Journal of Cystic Fibrosis 16 (2017) 139 – 145

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Original Article

Prevalence of elevated liver enzymes in children with cystic fibrosis diagnosed by newborn screen☆

Samantha A. Woodruff [a], Marci K. Sontag [c], Frank J. Accurso [b], Ronald J. Sokol [a], Michael R. Narkewicz [a,*]

[a] Department of Pediatrics, Section of Pediatric Gastroenterology, Hepatology and Nutrition and Digestive Health Institute, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO, United States

[b] Section of Pediatric Pulmonology, Colorado School of Public Health, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO, United States

[c] Department of Epidemiology, Colorado School of Public Health, University of Colorado School of Medicine and Children's Hospital Colorado Aurora, CO, United States

Received 29 December 2015; revised 9 August 2016; accepted 9 August 2016
Available online 20 August 2016

Abstract

Background: Prevalence and risks for elevated liver enzymes have not been studied systematically in children with CF identified by newborn screen.
Methods: 298 CF children identified by newborn screen since 1982. AST, ALT and GGT tested at annual visits. Percent of children with 1 or ≥2 values of elevated AST, ALT and GGT determined. Relationship of liver enzymes to clinical factors or subsequent liver disease was analyzed
Results: At least one abnormal value for AST (63%), ALT (93%) and ALT ≥1.5× ULN (52%) occurred by 21 years of age. Liver enzyme elevations were not correlated with CFTR mutation, meconium ileus or ethnicity. AST and GGT ≥1.5× ULN were associated with later advanced liver disease HR (CI) 6.53 (2.02–21.1) and 4.03 (1.15–13.45), respectively.
Conclusions: Elevated liver enzymes are common during childhood in CF patients identified by newborn screen. Elevated AST and GGT may be markers for risk of advanced liver disease.

Keywords: Cystic fibrosis liver disease; Newborn screening

1. Introduction

Cystic fibrosis (CF) is the most common lethal autosomal recessive disease in the United States, occurring in 1 in 3500 newborns [1,2]. There are over 30,000 affected individuals in the United States [3]. Liver involvement is common in CF, with many manifestations including hepatic steatosis, biliary fibrosis and cirrhosis. Advanced liver disease (multi-lobular cirrhosis with or without portal hypertension) is reported in 5–10% of patients with CF [4]. The pathophysiology is uncertain, but one theory is that abnormal CFTR function contributes to an abnormal composition, consistency, pH and flow of bile, with subsequent biliary plugging, inflammation and fibrosis, which leads to focal biliary or multi-lobular cirrhosis [5,6]. However, unlike pancreatic manifestations of CF there is no clear genotype–phenotype correlation with the development of cirrhosis. Liver disease accounts for 2.7% of deaths in patients with CF, making this the

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; CFTR, cystic fibrosis transmembrane conductance regulator; GGT, gamma-glutamyltranspeptidase; ULN, upper limit of normal.

☆ Supported in part by grants from the Cystic Fibrosis Foundation SONTAG07A0 and WOODRU06B0, 5T32DK067009 from NIDDK/NIH and UL1 TR001082 from NCATS/NIH.

* Corresponding author at: Children's Hospital B290, 13123 East 16th Ave, Aurora, CO 80045, United States.
E-mail address: narkewicz@childrenscolorado.org (M.R. Narkewicz).

http://dx.doi.org/10.1016/j.jcf.2016.08.002

3rd leading cause of death in CF [4]. Multi-lobular cirrhosis in CF was previously reported to be associated with meconium ileus, male sex and severe CFTR genotypes [7–9], but this has not been confirmed in other studies [10,11]. Older age at the diagnosis of CF has also been associated with development of liver disease, with the presumed mechanism being delay in diagnosis and subsequent poor nutritional status [12].

Annual determination of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltranspeptidase (GGT) as a screen for CF liver disease is recommended in current guidelines for CF management [6,13]. However, elevated liver enzymes are common (reported in 25%–50% of CF patients) [11] and may also be caused by malnutrition, specific nutrient deficiencies, drug toxicity and intercurrent illnesses. Moreover, the significance of asymptomatic elevations of AST, ALT and GGT and their persistence is unknown. Furthermore, the frequency of elevated AST, ALT and GGT levels at annual visits and their clinical associations in a CF population diagnosed by newborn screening is unknown. There is a need for these benchmark data to help guide the clinician's response to abnormal values in an individual patient. This has become even more necessary with recommendations for more frequent monitoring of AST, ALT and GGT with the new CFTR corrector and modifier treatments. We have had the unique opportunity to obtain annual liver blood tests longitudinally from one of the first large cohorts of screening-identified CF patients since newborn screening was initiated in Colorado in 1982. The objective of this study was to evaluate prospectively-obtained longitudinal annual visit liver enzyme data starting from infancy that has been collected during the past 30 years in this population. In contrast to other reports of cross-sectional liver enzyme data in CF, detection of CF in the first weeks of life in our patients has allowed for early airway, pancreatic enzyme replacement and nutritional therapy to be instituted, before the diagnosis of CF may have otherwise been clinically considered. Thus, these data should be useful to other centers that now employ newborn screening and early institution of such treatment measures. Moreover, newer treatments for CF such as the development of CFTR modulators require knowledge of liver enzyme levels for clinical trial design and the detection of adverse events, specifically, potential hepatic damage.

2. Materials and methods

2.1. Subject selection

We included all children with CF born in Colorado from 1982 to 2005, diagnosed by newborn screening, the presence of meconium ileus, or who were missed by newborn screening. A sweat chloride >60 mmol/L or two pathologic CFTR mutations consistent with CF were considered positive evidence of CF [14]. Children were followed annually through a research protocol approved by the Colorado Multiple Institutional Review Board, and informed consent was obtained from parents before participation in this study. Clinical and laboratory data were collected prospectively and entered into a research database. Twice per year for the first 2 years of life and then annually thereafter, we obtained AST, ALT and GGT. While ursodeoxycholic acid use data is not available in our database prior to 2005, we developed a standardized evaluation and management pathway, that included starting ursodeoxycholic acid therapy at 10–20 mg/kg/day only if AST, ALT or GGT were ≥2× the upper limit of normal for age (ULN) for ≥6 months or if there was clinical evidence of advanced liver disease (e.g., splenomegaly, firm hepatomegaly or complications of portal hypertension) from 1990 forward. Pancreatic enzyme replacement therapy was initiated on all infants at diagnosis and continued unless there was verification of pancreatic sufficiency. We followed CF Foundation guidelines for nutritional and pulmonary therapies as clinically indicated and added new therapies as they became available over time.

2.2. Data collection and analysis

ALT was determined at annual well CF visits starting in 1982 with subsequent inclusion of AST and GGT in 1990. Values were classified as normal, elevated (any elevation above the ULN), ≥1.5× ULN, ≥2× ULN and ≥3× ULN based on normal values for age and sex at the time of their determination. Since the laboratory methods and normal ranges changed over time, we present the data as × ULN. Data were collected from testing performed at annual visits, which were not always one year apart. Product-Limit Survival Estimates were used to assess the age at first abnormality for AST, ALT and GGT. We also evaluated early liver enzyme elevation (defined as present before 5 years of age) and persistent elevation defined as 2 or more abnormal values obtained at least 6 months apart at the annual visits. We specifically excluded values between annual visits from this analysis due to the potential impact of intercurrent illnesses on the values. Univariate relative risks were calculated for persistent elevation (for ≥1.5× and 2× ULN) with the presence of meconium ileus, sex, CFTR mutation severity and Hispanic ethnicity. Associations with nutritional (BMI or weight for height z-scores), or pulmonary status (FEV_1) in the years preceding persistent liver enzyme elevations were determined by calculating the mean values for nutritional parameters and FEV1 (± standard error of the mean) of all observations for each clinical parameter for the period of 1 year before the 2nd elevated liver enzyme, compared to newborn screened CF children of the same age without elevation in any liver enzymes. For this analysis, due to missing values in children who did not have an 'annual visit' recorded, data from all visits were used, and the mean clinical outcome for each year of age (rounded to the nearest year of age) was calculated.

We then evaluated elevations (≥1.5× ULN) of AST, ALT, and GGT present at any time prior to a clinical diagnosis of liver disease, as risk factors for an association with clinically defined advanced CF liver disease, adjusting for the presence of meconium ileus, sex, and CFTR genotype (2 severe mutations (class 1, 2 or 3) vs. 1 or more milder mutations (class 4 or 5)) [15] using proportional hazards models. Clinical advanced liver disease was defined as the presence of cirrhosis (by imaging or liver histology), portal hypertension (by the presence of ascites, splenomegaly or thrombocytopenia, esophageal or gastric