborn screening.[4,5] As the life expectancy of children and adults with CF has improved, there has been an increase in the recognition of the importance of non-respiratory complications of CF such as liver disease. It is known that the majority of children and adolescents with CF will at some time have evidence of liver abnormalities, including abnormal liver biochemistry, changes on ultrasound and/or hepatomegaly.[3,6,7] However, liver disease in CF is a broad definition, which includes a variety of different hepatic abnormalities with varying prevalence rates (Table 1).

NEONATAL CHOLESTASIS

The earliest manifestation of liver involvement in CF is neonatal cholestasis. Neonatal cholestasis in CF appears to be an uncommon complication, with meconium ileus (MI) being reported as a risk factor for its development.[8–10] The outcome of CF patients

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Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CF, cystic fibrosis; CFLD, cystic fibrosis-associated liver disease; CFTR, cystic fibrosis conductance regulator; GGT, γ-glutamyltransferase; HSC, hepatic stellate cell; LFTs, liver function tests; MCP-1, monocyte chemotaxis protein-1; MI, meconium ileus; UDCA, ursodeoxycholic acid.

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Table 1
Hepatic complications in cystic fibrosis (derived from[10,13–15,17,18,21,25–27]).

Type of Hepatic Complication	Prevalence Rate
Neonatal cholestasis	Rare
Hepatic steatosis	23-67%
Focal biliary cirrhosis	11-72%
Multilobular cirrhosis	5-10%
Synthetic liver failure	Rare

presenting with neonatal cholestasis varies widely from full recovery within the first months of life in the majority to occasional cases of early onset liver failure and death.[11,12]

HEPATIC STEATOSIS

Steatosis is the most common hepatic lesion in CF patients, with a prevalence of 23% to 67%.[13–15] Hepatic steatosis appears to be unrelated to the CF secretory defect but may be indirectly related to CFTR or associated with malnutrition and deficiencies of essential fatty acids, carnitine and choline.[6,10] Thus far, steatosis has been considered as a benign condition in CF, without a proven relationship to the subsequent development of cirrhosis.[6]

FOCAL BILIARY CIRRHOSIS

Focal biliary cirrhosis is the pathognomonic hepatic feature of CF. It results from biliary obstruction and progressive periportal fibrosis. Focal biliary cirrhosis is histologically characterised by scattered areas of portal fibrosis, cholestasis, bile duct proliferation, and plugging of bile ductules by eosinophilic material.[16] In autopsy studies, significant focal biliary cirrhosis is detected in 11% of infants and 25% to 72% of adults with CF.[17,18] Focal biliary cirrhosis is often clinically silent and does not have clinical consequences. However, it is thought that focal biliary cirrhosis can eventually progress to clinically significant multilobular biliary cirrhosis. Multilobular cirrhosis differs from focal biliary cirrhosis in the presence of multiple regenerative nodules and diffuse involvement of the liver (Figure 1). Although the progression from focal biliary cirrhosis to multilobular biliary cirrhosis may occur slowly, multilobular cirrhosis usually presents in middle childhood and adolescence.[10,15,19,20]

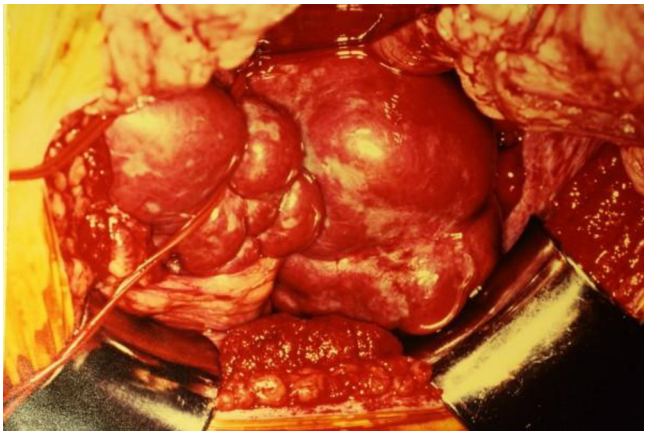

Figure 1. Multilobular cirrhosis in a patient with CFLD. The liver demonstrates multiple regenerative nodules and scattered areas of periportal fibrosis, which are the characteristic features of CFLD.

CYSTIC FIBROSIS-ASSOCIATED LIVER DISEASE

Cystic Fibrosis-associated Liver Disease (CFLD) is a well-known complication of CF that has become increasingly important. Overall prevalence rates of CFLD have varied considerably in the published literature due to the broad definitions and criteria used for the diagnosis of CFLD. For example, several studies have used the following definition for CFLD: The presence of at least 2 of the following conditions on at least 2 consecutive examinations spanning a 1-year period: 1) clinical hepatomegaly (increase in liver span and consistency, with liver edge palpable more than 2 cm below the costal margin in the mid-clavicular line), confirmed by ultrasonography; 2) abnormal serum liver enzyme levels, consisting of elevation above the upper normal limits of 2 of the following: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltransferase (GGT); (3) ultrasound abnormalities other than hepatomegaly (i.e., increased, heterogeneous echogenicity, nodularity, irregular margins, splenomegaly).[21–23] Other studies have used even broader criteria, in which only one of these conditions needed to be present over a 6-month period,[24,25] or the diagnosis of CFLD was made by the presence of hepatomegaly, splenomegaly or hepatosplenomagaly on clinical examination.[19] However, these criteria used for CFLD tend to overestimate the impact of liver disease in CF, since only 5-10% of CF patients will develop clinically significant multilobular cirrhosis and portal hypertension.[15,21,25,26] In 2007 the U.S. CF Foundation convened a group of international experts in CFLD, who proposed a new classification of liver involvement in CF in which CFLD is defined as: Cystic Fibrosis related Liver Disease with cirrhosis or portal hypertension (based on clinical examination, imaging, histology, laparoscopy). Thus, to date, only CFLD with multilobular cirrhosis and/or portal hypertension is considered as clinically significant liver disease.[10] As stated above, it is considered that focal biliary cirrhosis progresses to CFLD in a minority of CF patients. CFLD usually presents during the end of the first decade, with the median age of diagnosis being 10 years of age, and very few new cases are identified after 20 years of age.[10,15,19,20] Liver synthetic failure is a rare event in CFLD, occurring in approximately 10% of patients with CFLD.[27]

Pathogenesis

The pathogenesis of CFLD is complex and has not been fully elucidated. Current studies indicate that the development of CFLD is related to the CFTR defect in cholangiocytes. In the hepatobiliary system, CFTR is expressed exclusively in cholangiocytes, and not in hepatocytes or other cells of the liver.[28] Altered CFTR protein function on the apical membrane of cholangiocytes in combination with altered biliary transport in CFLD leads to retention of toxic bile acids including taurocholic acid.[29–31] Taurocholic acid induces expression of a key fibrogenic chemokine, monocyte chemotaxis protein-1 (MCP-1) in hepatocytes and cholangiocytes. MCP-1 and other chemokines induce hepatic stellate cell (HSC) chemotaxis to the peribiliary regions. HSCs are then activated into fibrogenic 'myofibroblast-like' cells.[29,31] These activated HSCs produce excess collagen, leading to peribiliary fibrogenesis, the pathognomonic focal biliary cirrhosis of CFLD.[31,32]

Diagnosis

The early detection of CFLD remains a challenge. The subtle nature and late appearance of clinical signs of CFLD, together with the absence of sensitive and specific tests to evaluate biliary cell function, make early detection of CFLD difficult. Most often, patients remain asymptomatic even when multilobular cirrhosis develops. To date, a combination of physical examination for

hepatomegaly, annual testing of liver function tests (LFTs) including AST, ALT, alkaline phosphatase (ALP) and GGT, together with abdominal imaging have been thought to hold the best promise for detecting CFLD.[33] However, these tests have not been shown to be sensitive for early stages of hepatic fibrosis or the identification of individuals who are at risk for cirrhosis.

Biochemical abnormalities have low sensitivity and specificity in detecting CFLD. Mild or intermittent elevations in serum liver enzymes that are not predictive of the development or presence of CFLD are present in 40-50% of patients.[3,10,15,34] Common findings include intermittent increases in serum AST and ALT, and/or increased serum levels of ALP and GGT. However, since these data are derived from cross-sectional studies, longitudinal studies should be implemented to investigate whether, long-term, biochemical abnormalities could have a predictive value. To further confound the issue, some CF patients with multilobular biliary cirrhosis can have completely normal liver biochemistry.[14,33] However, as progression of liver disease occurs, LFTs will eventually become abnormal in all patients with CFLD.

Evidence has been provided to suggest that ultrasonography is a more sensitive screening test for CFLD than clinical and biochemical abnormalities.[14,35,36] Abnormal echogenicity frequently precedes clinical and biochemical manifestations of liver disease, suggesting that routine ultrasonography may be a valuable tool for detection of CFLD. Whilst ultrasound can demonstrate multilobular nodularity indicative of multilobular cirrhosis, it is unreliable at detecting earlier stages of hepatic fibrosis. Additionally, a normal ultrasound does not preclude significant liver fibrosis or cirrhosis.[15,37] Therefore, the diagnosis of early liver disease cannot reliably be made on the basis of ultrasound alone.

Liver biopsy is regarded as the gold standard in the diagnosis of CFLD. Liver biopsy can detect CFLD at an early stage and can predict the development of clinically significant liver disease.[38] However, because of the patchy distribution of lesions in CFLD, liver biopsy may underestimate the severity and extent of CFLD or even give false-negative results. Additionally, the risks, costs and lack of ability to perform serial measurements, further limit the use of liver biopsy in CFLD. A new medical device for detecting liver disease is transient elastography, which measures liver stiffness in a non-invasive, rapid, and reproducible way. A recent study shows that transient elastography is a valuable tool for the detection and quantification of CFLD.[39] However, its usefulness in diagnosing CFLD at an early stage and assessing progression of liver fibrosis is currently being investigated.

Clinical consequences

Liver disease is regarded as the third leading cause of death in patients with CF after respiratory and transplantation complications, accounting for 2.5% of overall mortality[6,10] Besides the risk of mortality, CFLD is considered as a substantial threat to the quality of life and wellbeing of children with CF. Several studies show that children with CFLD are likely to have a more severe disease phenotype with poorer disease activity scores, altered nutrition, lower forced expiratory volume in 1 second values (FEV1) and higher risk of developing Cystic Fibrosis-related Diabetes.[23,27,40–44] However, the literature is inconclusive about the magnitude of the effect of CFLD on morbidity with other studies describing no effect of CFLD on clinical outcomes.[15,21,24,25,45] The broad and variable criteria used to define CFLD are thought to at least partly explain this discrepancy.

Primary complications of CFLD are restricted to individuals with multilobular cirrhosis and portal hypertension. Complications include ascites, hypersplenism (splenomegaly with thrombocytopenia and/or leukopenia), oesophageal or gastric variceal haemorrhages, hepatic encephalopathy and rarely synthetic liver failure.[10] Incidence rates of major complications of multilobular cirrhosis as well as mortality rates have also varied considerably in the literature. Mortality rates from variceal bleeding or liver failure vary between 0% and 20%, with more recent studies showing significantly lower mortality rates.[20,21,23,27,41]

Progression

The progression of liver disease exhibits a great degree of variability in terms of rapidity and severity. In most cases the progression from focal biliary cirrhosis to multilobular biliary cirrhosis takes many years and the majority of patients with focal biliary cirrhosis will not develop multilobular cirrhosis. However, in some patients there is a rapid progression to multilobular cirrhosis with portal hypertension and, rarely, liver failure. The reasons for the variability in liver disease progression and severity remain unclear but may be determined by the presence of modifier genes.[3,46,47] A recent study demonstrated that CFLD is associated with the Z allele of the *SERPINA1* gene.[47] It is thought that CF patients with the *SERPINA1* Z allele are at increased risk of developing CFLD. However, only 11.3% of the patients with CFLD in this study carried the *SERPINA1* Z allele, which indicates that other factors must be involved in the genesis of CFLD. Additionally, several other factors have been suggested to be associated with liver disease including severe genotype,[21,22,24,26] pancreatic insufficiency,[23–26,48] history of MI,[21,23,25,26,42,48,49] and male gender.[19,21,22,26,47] However, discrepancies between these associations exist.[14,15,50] Since there are no reliable tests for the early detection of CFLD as described above, recognition of CF patients at risk for developing CFLD remains a major clinical challenge. The identification of risk factors for the development of CFLD is an important step in targeting populations for early intervention and prophylactic treatments.

Management

To date, there is no effective therapy to prevent or treat CFLD. Currently, the only available therapeutic approach to potentially delay progression of CFLD is administration of ursodeoxycholic acid (UDCA). UDCA is an endogenous hydrophilic, and therefore protective, bile acid. UDCA increases bile flow and modifies the bile acid pool by decreasing levels of toxic bile acids while increasing the proportion of non-toxic hydrophilic bile acids. Further, it acts as a cytoprotective agent and possibly stimulates chloride and bicarbonate secretion in the biliary tract.[51–53] Treatment with UDCA can be started as soon as the diagnosis of CFLD is made at a dose of 20 mg/kg/day. UDCA has been shown to improve AST and ALT, bile drainage, liver histology as well as nutritional status and general condition.[54–59] However, there is no evidence that UDCA treatment changes the natural history of liver disease and its routine use in CF is not recommended.[60]

Once multilobular cirrhosis and portal hypertension are established, treatment relies on management of the complications of portal hypertension. Some advocate the use of oral propranolol as primary prophylaxis for the prevention of variceal bleeding. However in children, because of varying size the ideal suppression of heart rate indicating the efficacy of the dose of propranolol given is unknown, it is not routinely recommended. Moreover some would argue that in CF beta blockade is already present by the CFTR defect and others that even on propranolol, bleeding rates occur at 15.6% to 33%, which is not significantly improved from baseline bleeding rates seen in the natural history of disease.[61] Oesophageal and gastric variceal bleeding can be treated with sclerotherapy or preferably band ligation during the acute episode. Variceal band ligation is also the preferred approach for primary and secondary

variceal prophylaxis in CF patients.[10,61] Transjugular portosystemic shunts and surgical portosystemic shunts may be indicated in refractory cases as well as to prolong survival or as a bridge to liver transplantation.[26]

Liver transplantation is an effective therapeutic option for CF patients with end-stage liver disease. Recent studies have reported a significant survival benefit in patients who received a liver transplant for CFLD.[62,63] Further, survival is comparable with those of liver transplantation for indications other than CF, especially in paediatric patients.[62–64] Notwithstanding, it remains controversial which patients with CF and cirrhosis require liver transplantation. Several studies have shown stable or improved lung function, better nutritional status and increased quality of life in patients with CFLD after transplantation.[62,65–71] However, other studies found no improvement of long-term survival in patients after liver transplantation and the beneficial effects of liver transplantation on clinical outcomes remain controversial.[45,72,73] Additionally, the optimal timing of liver transplantation is a major discussion point. Poorer lung function prior to surgery has been associated with an increased risk of early mortality.[62,74] Therefore, some authors recommend that evaluation and transplantation should occur early in the disease course, before lung function is severely compromised and outcomes are likely to be better.[66–68,75] However, the reported beneficial effects of liver transplantation remain questionable,[20,72,73,76] and additionally, the one-year mortality rate after liver transplantation in children with CF lies between 10% and 25%.[65,68,70,77] Therefore, other authors have suggested that liver transplantation should be reserved for CF patients with evidence of hepatic decompensation or uncontrollable end-stage complications of liver disease.[45] Clear guidelines for liver transplantation in CFLD are lacking but should be developed to guide best practice in the management of CFLD.

CONCLUSION

Liver disease in CF includes a variety of hepatobiliary abnormalities, with CFLD being the most clinically significant hepatic complication. CFLD has been regarded to have a significant effect on the morbidity and mortality, as it is reported to be the third leading cause of death in CF patients. However, the impact of CFLD on morbidity and mortality remains controversial, at least partly because of the lack of a consistent definition of CFLD. Similarly, much remains unknown about the reasons for the variability in disease progression, factors associated with the development CFLD, and the best clinical approach towards diagnosing and managing CFLD. Therefore, further studies using a uniform definition of CFLD are necessary to accurately investigate these issues.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

RESEARCH DIRECTIONS

- Investigation of the true impact of CFLD on morbidity and mortality in CF patients using a uniform definition for CFLD.
- Determination of sensitive diagnostic methods for detecting and monitoring CFLD in an early stage.
- Identification of the factors that cause increased susceptibility for CFLD in children with CF.
- Evidence based treatment recommendations for the management of CFLD and development of novel therapeutic options for children with CFLD.

EDUCATIONAL QUESTIONS

1. What is clinically the most significant hepatobiliary complication in CF patients?

A. Hepatic steatosis
B. Focal biliary cirrhosis
C. Multilobular cirrhosis
D. Neonatal cholestasis
E. Biochemical derangements of LFTs

2. Cystic Fibrosis-associated Liver Disease is caused by

A. Neonatal cholestasis, which causes liver damage early in life.
B. Alterations in biliary flow with retention of hydrophobic bile acids.
C. Iatrogenic injury, caused by the toxic effects of CF mediations.
D. Meconium ileus, which causes liver damage early in life.
E. Pancreatic insufficiency with malnutrition and deficiencies of essential fatty acids, carnitine and choline.

3. What is the best approach to diagnosing Cystic Fibrosis-associated Liver Disease?

A. Liver biopsy
B. Ultrasonography
C. Determination of liver function test
D. Transient elastography
E. None of these

4. Certain risk factors have been thought to be associated with the development of Cystic Fibrosis-associated Liver Disease. These include:

A. Severe genotype, poor lung function and male gender
B. Meconium ileus, pancreatic insufficiency and Cystic Fibrosis-related Diabetes
C. Male gender, severe genotype and meconium ileus
D. *SERPINA1* Z allele, female gender, pancreatic insufficiency
E. Malnutrition, meconium ileus, severe genotype

5. What is the first line evidence-based treatment for children with Cystic Fibrosis-associated Liver Disease:

A. Pancreatic enzyme replacement
B. Multivitamin supplements
C. Ursodeoxycholic acid (UDCA)
D. Liver transplantation
E. None of these

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