Baseline Ultrasound and Clinical Correlates in Children with Cystic Fibrosis

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Objective To investigate the relationship between abdominal ultrasound findings and demographic, historical, and clinical features in children with cystic fibrosis (CF).

Study design Children age 3-12 years with CF without known cirrhosis, were enrolled in a prospective, multicenter study of ultrasound to predict hepatic fibrosis. Consensus ultrasound patterns were assigned by 3 radiologists as normal, heterogeneous, homogeneous, or cirrhosis. Data were derived from direct collection and US or Toronto CF registries. χ^2 or ANOVA were used to compare variables among ultrasound groups and between normal and abnormal. Logistic regression was used to study risk factors for having abnormal ultrasound.

Results Findings in 719 subjects were normal (n = 590, 82.1%), heterogeneous (64, 8.9%), homogeneous (41, 5.7%), and cirrhosis (24, 3.3%). Cirrhosis (P = .0004), homogeneous (P < .0001), and heterogeneous (P = .03) were older than normal. More males were heterogeneous (P = .001). More heterogeneous (15.0%, P = .009) and cirrhosis (25.0%, P = .005) had CF-related diabetes or impaired glucose tolerance vs normal (5.4%). Early infection with *Pseudomonas aeruginosa* (<2 years old) was associated with a lower risk (OR 0.42, P = .0007) of abnormal. Ursodeoxycholic acid use (OR 3.69, P < .0001) and CF-related diabetes (OR 2.21, P = .019) were associated with increased risk of abnormal.

Conclusions Unsuspected cirrhosis is seen in 3.3% of young patients with CF, heterogeneous in 8.9%. Abnormal ultrasound is associated with CF-related diabetes, and early *P aeruginosa* is associated with normal ultrasound. Prospective assessment of these risk factors may identify potential interventional targets. *(J Pediatr 2015;167:862-68)*.

Trial registration ClinicalTrials.gov: NCT01144507.

There are significant limitations in the identification and classification of liver disease in patients with cystic fibrosis (CF).[1,2] This gap primarily reflects a lack of reliable, sensitive, and specific diagnostic markers of liver involvement in CF prior to the development of clinically evident cirrhosis with portal hypertension. A mild degree of liver involvement is common among patients with CF, but most natural history studies suggest a prevalence of multilobular cirrhosis in CF of between 5% and 15%. Virtually all cases are identified before 20 years of age,[3-5] indicating that advanced liver disease in CF is a disorder of children.

A heterogeneous echogenicity pattern of the liver on abdominal ultrasound has been suggested to identify patients with CF at increased risk for cirrhosis.[6] Between 9% and 25% of children with CF are reported to have a heterogeneous

BMI	Body mass index
CF	Cystic fibrosis
CFLD	CF liver disease
CFLD NET	Cystic Fibrosis Liver Disease Network
FEV_1	Forced expiratory volume in 1 second
NAFLD	Nonalcoholic fatty liver disease
PUSH	Prediction by Ultrasound of the Risk of Hepatic Cirrhosis in Cystic Fibrosis

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pattern on ultrasound.[6-8] In a single center study, 67% of patients with a heterogeneous pattern on ultrasound progressed to features consistent with cirrhosis, and 46% of these progressed to portal hypertension with an average follow-up of 10 years.[6] In patients with a normal echogenicity pattern on ultrasound, only 7%-13% developed ultrasound findings of cirrhosis, and 5%-7.5% progressed to portal hypertension.[6] Thus, patients with a heterogeneous pattern of the liver on ultrasound demonstrated a 5.2-fold increased incidence of cirrhosis and a 6.1-fold increased incidence of portal hypertension compared with children with a normal echogenicity pattern.

In prior studies, sample size has limited the ability to investigate potential correlations between demographic, historic or clinical factors, and ultrasound findings. We hypothesized that there would be demographic and clinical features associated with each ultrasound pattern. Specifically, we sought to determine if early or current nutritional status, early infections, antibiotic use, and access to care were associated with abnormal baseline ultrasound.

Methods

The Cystic Fibrosis Liver Disease Network (CFLD NET) is a North American multicenter group conducting a prospective study investigating the utility of abdominal ultrasound to identify young children at risk for the development of cirrhosis (Prediction by Ultrasound of the Risk of Hepatic Cirrhosis in Cystic Fibrosis [PUSH]; ClinicalTrials.gov: NCT01144507). Official registration for this trial was delayed because of administrative issues requiring clarification by the multiple sponsors. As such, 146 of the 722 subjects (20%) reported in this study were enrolled prior to the registration approval date of June 14, 2010. However, no data were examined, and no interval analysis was conducted prior to registration. The protocol was reviewed and approved by the Institutional Review Boards at all participating centers. Study subjects were recruited from 11 CF centers within the network. All guardians provided informed consent and appropriate assent was obtained. Children 3-12 years of age were eligible for the study based on the following inclusion criteria: (1) diagnosed with CF as determined by a sweat chloride of >60 mEq/L or 2 disease-causing *CFTR* genetic mutations with evidence of end organ involvement; (2) enrolled in either the US or Toronto CF registry; and (3) diagnosed with pancreatic insufficiency as indicated by one of the following: *CFTR* mutations associated with pancreatic insufficiency,[9] fecal elastase <100 μg/g (at any time), or 72-hour fecal fat with coefficient of fat absorption <85% (at any time).

Exclusion criteria were known cirrhosis or portal hypertension (ie, splenomegaly, ascites), prior identification of *Burkholderia* species on respiratory cultures, or short bowel syndrome, defined as requiring any parenteral nutrition after 3 months of age.

Data collected included demographics, *CFTR* genotype, and abdominal ultrasound findings. The US and Toronto CF registries were used for historical and clinical data, including medical insurance, symptoms at diagnosis, history of malnutrition, infection, lung function, complications, and medications. CF-related diabetes or impaired glucose tolerance is defined in the registries as 2-hour glucose levels of 140 to 199 mg per dL on the 75-g oral glucose tolerance test. Ultrasound was performed with state-of-the-art equipment with both gray-scale and Doppler imaging at each site.

Grading followed the system of Williams et al.[10] Liver echogenicity and contours were assessed to classify a patient into 1 of 4 ultrasound patterns. Normal denoted that the subject had normal hepatic echogenicity. Heterogeneous denoted that the subject had increased echogenicity that was diffusely patchy or limited to periportal regions. Homogeneous denoted that the subject had diffusely increased hepatic parenchymal echogenicity relative to renal echogenicity, absent or poor definition of portal venous and hepatic structures, and posterior beam attenuation with absent or incomplete diaphragm visualization. Cirrhosis pattern denoted that the subject had a heterogeneous echogenicity and coarse echotexture of the liver parenchyma and obvious nodularity of the liver contour.

A single radiologist from each center participating in the PUSH Study read all the ultrasound studies locally. Participating radiologists underwent web-based training for the grading of the ultrasound studies. A training set of representative images from each grade was developed by the lead radiologist. Validation of consistency ($\kappa > 0.7$) in the readings was assessed with the training set prior to initiation of the study. In addition, the lead radiologist reviewed the first 5 ultrasound studies from every site for quality to ensure uniform quality and validated degree of concordance before study continuation. The same training set used for the radiologists was used to train the sonographers. In addition, there was a written guide documenting the required images for the sonographers.

At study entry, each enrolled subject underwent a standardized abdominal ultrasound to include a survey examination of the entire abdomen and a detailed examination of the liver and spleen to assess for presence or absence of liver disease. The gray-scale images were the determinant of those who had longitudinal follow-up. Ultrasound findings were independently graded as normal, heterogeneous, homogeneous, or cirrhosis by 3 study radiologists randomly assigned from the different participating study sites in regular rotation and blinded to the results of the other interpretations. The consensus grade was assigned by majority. In rare cases, a fourth reader was invited to grade the ultrasound if there were 3 different grades, as a tiebreaker. If 4 different grades were submitted, the patient was excluded from the study.

Statistical Analyses

We used descriptive statistics to describe demographic and clinical features, and medical history of patients in the normal and abnormal groups separately. ANOVA or Kruskal-Wallis test for continuous variables and χ^2 or Fisher exact tests for categorical variables were used to test

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