Cystic fibrosis-related liver disease: a single-center experience

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Abstract

Prospective studies concerning liver disease in pediatric cystic fibrosis patients are scarce. The present study aimed to describe the prevalence and clinical expression of cystic fibrosis - related liver disease, in a cohort of 62 pediatric patients. Descriptive study, resulting from the prospective evaluation, between 1994 and 2009, of 62 pediatric patients (age <18 years) with cystic fibrosis. The follow-up protocol included a clinical assessment every 2 months, liver function tests every 6 months and annual liver ultrasonography. The cumulative prevalence of liver disease was 11.2% (7/62 cases). All patients had ΔF508 mutation and pancreatic insufficiency, none had meconium ileus. The liver involvement became clinically evident at a mean age of 8 years (3-15 years), revealed by hepatomegaly or hepatosplenomegaly (3 cases) and/ or abnormalities of liver function tests (3 cases) changes of liver ultrasound (7 cases) with evidence of portal hypertension (2 cases). Four patients were submitted to liver biopsy; biliary fibrosis was documented in one case, focal biliary cirrhosis in 2 cases and multilobular cirrhosis in another case. Within a median 11.6 years follow-up period (all patients under UDCA therapy after liver disease diagnosis), progression of liver disease was observed in 2 patients; one patient developed refractory variceal bleeding and progressive hepatic failure, requiring liver transplant. The results of the present study agree with those of previous pediatric studies, further documenting clinical expression of liver disease in CF patients, which is usually detected in the first decade of life and emphasize the contribution of ultrasound to early diagnosis of liver involvement. Moreover, although advanced liver disease is a relatively rare event, early isolated liver transplantation may have to be considered at this age group.

Introduction

When first described in 1938, cystic fibrosis (CF) was invariably fatal during early childhood. Today, the average life expectancy is 35 years and therefore CF is no longer considered an exclusively pediatric condition.[1] Although major CF morbidity and mortality are determined by pulmonary involvement, other manifestations of the disease have emerged, particularly the hepatobiliary involvement, in association with improved survival related to early multidisciplinary intervention.

The prevalence of CF-related liver disease, currently considered the third cause of death in CF,[2] is difficult to assess because of the lack of sensitive and specific markers. Although a wide prevalence range has been reported, accordingly to the methodology and the characteristics of the studied population, it is estimated that liver disease occurs in about one third of patients.[3-5]

Oral therapy with ursodesoxycholic acid (UDCA), aiming to improve bile secretion, is currently the only available pharmacological intervention, although its impact on the natural history of liver disease and long-term efficacy remains to be established.[6,7] Liver transplantation should be proposed in patients with progressive liver failure and/or evidence of major portal hypertension in the absence of significant pulmonary involvement.[8,9] The present study thus aimed to describe the prevalence and clinical expression of cystic fibrosis - related liver disease, in a cohort of 62 pediatric patients prospectively followed in a single pediatric reference CF centre, within a median period of 11.6 years (seven CF cases with liver involvement). The present series represents the first report from our country concerning CF-related liver disease, furthermore including the first national case of liver transplant for end-stage liver disease.

Materials and Methods

The analyzed cohort concerns 62 pediatric patients prospectively followed in the CF centre (Unit of Paediatric Pneumology) of University Hospital de Santa Maria, from 1994 to 2009. Within the study period, no patient has been transferred to the CF Adult Clinic. The diagnosis of CF was established in all patients accordingly to conventional criteria, including two positive sweat chloride tests (>60 mEq/L) and the identification of CFTR gene described mutations. Pancreatic insufficiency was considered when fecal elastase level was lower than 200 mcg/g. The follow-up protocol included clinical evaluation every 2 months, laboratory evaluation every 6 months

(alanine aminotransferase-ALT, aspartate aminotransferase-AST, gamma-glutamyl transpeptidase-GGT, prothrombin time and serum albumin) and annual liver ultrasonography. This follow-up protocol was integrated in the routine of the CF clinic evaluation. The diagnosis of liver disease was considered if at least one of the following was present in two consecutive evaluations in a period of 6 months: i) Hepatomegaly (increased liver span with liver edge palpable more than 2 cm below the costal margin on the mid-clavicular line) or splenomegaly and/or; ii) Elevation of ALT, AST or GGT> 1.5 the normal value (excluding the periods of lung exacerbation) and/or; iii) Ultrasound abnormalities consistent with liver involvement according to conventional criteria,[10] namely: abnormalities of the liver parenchyma, the characteristics of the liver edge and the presence of periportal fibrosis. Signs of portal hypertension (such as splenomegaly, enlarged portal vein diameter, presence of collateral vessels, thickening of lesser omentum and reversal portal flow) were also systematically reported if present. In the patients with documented liver involvement, other causes of chronic liver disease (alfa1-antitrypsin deficiency, viral hepatitis B and C, Wilson disease and autoimmune hepatitis) were excluded. Upper digestive endoscopy for detection of oesophageal varices was performed whenever evidence of portal hypertension was observed. Percutaneous liver biopsy was performed in the first four cases, which had evidence of more advanced liver disease. All patients with documented liver disease were submitted to UDCA therapy, with an oral daily dose of 20 mg/kg in two doses. Local institutional Ethics Committee has approved the study and informed consent to study inclusion was obtained from all the parents.

Results

Liver involvement was documented in 7/62 patients (11.2%) and the mean age of liver disease diagnosis was 8 years (range 3-15 years). The clinical characteristics of the 7 patients are shown in the Table 1. The diagnosis of CF in this cohort of patients was established at a mean age of 3 years (range 3.5 months - 12 years), in the setting of recurrent pulmonary infections and failure to thrive (five patients), hepatosplenomegaly (one patient) and recurrent abdominal pain associated with intermittent diarrhea (one patient). CF genotypes included the identification of ΔF508 mutation in homozygosity in 6 patients and in heterozygosity in 1 patient. All the patients had a positive sweat chloride test and severe pancreatic insufficiency at the moment of the CF diagnosis and none was associated with meconium ileus. Early lung colonization with polymicrobial flora was documented in four patients; the remaining had colonization with a single agent (Staphylococcus aureus in two cases and *Pseudomonas aeruginosa* in another case). *Aspergillus fumigatus* was identified during the follow-up period in two patients. Liver involvement (clinical, laboratory and/or ultrasound abnormalities) became clinically evident at a median age of 7 years, occurring in the first decade of life in five children (Table 2). The more severe patient (case 4) had an early presentation at 3 years of age. Clinical signs of liver disease were present in only three patients, including isolated hepatomegaly in one and hepatosplenomegaly in the remaining two. Biochemical abnormalities (raised ALT, AST and /or GGT) were present in six patients (three with AST/ALT >1.5 upper limit). In patient 7, liver enzymes were persistently normal. With the exception of patient 4, submitted to liver transplant, no abnormalities in the liver synthesis tests have been detected. All patients showed ultrasound changes. The most frequently identified abnormality was heterogeneous echogenicity of the hepatic parenchyma (6/7), with nodularity additionally present in 2/7 patients, nodular liver edge in 1/7 patients and signs of portal hypertension in 2/7 patients (with inversion of the portal vein and collateral vessels flow in case 4). Patient 6 had homogeneous echogenicity of the hepatic parenchyma.

Three from four patients submitted to upper digestive endoscopy revealed oesophageal varices grade I to III; two of them also had clinical criteria (thrombocytopenia and splenomegaly) and/or ultrasound signs of portal hypertension. These two patients were submitted to prophylactic elastic ligature. Liver biopsy was performed in four patients, documenting the presence of focal biliary cirrhosis (2/7), multilobular biliary cirrhosis (1/7) (these three patients had ultrasound evidence of more advanced hepatic disease) and of focal biliary fibrosis (1/7). All the patients were maintained under UDCA therapy since the diagnosis of liver disease. During a mean follow-up period of 7 years (range 3-15 years),

Table 1. Characteristics of the patients with liver disease.

Case	Gender	Age at CF diagnosis, years	Genotype	Fecal elasase (mcg/g)	Pulmonary Colonization
1	M	0,3	ΔF508/ΔF508	27	SA, PA
2	M	3	ΔF508/ΔF508	17	PA, BC, AF
3	M	12	ΔF508/S549C	25	SA
4	F	0,4	ΔF508/ΔF508	20	SA, PA, BC, AF
5	M	1,4	ΔF508/ΔF508	8	PA, BC
6	F	5	ΔF508/ΔF508	1	PA
7	F	1	ΔF508/ΔF508	26	SA

CF, Cystic fibrosis; SA, *Staphylococcus aureus*, PA, *Pseudomonas aeruginosa*, BC, *Burkholderia cepacia*, AF, *Aspergillus fumigatus*).

Liver disease manifestations on clinical presentation.

Case	Onset of liver disease, years	Physical findings	Laboratory findings (U/L)**	Hepatobiliary ultrasound	Upper digestive endoscopy	Liver histology
1	5	Hepatomegaly	AST 141 ALT 96 GGT 87	Heterogeneous echogenicity, nodularity	No varices	Focal biliary cirrhosis
2	9	No abnormalities	AST 41 ALT 49 GGT 40	Heterogeneous echogenicity	Oesophageal varices grade I	Moderate biliary fibrosis
3	12	Hepatomegaly Splenomegaly	AST 80 ALT 84 GGT 114	Heterogeneous echogenicity, nodular liver edge, reverse flow on portal vein	Oesophageal varices grade I/II	Focal biliary cirrhosis
4*	3	Hepatomegaly Splenomegaly	AST 39 ALT 41 GGT 33	Heterogeneous echogenicity, nodularity, collateral circulation	Oesophageal varices grade II/III	Multilobular biliary cirrhosis
5	7	No abnormalities	AST 40 ALT 30 GGT 35	Heterogeneous echogenicity	-	-
6	5	No abnormalities	AST 48 ALT 43 GGT 24	Heterogeneous echogenicity	-	-
7	15	No abnormalities	AST 23 ALT 25 GGT 14	Heterogeneous echogenicity	-	-

*Patient submitted to liver transplantation; **Reference levels: AST/ ALT: 35/45 IU/L, y-GT: 38 IU/L.

progression of liver disease was verified in two patients. Patient 1 developed splenomegaly as well as ultrasound signs of portal hypertension, associated with the presence of oesophageal varices, without variceal bleeding. Patient 4 developed severe portal hypertension (first variceal bleeding at age of 5 years), complicated by progressive hepatic failure plus refractory variceal bleeding and underwent liver transplant at age of 8 years. Under conventional immunosuppression, a good outcome has been observed so far, including normality of the liver function tests, as well as pulmonary improvement (absence of hospital admissions and improvement on the lung function tests) and significant catch-up growth.

Discussion

Very few prospective studies have previously evaluated the occurrence of CF-related liver disease at pediatric age. In this single centre study (first national study of liver involvement in CF-related liver disease), evaluating 62 pediatric patients prospectively followed during a median 11.6 years follow-up period, we aimed to report the prevalence and the clinical profile of CF-related liver disease. In our cohort, the prevalence of liver disease associated to CF assessed according to the current recommended criteria, was relatively lower (11.2%), as compared to the prevalence of 27% and of 35% reported in other similarly prospective studies.[5,11] Additionally to the use of non-invasive tests, this might be partially explained by a lower median follow-up period in our study, potentially contributing to underestimation of the true prevalence of CF-related liver disease.

The reported prevalence of liver disease in CF pediatric patients has revealed a wide variability,[3,5,11,12] greatly influenced by the study design (retrospective/prospective) and by the selected diagnostic criteria. In fact, the absence of diagnostic markers sufficiently sensitive and specific, is a major recognized limitation and the use of the current standard criteria for evaluation of liver disease in this setting, probably underestimates its true prevalence. Furthermore, liver biopsy, which should be the election technique to diagnose liver disease, has been considered of questionable interest due to its invasivity and the heterogeneous distribution of the hepatic lesions in CF.[4] Some studies have suggested the potential association between the development of liver disease and the previous history of meconium ileus and the presence of pancreatic insufficiency.[5] In our series, no case had previous history of meconium ileus, but severe pancreatic insufficiency was present in all cases at

the diagnosis, accordingly to ΔF508 genotype. The mean age of liver disease diagnosis, 8 years, is in agreement with previous reports describing a characteristic presentation in the first two decades of life, with a peak at prepuberty age.[3] Hepatomegaly or hepatosplenomegaly was detected in only 3/7 cases, furthermore confirming that the absence of physical signs does not necessarily exclude the presence of potentially advanced liver disease.[5,11] Moreover, an intermittent elevation of the liver enzymes due to pulmonary exacerbations requiring antibiotic therapy is a common occurrence in these patients. For this reason, an enzyme increase for a period superior to 6 months outside the pulmonary exacerbation period is usually a required criterion for detection of liver involvement.[13] Similarly as Colombo et al.,[5] reporting a frequency of 56% of patients with raised liver enzymes, we noticed, in our series (using identical diagnostic criteria), an increase in liver enzymes in 42.5% of the patients.(3/7 cases) As predictable, the liver synthesis parameters remained preserved, with the exception of the case that progressed to end-stage liver disease. On the other hand, we also observed, as usually recognized, that the liver enzymes can be normal or just slightly raised in patients with clinically evident disease, as it was the case of patient 4. Our results clearly emphasize the role of ultrasonography in the screening of liver disease in this setting, as it detected abnormalities in 4/7 children without laboratory or physical findings, with three of them having advanced liver disease. Given the low sensitivity and specificity of other diagnostic tests, ultrasound is a non-invasive tool of relevance in the early assessment of liver disease in the CF, if performed by an experienced radiologist.[14,15] The relevance of an early diagnosis of the liver involvement has also therapeutic implications, since early therapy with UDCA is recommended. The available evidence shows an improvement of the biliary secretion, reflected by persistent normalization of cholestasis markers and histology improvement.[6,7] Although in our series all cases have been submitted to treatment with UDCA since the diagnosis of liver disease, it is difficult to evaluate objectively its contribution to the natural history of the disease. The morbidity associated with liver involvement in CF arises mainly from complications of portal hypertension, including upper gastrointestinal bleeding and hypersplenism. The management of portal hypertension is one of the most problematic and controversial aspects in CF patients. Several therapeutic modalities have been recommended, including conventional support therapy (variceal banding or sclerosis), porto-systemic shunts,[16,17] or other alternatives such as splenectomy or selective splenic embolization.[18-20] The results of these therapeutic interven-

tions are of difficult evaluation given the reduced number of patients included in the available reports. Patient 4 in our series, concerning a child with end-stage liver disease, which required liver transplant, is illustrative of the therapeutic dilemmas in this clinical setting. Refractory bleeding secondary to oesophageal varices, associated with progressive deterioration of liver function in the setting of preserved lung function, determined the choice of an isolated liver transplant. The potential indication to perform a porto-systemic shunt at an earlier stage has been questioned by several authors, as a previous surgery in the portal area might determine technical constraints to liver transplantion. Liver transplantion should be considered in patients with progressive liver failure and/or evidence of major portal hypertension, in the absence of significant pulmonary involvement (forced expiratory volume at 1 second >50%).[8,9] The reported survival rate one year after the liver transplant has been of approximately 80% (similarly to the reported survival in other indications for liver transplant)[8] and in most cases it is associated with evident benefit in the pulmonary function, in the nutritional state and in the quality of life, as illustrated by our patient.[21-23] In conclusion, the present series, representing a first national report concerning liver involvement in the setting of CF, aimed to further contribute to the knowledge of its prevalence and clinical expression at pediatric age. Our data confirmed that although advanced liver disease is a relatively rare event at this age group, early isolated liver transplantation might have to be considered. Emerging evidence from novel studies evaluating putative polymorphisms in genes other than the cystic fibrosis transmembrane conductance regulator (CFTR) gene, may further elucidate CF-related liver disease pathogenesis.[24] It is predictable that liver disease occurring both at childhood and adulthood, will have an increasing impact on survival and quality of life of these patients, emphasizing the importance of its early recognition and intervention, as well as of an adequate coordination between the Pediatric and Adult CF teams in this setting.

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