

The evolution of liver disease in cystic fibrosis

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Abstract

Objectives—To describe prospectively the evolution of liver abnormalities in cystic fibrosis (CF), and to assess their impact on nutritional status.

Study design—124 children (61 boys) with CF (median age, 5.4 years; range, 0.1–13.9) were followed longitudinally for a median of four years. Annual clinical examination, biochemistry, and ultrasound assessment were performed. Chrispin-Norman score, anthropometry, and bacterial colonisation of airway secretions were measured at each assessment.

Results—At initial assessment, 45% of the patients had no liver abnormalities, 42% had biochemical abnormality, 35% ultrasound abnormality, and 6% had clinical abnormality of the liver. In this cross sectional analysis, abnormal biochemistry was present in 40% of children with ultrasound or clinical abnormalities, but when longitudinal follow up data were analysed, abnormal biochemistry preceded or coincided with abnormal ultrasound or clinical hepatosplenomegaly in three quarters of 53 children developing new abnormalities. Eighty four of 124 children (68%) showed ultrasound or clinical evidence of liver abnormality at some point during the four years of follow up. No association was found between liver disease and nutritional status.

Conclusions—Hepatic abnormality was common in this group of children with CF, was often predicted by intermittent biochemical abnormalities, and was not associated with deterioration in nutritional status.

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Children with cystic fibrosis (CF) are predisposed to liver disease because of the lack of a functional CF transmembrane conductance regulator protein on the biliary epithelium.¹ Cross sectional studies have described a prevalence of CF liver disease of 1.4–7% when diagnosed as hepatosplenomegaly on clinical examination.^{2,3} However, clinical experience and cross sectional studies suggest a far greater prevalence of abnormal liver ultrasonography and biochemical liver function tests.⁴⁻⁶ It is not known whether these abnormalities reflect CF liver disease characterised by focal biliary fibrosis and fatty infiltration of the liver, or the effects of drugs, infections, malnutrition, or venous congestion. A recent review of CF liver disease highlighted the lack of published longi-

tudinal data describing and quantifying these abnormalities.⁷

The prompt recognition of CF liver disease is now important because of the potential beneficial effects of treatment with ursodeoxycholic acid and the need to design trials of its prophylactic use.⁸ In our study, we aimed to investigate the early evolution of clinical, biochemical, and ultrasound features of liver disease in a cohort of children with CF, and to measure the effect of CF liver disease on nutritional status.

Methods

PATIENTS AND ASSESSMENTS

One hundred and twenty four children with CF (median age, 5.4 years; range 0.1–13.9; 61 boys) were followed longitudinally for a median of four years (range, 2–5) and assessed annually for evidence of liver disease. Six (4.8%) were pancreatic sufficient. Genetic mutations were identified as $\Delta F508/\Delta F508$ in 72 (56.5%), $\Delta F508/G551D$ in eight (6.5%), $\Delta F508/G542X$ in 11 (8.1%), $\Delta F508$ /other in 25 (19.4%), and other/other or unidentified in eight (6.5%). Ursodeoxycholic acid was not used in any of the subjects during the study period.

Each assessment involved the following: a clinical examination at which hepatomegaly, splenomegaly, height, and body weight were measured; a blood test for measurement of aspartate aminotransferase (AST) and alanine aminotransferase (ALT); and abdominal ultrasound and Doppler scan. Clinical and biochemical data, Chrispin-Norman chest x ray score⁹ and details of respiratory colonisation with *Pseudomonas aeruginosa* or *Burkholderia cepacia* were recovered from a review of annual review data sheets filed in the case sheets. All ultrasound scans were performed by one consultant radiologist (ASH), who used a standard protocol and recorded results prospectively on a standard form. In children with evidence of liver disease on clinical examination, hepatitis B and C, α_1 antitrypsin deficiency, and Wilson's disease were excluded. All investigations formed part of the routine clinical management of the subjects.

DEFINITIONS

Clinical liver abnormality was defined as hepatomegaly greater than 2 cm below the rib margin in the right mid-clavicular line,¹⁰ or an enlarged left lobe of liver, or splenomegaly. Clinicians involved in the study were experienced in identifying hyperexpansion as a cause of apparent hepatomegaly. Biochemical liver abnormality was defined as AST or ALT above the upper limit of normal defined by our laboratory (AST, 45 IU/litre; ALT, 40 IU/litre;

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based on a reference range derived from a local population). Ultrasound liver abnormality was defined as abnormal liver size, abnormal parenchymal texture, scalloping of the liver edge, loss or damping of portal vein diameter variability with respiration,¹¹ or loss or damping of hepatic vein flow reversibility.¹² The presence of varices on ultrasound was also noted. These definitions were deliberately inclusive to incorporate all evidence of hepatic abnormality and to detect early changes.

STATISTICS

We summarised data using standard descriptive indices (mean, standard deviation, median, and range). We expressed nutritional status as standard deviation scores of weight for age (WAZ), height for age (HAZ), and body mass index for age (BMIZ), based on 1990 UK growth standards (Child Growth Foundation, London, UK). Groups were compared by Mann-Whitney test, or Student's *t* test for normally distributed data. Associations between liver abnormalities, age, sex, Chrispin-Norman score, and colonisation on WAZ, HAZ, and BMIZ were measured by comparison of groups using the Mann-Whitney test. To measure the effect of age and liver disease on changes in WAZ, HAZ, and BMIZ during follow up, biochemical, ultrasound, and clinical liver abnormalities at each assessment were expressed as present or absent (scored 1 or 0, respectively). To take into account the duration of presence of an abnormality and to allow for missing observations, the individual scores were summed and averaged for all assessments of each child. Correlation coefficients were then calculated between the averaged liver score and changes in WAZ, HAZ, and BMIZ per year of follow up.

Results

CROSS SECTIONAL RESULTS

At the initial evaluation, 45 (36%) of the children had no liver abnormalities detected, 48 (39%) had biochemical abnormalities, 45 (36%) had ultrasound abnormalities, and seven (6%) had clinical abnormalities (fig 1; table 1). In this cross sectional study, 18 (40%) of the 45 children with ultrasound abnormalities also had biochemical abnormalities, and 34 (27%) of 124 children had biochemical abnormalities alone. The liver was not palpable beyond 2 cm in the right mid-clavicular line in any of the infants included in our study.

Figure 1 Liver abnormalities on follow up of 124 children with cystic fibrosis. Each circle in the first column represents the initial assessment of one child. Sequential assessments of each child are represented by the corresponding rows. Spaces remain where data are incomplete. (A) No evidence of liver abnormality; (B) biochemical liver abnormality; (C) ultrasound liver abnormality; (D) biochemical and ultrasound liver abnormality; (E) clinical liver abnormality; † death after last assessment. Biochemical, ultrasound, and clinical liver abnormalities at each assessment were expressed as present or absent (scored 1 or 0, respectively). To take into account the duration of presence of an abnormality and to allow for missing observations, the individual scores were summed and averaged for all assessments of each child.

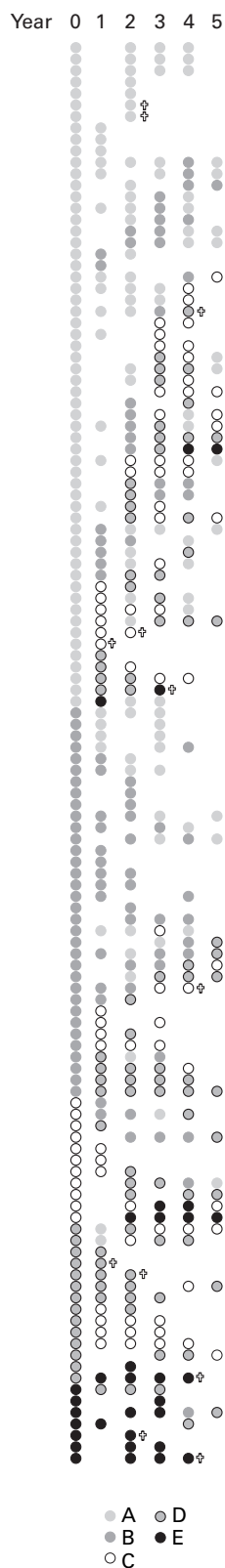


Table 1 Prevalence of liver abnormalities at the initial assessment of 124 children with cystic fibrosis

Type of liver abnormality	n
None	45
Biochemical	34
Ultrasound	24
Biochemical and ultrasound	14
Ultrasound and clinical	3
Biochemical, ultrasound, and clinical	4

LONGITUDINAL RESULTS

During follow up, 51 of the 124 children developed ultrasound or clinical liver abnormality, having had neither initially. Biochemical abnormality preceded (*n* = 25) or coincided (*n* = 11) with ultrasound or clinical abnormalities in 36 of these 51. Thirty one children had biochemical abnormalities without developing other evidence of liver disease during their follow up. Thirty nine of the 53 children (74%) who developed new ultrasound or clinical abnormalities during follow up had biochemical abnormalities before or coinciding with the ultrasound or clinical abnormalities.

Ninety nine children (80%) during follow up were found to have biochemical liver abnormality, usually a modest rise in plasma transaminase concentrations (fig 2). Of the 91 children with further assessments after the biochemical abnormality was first noted, the abnormality was present intermittently in 58. Eighty three children (67%) had ultrasound abnormalities on follow up. The ultrasound abnormality was present intermittently in 21 of 70 children with further assessments after the ultrasound abnormality was first noted (damping of hepatic vein flow reversibility (*n* = 6); damping of portal vein diameter variability (*n* = 1); abnormal liver size, texture, or edge (*n* = 10); and a combination of these (*n* = 4)). Fourteen children (11%) showed clinical liver abnormality at some point during follow up, with hepatomegaly subsequently becoming impalpable in five of 13 who had subsequent assessments.

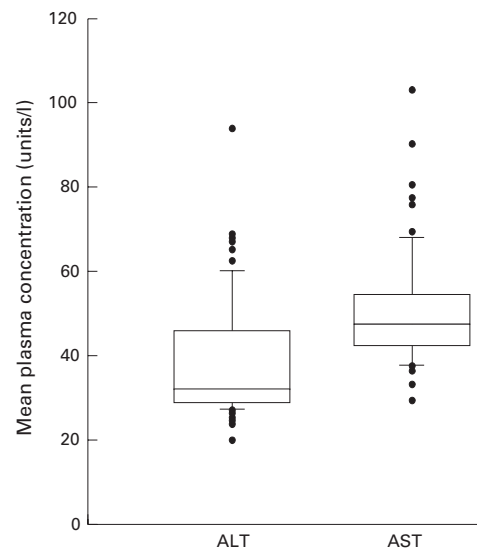


Figure 2 Box plot of mean concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) during follow up of 124 children with cystic fibrosis.

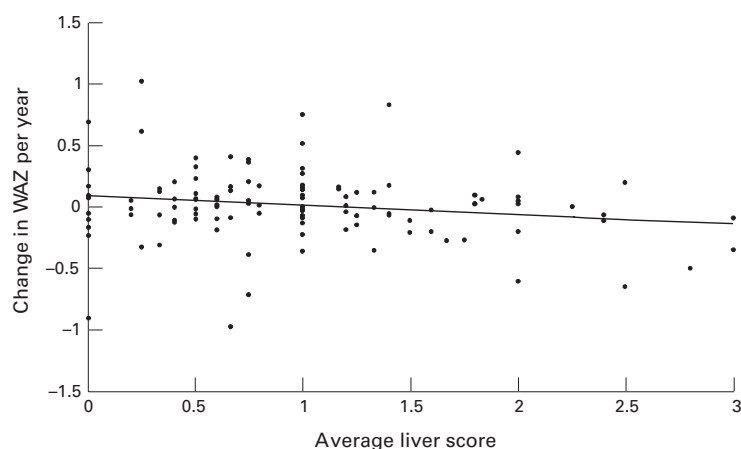


Figure 3 Average liver score related to change in weight for age standard deviation score (WAZ) per year of follow up.

Overall, some evidence of liver abnormality (clinical and/or biochemical and/or ultrasound abnormality) was found at every assessment during follow up in 48 (39%) of the 124 children with CF. In 66 (53%) children, evidence of liver abnormality was found at some of their assessments—in only 10 (8%) children there was no evidence of hepatic abnormality identified during follow up (fig 1).

Initial WAZ (median, 0.91; interquartile (IQ) range, -1.92 to -0.25), HAZ (median, -0.74 ; IQ range, -1.55 to 0.23), BMIZ (median, -0.69 ; IQ range, -1.40 to -0.03), and Chrispin-Norman score (median, 4.09; IQ range, 2.81 to 6.90) did not differ between children with and without liver abnormalities, splenomegaly, or varices. Changes in WAZ, HAZ, or BMIZ per year of follow up were not associated with average liver abnormality score (fig 3), Chrispin-Norman score, sex, or colonisation with *P aeruginosa* or *B cepacia*. However, there was an association between age and both liver abnormality score (regression coefficient, -0.04 ; $p < 0.01$) and decline in WAZ (regression coefficient, -0.02 ; $p < 0.05$). The presence of splenomegaly or varices was not independently associated with deterioration in nutritional status. The presence of liver abnormalities did not differ with sex, genotype, colonisation with *P aeruginosa* or *B cepacia*, history of meconium ileus at birth ($n = 29$), or death during follow up ($n = 12$).

Discussion

Our study focuses on biochemical, ultrasound, and clinical signs of liver abnormality and their evolution in children with CF. The initial cross sectional assessment of 124 children with CF showed that 6% had evidence of liver abnormality on clinical examination, 42% had raised serum transaminases, and 35% had liver ultrasound abnormalities, which were common in those with no clinical or biochemical abnormalities. Ninety two per cent of the children followed for an average of four years showed some evidence of liver abnormality during follow up, and 68% showed ultrasound or clinical liver abnormalities at some point. Biochemical abnormality was often intermittent, but tended to precede ultrasound abnormalities, which in

turn preceded or coincided with clinical abnormalities. Liver abnormality was not associated with decline in nutritional status.

To date, no blood test is available to detect damage to the biliary epithelial cell, where the primary lesion in CF liver disease occurs,¹ and existing biochemical tests lack sensitivity and specificity in identifying biopsy proven disease.⁵ Hitherto, biochemical tests have been seen as unreliable indicators of liver disease in CF.¹³ False positive tests can arise from septicaemia, drug treatment, right heart failure, or malnutrition; false negative tests can arise as a result of the patchy parenchymal involvement. However, our longitudinal study of 124 children with CF suggests that biochemical abnormalities occur early and are often intermittent. Cross sectional studies will therefore underestimate the sensitivity of intermittent biochemical tests to detect early liver disease. Abnormal biochemistry occurred in only 40% of children with ultrasound abnormalities at the initial, cross sectional assessment, but preceded or coincided with the initial appearance of 74% of ultrasound or clinical abnormalities on longitudinal follow up. In our study, the true sensitivity and specificity of biochemical tests cannot be measured because children were not all followed from birth to development of liver disease or death.

Biopsy is the gold standard for the diagnosis of most chronic liver diseases. However, percutaneous needle biopsy may miss the patchy early lesions of CF liver disease, it agrees poorly with clinically evident hepatic involvement,¹⁴ and it is associated with a risk of haemorrhage.¹⁵ We believe that the prediction of ultrasound or clinical liver abnormalities by biochemical tests in our study provides support for their use in the early identification of liver disease in CF. However, the intermittent presence of ultrasound and clinical abnormalities in some children suggests that these children may have had less severe abnormalities, such as hepatic steatosis.

We found no relation between liver abnormality or portal hypertension and decline in nutritional status although, in general, the group of children studied was of good nutritional status, with relatively mild liver disease, and the most sensitive indicators of malnutrition in liver disease (triceps skin fold thickness and mid-arm circumference) were not available in all patients. However, longevity and weight for age are associated in children with CF,¹⁶ and our study therefore suggests that liver disease may not affect survival through an effect on nutritional status. To our knowledge, the association between liver disease and malnutrition in CF has not been studied previously, and studies of the effect of ursodeoxycholic acid treatment on nutritional status in CF liver disease have had conflicting results.^{17 18} Further studies are needed to examine the relations between malnutrition, inflammation, and liver disease.

The limitations of our clinical study must be acknowledged. First, patients were examined by different clinicians, and the findings of hepatomegaly and splenomegaly may differ

between them. Second, measurement of γ -glutamyl transferase (unavailable locally in the early years of our study) may have improved detection of early liver disease,¹⁰ although in other studies the improvement has been only marginal.⁵ While acknowledging these limitations, our study represents 414 patient years of follow up, provides a unique picture of the evolution of liver disease in CF, and demonstrates that it develops early in childhood.

In conclusion, these children with CF showed a spectrum of liver abnormalities when followed for a number of years, with intermittent rises in serum transaminases a common early finding. We recommend that future longitudinal studies should attempt to identify the underlying pathology of these abnormalities and patterns of early biochemical abnormalities that might more reliably predict evolving liver disease in CF, perhaps using the liver isoenzyme of alkaline phosphatase.¹⁹ The relation between liver abnormality and nutrition needs further study, both in CF and in other liver diseases.

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