

CYSTIC FIBROSIS ASSOCIATED WITH HEPATOBILIARY DISEASE

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Abstract

Cystic fibrosis (CF) is the most frequent monogenic disease in population with Caucasian origin, potentially lethal, with marked clinical variability. With improved life expectancy of CF patients, it has become clear that cystic fibrosis associated hepatobiliary disease is a relatively frequent and serious complication which can affect quality of life and survival of affected patients. Data from literature mention the association of LD with, male gender, history of meconium ileus and severe genotype.

The paper aim is to review data concerning cystic fibrosis associated liver disease (CFLD) epidemiology, diagnosis and natural history.

Key words: cystic fibrosis, liver disease, children.

Background

In recent years, clinical attention for cystic fibrosis associated hepatobiliary disease (CFHD) has significantly increased from a small proportion (2-5%) of patients with end-stage multilobular biliary cirrhosis and portal hypertension, to the increasingly recognized asymptomatic patients with focal biliary cirrhosis. Cystic fibrosis associated hepatobiliary disease (CFHD) include entities like: liver disease, microgallbladder, cholelithiasis, neonatal cholestasis, common bile duct stenosis, the most important clinical expression is liver disease (LD).

Screening for liver disease (LD) has indicated that in the majority of affected patients, LD becomes clinically apparent by the end of the first decade of life, suggesting that this is a relatively early complication of CF. A slow progression is characteristic, hepatocellular failure is a delayed episode, whereas development of portal hypertension and related complications tends to occur earlier and more frequently.

Treatment with ursodeoxycholic acid (UDCA) is widely employed in these patients, even if its impact on the natural history of the disease remains to be defined.

CFLD is the initial diagnostic finding in 1.5% of patients, suggesting that all patients with unexplained cirrhosis should have a sweat test as part of their diagnostic assessment.

CFHD diagnosis

Detection of hepatobiliary disease, particularly LD, at an early stage, when therapeutic intervention is likely to be more effective, is a significant clinical problem.

Even though the pathological injuries are present since birth, the liver diseases become clinically evident in

unpredictable period of time. Early diagnosis of this complication allows much efficient therapeutical intervention. Expression of CFTR at the hepatobiliary level has been shown to occur exclusively at the apical membrane of epithelial cells lining intra and extra-hepatic bile ducts and gallbladder.

CF-associated liver disease is the first congenital liver disease in which the primary defect affects cholangiocytes rather than hepatocytes. Deficiency or dysfunction of CFTR at this level results in decreased bile fluidity and alkalinity and abnormalities in mucin secretion.

Bile duct obstruction and the development of mucus plugs, followed by cholangiocyte injury stimulate the development of focal biliary cirrhosis, the pathognomonic lesion of CF; extension of the initially focal fibrogenic process may lead to multilobular biliary cirrhosis (Fig.1).

LD is defined by the presence of at least 2 of the subsequent findings:

- (1) abnormal values of liver tests (AST, ALT, gamma-GT);
- (2) hepatosplenomegaly detected on physical examination;
- (3) ultrasound (US) changes consistent with LD.

Liver biochemistry tests (cholestasis and hepatocytolysis analysis) do not correlate with liver histology.

On liver biopsy even early changes are detectable, but is an invasive procedure, being rarely performed in children (Fig..1). The risk of error sampling is increase because of the focal distribution of hepatic lesions in CF.

Ultrasonography(+/- Doppler color) is an accurate method for LD assessment, detecting early structure changes like steatosis, but is also useful in the evolution assessment, detecting sign of cirrhosis, portal hypertension, ascitis. Abdominal US diagnose also gallbladder CF associated disease, like cholelithiasis, microgallbladder. Hepatobiliary scintigraphy (with iminodiacetic acid) (Fig.2) provides morphologic and functional information; can document a picture of biliary drainage impairment, the progression of liver disease and response to treatment. MR-cholangiography is a method more accurate for the diagnosis and assessment of hepatobiliary disease, but need sedation for children and is expensive.

Our aim study is to establishing the incidence of CFHD, evaluate risk factors for its development, and assessing the clinical course management of CFHD patients.

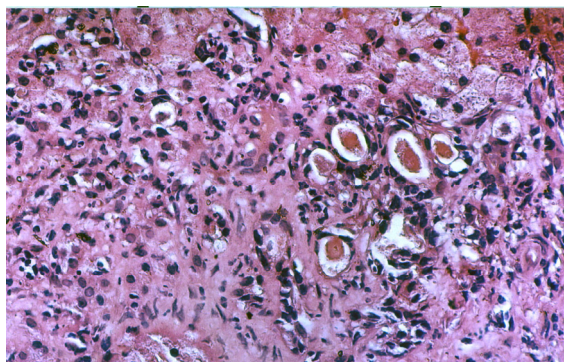


Fig.1.

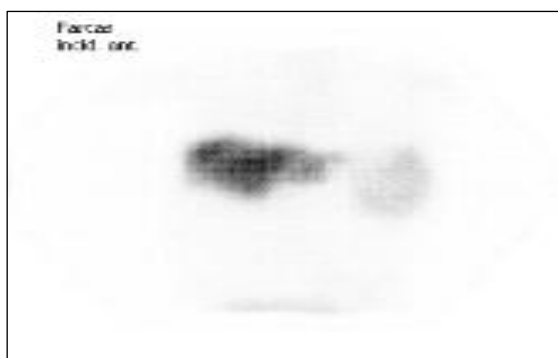


Fig.2.

Epidemiology and risk factors

Incidence of liver disease (LD) associated with cystic fibrosis (CF) and its clinical description is still unsettled, being also difficult to determine the prevalence of the disease. Autopsy studies have shown this lesion to be present in over 70% of patients over the age of 20 years (Vouter & Shwachman, 1979). The development of multilobular biliary cirrhosis occurs in 2 - 5% of patients.

There is no current explanation why liver disease develops in some patients and not in others. Some studies have shown a four fold risk for the development of liver

disease in patients with a history of meconium ileus, male sex, and severe genotype.

We have assessed the prevalence and risk factors of this complication, and its impact on the clinical course of CF.

Material and methods

Lot study included 85 patients with typical CF: 56 children, younger than 10 years 29 patients, older than 10 years (Fig.3).

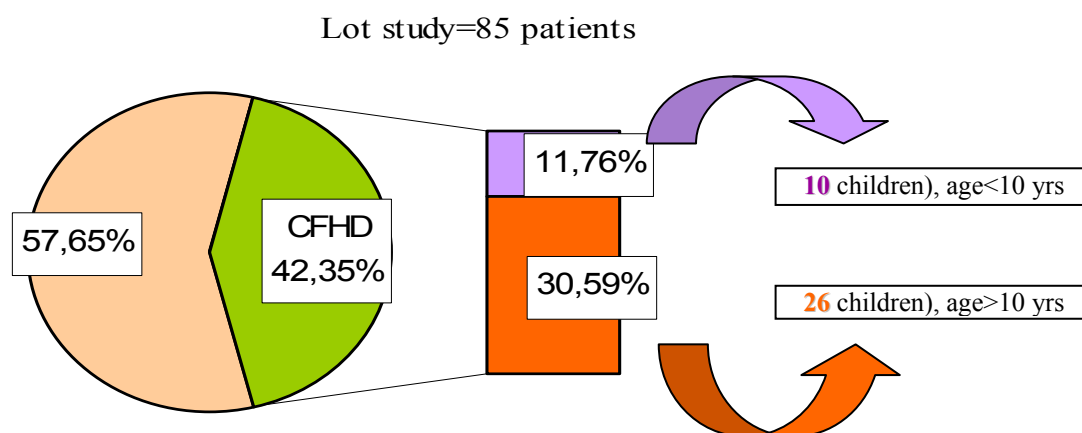


Fig.3

Patients characteristics: age ranging from 1 month → 18 years; median age at diagnosis was 10,5 years. CF studied lot included 56 female and 29 male. Patients were followed-up by: clinical examination biochemical markers, ultrasound examinations, hepatobiliary scintigraphy, liver biopsy and MRI cholangiography (in some cases).

Over a median follow-up period of 5 years, cumulative incidence of CFHD was 42,35% (36 patients); age at diagnosis of LD was 10.5 yrs, ranging from 1 mo. to 18 yr, with no incidence peak in any age group. Concerning the sex distribution, male predominated (66,6%). At present

regular physical examination, liver biochemistry and abdominal ultrasound are recommended.

CFHD was diagnosed in 36 patients, 11,76% from all patients (10 children), were younger than 10 years, twenty-six (30,59%) aged over 10 yrs. Liver disease occurred in 63,88%(23 patients), microgallblader was found in 19,44% (7 patients) and cholelithiasis in 16,66% (6 patients).

Multilobular chirosis with severe liver disease was diagnosed in 6 patients (16,66%) and focal biliary cirrhosis in 13,88% (5 patients). Neonatal cholestasis occurred in 2 neonates (5,55%) (Fig. 4).

Multiple hepatobiliary conditions were associated in one patient, creating miscellaneous CFHD entities.

All patients were genetically tested for the most common 29 CF mutations.

Genotype structure of the 85 patients: 32 $\Delta F508$ homozygous genotypes (5 with CFHD), 22 $\Delta F508/x$ (13

with CFHD), 5 non - $\Delta F508/x$, 4 with CFHD, 26 unknown (x/x), 14 with CFHD (Fig. 5).

The frequency of $\Delta F508$ allele was 50,58%. Among 32 $\Delta F508$ homozygous genotypes, only 15,62% had a hepatobiliary expression. We could not establish a specific correlation between HD expressions and a certain mutation.

Hepatobiliary CF associated entities

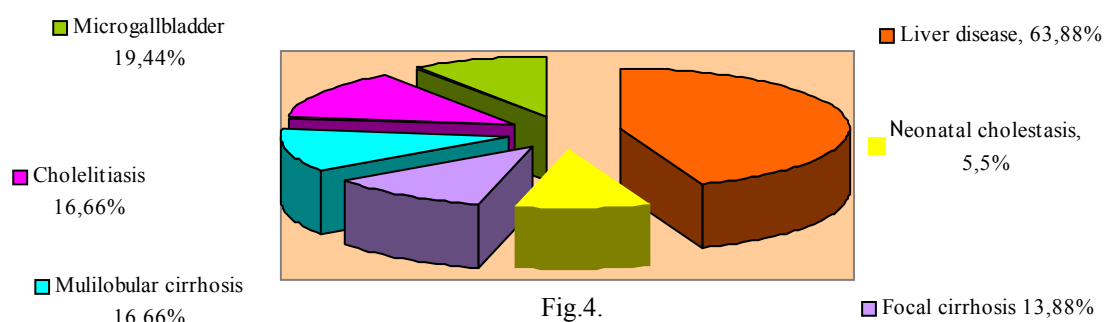


Fig.4.

Genotype structure in CFHD patients

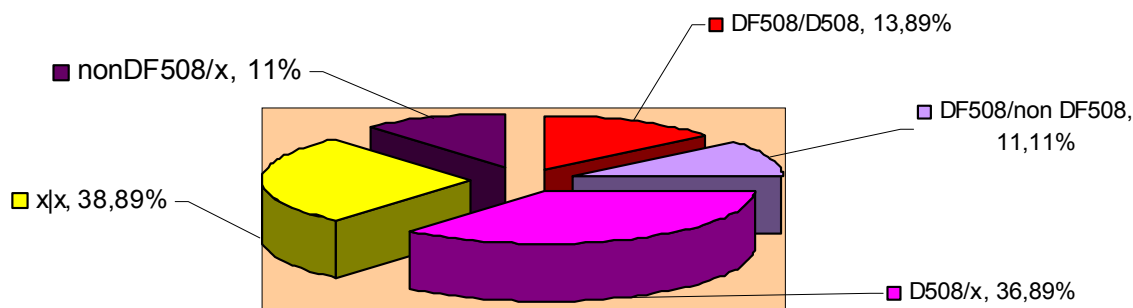


Fig. 5.

The heterogeneous phenotypes in CF patients having the same genotype suggest that other environmental and/or genetic factors are implicated. The actual role of possible risk factors for development of LD remains controversial.

Recent observations suggest that clinical expression of LD in CF may be influenced by genetic modifiers; their identification is an important issue because it may allow recognition of patients at risk for the development of LD at the time of diagnosis of CF and early institution of prophylactic strategies. Several examples show that other nondisease causing genes can alter the course of monogenic disorders.

Natural history and CFHD management

In the majority of affected patients liver disease becomes clinically apparent by the end of the first decade of life; patients are initially asymptomatic. Rate of progression

may differ markedly: the majority of patients show a slow progression with a limited impact on the outcome of the disease, but in a few patients, often in the pediatric age, liver disease may represent the main clinical problem and its progression may be unusually rapid. When this disturbed liver architecture is apparent, major clinical problems occur, like portal hypertension with the development of splenomegaly and oesophageal varices; massive enlargement of the spleen causing abnormal pain, dyspnoea, signs of hypersplenism and upper gastrointestinal bleeding secondary to esophageal varices.

According to literature data concerning the therapy with ursodeoxycholic acid(UDCA), especially for patients with risk factors for the developing of liver disease, early treatment registered favorable effect in the majority of cases. Oral bile acid therapy, aimed at improving biliary secretion in terms of bile viscosity and bile acid composition, is currently the only available therapeutic approach for CFLD.

The effect of UDCA consist in replacement/displacement of toxic endogenous bile acids, having a cytoprotective, antiapoptotic and immunomodulatory effect. UDCA has been employed in CFHD at the dose of 20/mg/kg/day, with beneficial effects on liver biochemistry, hepatic excretory function and biliary drainage, liver histology and nutritional status, but data on long-term efficacy on clinically relevant endpoints are still deficient. A European randomized, placebo controlled trial to evaluate the preventive efficacy of UDCA is presently underway.

Liver transplantation is increasingly performed in CF-patients with end-stage liver disease; indications often differ from other chronic liver diseases because liver function may be relatively preserved, portal hypertension and its complications (varices, hypersplenism, ascites) are the main clinical problems and there is a concomitant involvement of other organs, particularly the lungs. Liver transplantation should be offered to CF patients with progressive liver failure and/or with life threatening

sequelae of portal hypertension, who also have mild pulmonary involvement that is expected to support long-term survival.

Future therapies will likely be directed at gene transfer. A recent study showed delivery of adenoviral human CFTR gene to the biliary tree via ERCP with successful gene expression in bile duct cells. This would represent the ideal response to all liver problems in CF.

Conclusions

Liver disease is an early complication involving more than one fourth of CF patients. Active follow-up directed at its detection should be focused at the first decade of life. Better tools are needed for detection of liver disease at an early stage when therapeutic intervention is more likely to be effective, and for this purpose a test to detect cholangiocyte damage would be desirable. Until the most advanced stages are attained, presence of liver disease does not implicate a different clinical course of CF in terms of respiratory complications or nutritional problems.

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