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Original Article

Outcome in patients with cystic fibrosis liver disease

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Abstract

Background: Liver disease is an important complication in CF.
Aims: To determine if CFLD is a risk factor for mortality in CF, and which baseline characteristics predict all-cause mortality.
Methods: Irish children with CFLD, and their age and gender matched controls were enrolled at baseline and reviewed after 10 years to determine which characteristics predict mortality.
Results: 72/84 (85.71%) participants were followed, (mean age Cases 21.71 yrs SD 6.5, CF controls 23.62 SD 5.6, 22 (61%) males), with no difference in duration of follow-up. Nineteen participants (26.4%) died, 38.9% (14/36) with CFLD and 13.89% (5/36) CF controls (Odds Ratio (OR) 3.94 95% CI:1.23–12.56 p = 0.005). In logistic regression, liver disease (OR 4.28 95% CI 1.07–17.16) female gender (OR 12.25 95% CI 2.37–63.24), reduced pulmonary function, (OR 5.11 95% CI 1.09–23.81) were each independent risk factors for mortality in CF.
Conclusions: Liver disease is an independent risk factor for mortality in CF.

Keywords: Cystic fibrosis liver disease; Mortality; Outcome; Nutrition; Female gender

Cystic fibrosis (CF) is a multi-organ disease due to mutations in the *CFTR* gene (cystic fibrosis transmembrane conductance regulator) leading to defective clearance of secretions from epithelial surfaces [1–5]. While pulmonary disease still remains the main cause of morbidity and mortality in CF, understanding the consequences of other manifestations of CF such as liver disease is of increasing importance if we are to further improve the outcome for patients.

The diagnosis of CFLD is not straightforward and the lack of a gold standard for the diagnosis has hampered our understanding of CFLD [2–6]. Many children with CF will develop evidence of liver abnormalities including raised liver enzymes, abnormalities on liver ultrasonography or hepatomegaly [2–5]. However, less than 10% of children with CF have clinically significant liver disease with portal hypertension [2,4]. The lack of a consistent definition of CFLD has led to significant disparities in the reported

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prevalence and outcome for CFLD [4]. The CF Foundation has proposed a classification of CFLD which separates cirrhosis with or without portal hypertension from other forms of liver disease such as raised aminotransferases and hepatic steatosis, and the use of this classification may help improve our understanding of CFLD [4].

A number of reports have suggested that liver disease is not a risk factor for mortality in CF [7–9]. However, many of these studies lack an adequate control group with which to compare outcome. Liver disease, even in the presence of portal hypertension is not considered a contraindication to lung transplantation in CF [10,11], and the outcome following lung transplantation is not reported to be compromised by the presence of liver disease [12]. Nevertheless, there is emerging evidence, which supports the hypothesis that liver disease may be a poor prognostic factor in CF [13–15]

In a national study of CFLD we have shown that children with clinically significant CFLD are shorter and lighter than their age and gender matched controls and have worse pulmonary function [16]. At a 7-year follow-up, while there was no difference in mortality between CF participants and CF controls, there was evidence that participants with CFLD had a more severe phenotype, with reduced nutritional parameters, poorer lung function and a greater rate of decline in Forced expiratory volume in 1 sec (FEV_1) compared to controls [15]. In the present study we continue to follow this cohort 10 years after they participated in the baseline study to examine differences in all cause mortality between participants with CFLD and CF controls with no evidence of liver disease and to identify risk factors for mortality [17].

1. Methods

Persons with CF who participated in the baseline study in 1999–2000 [16] and in the 7 year follow-up [15] were invited to participate in a review at 10-years. At baseline cases were defined as any child aged between 5 and 18 years with CF (confirmed by sweat chloride), who had liver disease with portal hypertension. Portal hypertension was defined clinically (splenomegaly/hypersplensim), or ultrasonographically splenomegaly (increased compared with body-size-appropriate values,) varices, ascites, reversal of portal vein flow or endoscopically. Controls were children with CF who had no biochemical, ultrasonographic or clinical evidence of liver disease. At baseline CF controls were pair-matched for age and sex with CFLD participants.

Exclusions and losses to follow-up at 10 years were as follows: 5 cases of CFLD were excluded because they had not been reviewed by a paediatric hepatologist at baseline; it was determined on re-examination of their baseline data that their radiological or clinical assessment was not adequate to support a diagnosis of portal hypertension [15]. Participants were not matched for FEV_1 at baseline, and there were no a priori exclusion criteria based on pulmonary function tests at baseline. An FEV_1 of less than 30% predicts mortality within 2 years. On this basis, 3 controls with an $FEV_1 < 30\%$ at baseline were excluded from follow-up [15].

To review the validity of the baseline findings, the data was re-analysed without the 8 participants (5 cases and 3 controls) excluded from the follow-up data. Exclusion of this group of participants did not alter the findings of the baseline study.

In this follow-up study we used data collected at baseline in 1999–2000 to examine risk factors for mortality after 10 years follow-up. This included baseline pulmonary function tests (FEV_1 Z scores (Standard Deviation Scores)) anthropometric data with skin fold measurements, clinical biochemistry, and gender and liver disease. Baseline data for height, weight, and body mass index were expressed as centiles and Z scores using the Centre for Disease Control (CDC) 2000 reference data [18]. Upper arm circumference and skin fold thickness measurements were calculated as described previously [15,16]. FEV_1 was recorded as absolute values and the reference range described by Stanojevic et al. [19] (www.growinglungs.org.uk) was used to calculate centiles and Z scores of FEV_1 per cent predicted based on age height and gender, because Z scores allow a more accurate comparison of pulmonary function across a range of ages [19,20].

2. Ethical approval

This study was approved by all hospital Research Ethics Committees providing care for study participants, with the guidance that eligible participants should not undertake any extra investigations or hospital visits. Consent was obtained from participants and/or their parents.

3. Statistical analysis

The baseline study used a paired analysis design to compare patients with and without CFLD [16]. Losses to follow-up, exclusions and deaths required un-pairing of the data at follow-up. The end point for the comparison of the two groups was death or transplant (liver or lung) referred to as mortality. Transplant was classified as mortality because in the absence of a transplant the outcome was death.

Results are presented as median and interquartile range, as most of the data showed a degree of skewness. Wilcoxon Log-Rank tests were used to compare groups, and chi-square tests for differences in proportions. Multiple logistic regression was used to examine the simultaneous effect of several different explanatory variables on risk of death in CF. To avoid any linearity assumptions in the final logistic regression model FEV_1 Z score and BMI Z score were dicotomised into an FEV_1 Z score of <-2 SD below the mean compared to an FEV_1 Z score of ≥ -2 SD below the mean; a BMI Z score <-1 SD below the mean, and a Z score ≥ -1 SD below the mean. Significance was set at the 5% level. Data was analysed using Epi-Info (CDC, Atlanta USA).

4. Results

At baseline there were 42 CFLD participants with CFLD who were pair matched for age and sex with 42 participants with CF but no evidence of liver disease (CF Controls). Seventy two (85.7%) of the original 84 participants were available for follow-up. Fig. 1 is a schematic representation of the outcome