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Review

Liver Disease in Cystic Fibrosis

Lisette Leeuwen [1,2], Dominic A. Fitzgerald [1,3], Kevin J. Gaskin [3,4,5,*]

[1] Department of Respiratory Medicine, The Children's Hospital at Westmead, Sydney, Australia
[2] Medical School, University of Groningen, Groningen, The Netherlands
[3] Discipline of Paediatrics and Child Health, Sydney Medical School, University of Sydney, Australia
[4] Department of Gastroenterology, The Children's Hospital at Westmead, Sydney, Australia
[5] James Fairfax Institute of Paediatric Nutrition, University of Sydney, Sydney, Australia

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

* Corresponding author. Department of Gastroenterology, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia; Tel.: +61 2 9845 3999; fax: +61 2 9845 3970.
E-mail address: kevin.gaskin@health.nsw.gov.au (K.J. Gaskin).

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]

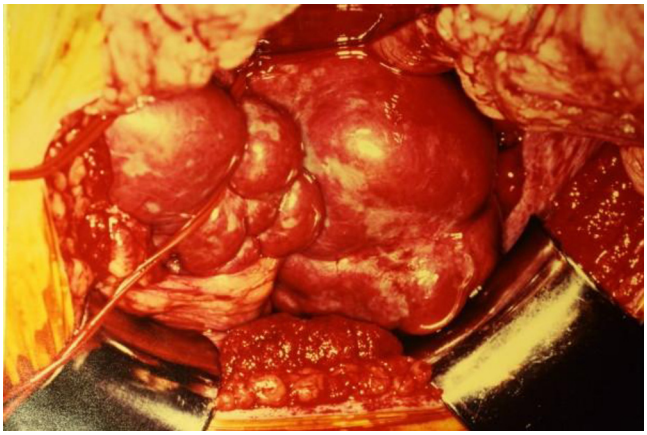

Figure 1. Multilobular cirrhosis in a patient with CFLD. The liver demonstrates multiple regenerative nodules and scattered areas of periportal fibrosis, which are the characteristic features of CFLD.

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