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Neonatal cholestasis in children with Alpha-1-AT deficiency is a risk for earlier severe liver disease with male predominance

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Abstract

Background: Our objective was to better understand the natural history and disease modifiers of Alpha-1-antitrypsin deficiency (AATD), a common genetic liver disease causing hepatitis and cirrhosis in adults and children. The clinical course is highly variable. Some infants present with neonatal

Abbreviations: AAT, Alpha-1-antitrypsin; AATD, Alpha-1-antitrypsin deficiency; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ChiLDReN, Childhood Liver Disease Research Network; dpCEPH, definite or possible clinically evident portal hypertension; GGT, gamma-glutamyl transpeptidase; LOGIC, Longitudinal Observational Study of Genetic Intrahepatic Cholestasis; NIH, National Institutes of Health; PHT, portal hypertension; PROBE, Prospective Database of Infants With Cholestasis; SZ, S and Z alleles; ZZ, Z alleles.

cholestasis, which can resolve spontaneously or progress to cirrhosis; others are well in infancy, only to develop portal hypertension later in childhood.

Methods: The Childhood Liver Disease Research Network has been enrolling AATD participants into longitudinal, observational studies at North American tertiary centers since 2004. We examined the clinical courses of 2 subgroups of participants from the several hundred enrolled; first, those presenting with neonatal cholestasis captured by a unique study, enrolled because of neonatal cholestasis but before specific diagnosis, then followed longitudinally (n = 46); second, separately, all participants who progressed to liver transplant (n = 119).

Results: We found male predominance for neonatal cholestasis in AATD (65% male, $p = 0.04$), an association of neonatal gamma-glutamyl transpeptidase elevation to more severe disease, and a higher rate of neonatal cholestasis progression to portal hypertension than previously reported (41%) occurring at median age of 5 months. Participants with and without preceding neonatal cholestasis were at risk of progression to transplant. Participants who progressed to liver transplant following neonatal cholestasis were significantly younger at transplant than those without neonatal cholestasis (4.1 vs. 7.8 years, $p = 0.04$, overall range 0.3–17 years). Neonatal cholestasis had a negative impact on growth parameters. Coagulopathy and varices were common before transplant, but gastrointestinal bleeding was not.

Conclusions: Patients with AATD and neonatal cholestasis are at risk of early progression to severe liver disease, but the risk of severe disease extends throughout childhood. Careful attention to nutrition and growth is needed.

INTRODUCTION

Alpha-1-antitrypsin (AAT) deficiency (AATD) is a common metabolic-genetic liver disease occurring in one in 2000–3500 births in North American and European populations.[1] It is associated with chronic liver disease, cirrhosis, and end-stage liver disease in children and adults. The Z mutant allele of the AAT gene is associated with the vast majority of AAT deficiency liver disease, either as the classical form of homozygous Z alleles (ZZ) AAT deficiency or as the S and Z alleles (SZ) compound heterozygous form, which also has an increased risk of liver disease.[1,2] The most common childhood presentation of AAT deficiency is neonatal cholestasis. Some of these infants rapidly progress to portal hypertension (PHT) and end-stage liver disease, while others improve spontaneously and remain well until adulthood. However, some children with AAT deficiency without preceding neonatal cholestasis present later with chronic hepatitis, cirrhosis, or end-stage liver disease, indicating that not all children with severe disease have a history of neonatal cholestasis. With current information, clinicians cannot predict the clinical course of any individual patient.

The Childhood Liver Disease Research Network (ChiLDReN) is a National Institutes of Health (NIH)-supported consortium of pediatric tertiary care centers in North America focused on the study of rare pediatric liver diseases, including AATD, with the aim of better defining disease natural history and identifying genetic and environmental disease modifiers.[3–5] We recently reported the outcomes of 350 participants with AATD with their native livers enrolled in ChiLDReN, examined their clinical and laboratory characteristics, their rate of progression to PHT, and the modest effect of neonatal cholestasis on increasing the likelihood of development of PHT.[3–5] In this current report, we continued to examine factors that influence the outcomes of AAT deficiency by focusing on 2 specific groups within ChiLDReN. First was an analysis of subjects enrolled in

ChiLDReN through the Prospective Database of Infants with Cholestasis (PROBE) study, which enrolled infants with the neonatal cholestasis syndrome prior to the establishment of a specific diagnosis and followed them prospectively from evaluation to diagnosis and through follow-up.[6,7] We examined data for those ultimately diagnosed with AATD but not with biliary atresia or other causes of neonatal cholestasis. This is a highly unique data set of participants with AATD and native liver, with detailed, longitudinal data collected prior to diagnosis that is unlike any other data available. Our previous publication did not examine the data collected prior to diagnosis, or its prognostic value. This is an important area on which to focus, given that clinicians and families are anxious for information when a new diagnosis is made. The second group we focused on was participants in ChiLDReN enrolled in the Longitudinal Observational Study of Genetic Causes of Intrahepatic Cholestasis (LOGIC) who had undergone liver transplantation, either before or after LOGIC enrollment, which has also not been previously analyzed in detail.[8,9] We sought to test the hypothesis that following the course of young participants with AAT deficiency in these highly defined, specific groups would better delineate the natural history and aid in the identification of prognostic markers related to disease outcomes. We are in a unique position to analyze multicenter data from North America with a large "n" of participants with liver transplants.

METHODS

Population and assessments

This report includes participants with AATD enrolled into PROBE (https://clinicaltrials.gov/ct2/show/NCT00061828) and LOGIC (NCT00571272) from April 2004 through November 2020.[3,4,9–11] Institutional Review Board approvals in accordance with the Declarations of Helsinki and Istanbul and written consents were obtained at each site. PROBE inclusion criteria were designed to capture infants with neonatal cholestasis syndrome prior to an established, unifying diagnosis, as described: (1) age 180 days or below at presentation to a ChiLDReN center; and (2) serum direct or conjugated bilirubin $>20\%$ of total bilirubin (TB) and ≥ 2 mg/dL, and with exclusions, as described.[3,4,9–11] Clinical features (including stool color), demographics, physical findings, laboratory data, and gallbladder sonography findings were collected prospectively and recorded prior to the ultimate assignment of a clinical diagnosis. Evaluations of neonatal cholestasis were not prescribed and were according to local practice and conducted at local facilities. AATD in PROBE was diagnosed based on a result of ZZ or SZ on either AAT genotype testing or serum protein phenotype testing. None of the participants in this report had biliary atresia or underwent Kasai.

Eligibility for enrollment of AAT participants with native liver in the LOGIC study includes ZZ or SZ serum protein phenotype or genotype, with a corresponding low serum level of AAT protein (defined as less than laboratory wild-type reference range), age birth to 25 years, and evidence of liver disease as defined by documentation of one of the following: neonatal cholestasis (conjugated hyperbilirubinemia and jaundice within the first 3 months of life); $\geq 1.25\times$ the upper limit of normal alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma-glutamyl transpeptidase (GGT); chronic hepatomegaly; clinical findings or complications of PHT or cirrhosis; impaired liver synthetic function; or abnormal liver biopsy histology, other than globular inclusions of AAT, showing liver injury (inflammation, fibrosis, or necrosis), as described.[3,4,9–11] At enrollment, medical history and physical exam were obtained, including a review of available medical records and standard of care labs. Updates in medical history and physical exam were documented at annual follow-up visits, and other data were collected as described.[8] Participants could also enroll in LOGIC status post-liver transplant for a confirmed diagnosis of AAT deficiency, in which case the enrollment evaluation focused on collecting only a limited data set, including AAT phenotype, age at diagnosis, age at transplant, and liver-related complications as far back as the family or medical record could provide, but excluded previous or current physical exam findings and laboratory testing.[3,4,9–11]

Outcomes

Primary outcomes were liver transplant, death, laboratory parameters as described, and the onset of either definite or possible clinically evident portal hypertension (dpCEPH).[4] Definite clinically evident portal hypertension was defined as either clinically evident ascites (treatment with diuretics for a history of or currently present ascites) or endoscopic evidence of esophageal or gastric varices or clinical findings consistent with PHT. The clinical findings indicative of PHT were the presence of both splenomegaly (spleen >2 cm below the costal margin) and thrombocytopenia (platelet count $<150{,}000/\text{mm}^3$). Possible clinically evident portal hypertension was the term designated for when either splenomegaly or thrombocytopenia was present, but not both (definition adapted from the study by Shneider et al[4]). For this analysis, these groups were considered together as dpCEPH. dpCEPH was considered to be absent if none of these criteria were met. Splenomegaly was determined by physical exam, as described.[4] Other outcomes assessed were weight, height, and weight-for-height Z-scores.

Statistical analysis

For the descriptive analyses, number and frequency for categorical characteristics and number, mean and SD or median [first quartile (Q1), third quartile (Q3)], and range (minimum and maximum) are provided to describe participant characteristics, follow-up, and longitudinal patterns for outcomes for the study populations. In most cases, medians (Q1, Q3) are provided for follow-up and laboratory values instead of means and SDs to provide more robust measures of central tendency when sample was small, or the distribution was skewed. The tables present both mean (SD) and median (Q1, Q3) when considered of interest. All observations are included in analyses. Comparisons between groups (ie, with or without neonatal cholestasis) were made using chi-squared or Fisher exact test for categorical variables and two-sample *t* or Wilcoxon tests for continuous variables. Two-sided *p*-values from these tests are provided without adjustment for multiplicity. Group differences and associated 95% CIs are presented to assist with the interpretation of the clinical meaningfulness of group differences. For continuous variables, the group difference was calculated as the mean in the no neonatal cholestasis group—mean in the neonatal cholestasis group. Bootstrap resampling was used to estimate the SEM difference when the normality assumption was not met. For categorical variables, the group difference was calculated as the OR from a logistic model where the reference was the no neonatal cholestasis group.

RESULTS

Characteristics of the PROBE AAT deficiency cohort

Here, we report characteristics of infants diagnosed with SZ or ZZ AAT deficiency, resulting from the initial workup (n = 46, mean age PROBE enrollment 2.1 months, mean age at diagnosis of participants with AATD 2.6 months, Table 1). First, we note there are nearly twice as many male infants as females (30 vs. 16). The cohort is overwhelmingly non-Hispanic White (89%). At diagnosis, the standard biochemical indices were predominantly cholestatic, with median serum TB 6.0 mg/dL, median conjugated bilirubin 3.6 mg/dL, median serum AST 135 IU/L, and median ALT 87 IU/L. As has been reported previously from ChiLDReN in subjects with AAT deficiency,[9] the elevation of GGT in our cohort was common, sometimes of high magnitude, and with a very broad range (interquartile range 316–985). Nine participants (23%) had very high elevations of GGT > 1000 U/L at diagnosis.[9] We note an impactful presenting characteristic that the majority (> 75%) of participants were below the mean for weight, length, and weight-for-length Z-scores, suggesting significant growth disturbance was present even in early life (Table 1). There was only 1 SZ participant in PROBE, which was insufficient to attempt SZ versus ZZ comparisons, except we noted that the SZ participant followed a clinical course not noticeably different from several of the ZZ.

Longitudinal outcomes of the PROBE AAT deficiency cohort

The 46 participants with AATD PROBE were followed up for a median of 3.9 years, according to the local standard of care over the intervals shown in Table 2, and their outcomes were recorded. Neonatal cholestasis resolved in 87%, as defined by TB <1.2 mg/dL, at a median age of 5 months (Q1, Q3: 3, 6). Of the 13% (6 of 46) of participants whose neonatal cholestasis did not resolve, only 3 have gone on to liver transplant thus far during follow-up. However, liver injury continued to progress in a substantial proportion of the cohort despite the resolution of cholestasis. Nineteen of the 46 (41.3%) have developed dpCEPH at a median of approximately 5 months of age. The majority (85%) were treated with ursodeoxycholic acid at some time during their course, although this was according to local care team preference and not controlled, which limited drawing any conclusions. Two participants died at 0.5 and 3.3 years, 1 following a liver transplant. A total of 7 subjects underwent liver transplant (4 who resolved their neonatal cholestasis and three who did not) at a median age of about 4 years. This left 12 subjects, or 26% of the cohort, with evidence of PHT, but without a liver transplant as they entered school age.

Characteristics of participants with AAT deficiency who progressed to liver transplantation

To describe liver transplant outcomes in AAT deficiency as broadly as possible, we examined the characteristics of participants enrolled in PROBE, combined with subjects enrolled in LOGIC who had not been in PROBE (total n = 119). LOGIC included previously transplanted participants with retrospective data gathering (“prevalent” cases n = 78) and participants in LOGIC or PROBE enrolled with native liver, then receiving liver transplantation during the longitudinal observation period (“incident” cases n = 41, Table 3). About half were transplanted before the age of 3 years, but the range was long (range 0.6–16.6 years). Nearly twice as many transplanted participants are males compared with females (incident plus prevalent: 77 males vs. 41 females). We recorded liver-related complications up until the time of transplant and found that some were common, including ascites (70%),

TABLE 1 Demographics and characteristics at enrollment into PROBE study or at the time of AAT diagnosis

	At enrollment into PROBE	At AAT diagnosis
Age (mo)		
N	46	46
Mean (SD)	2.1 (1.1)	2.6 (4.2)
Median (Q1, Q3)	1.9 (1.4, 2.8)	1.8 (1.4, 2.7)
Min, max	0.4, 5.4	0.2, 29.9
Time from consent to diagnosis (d)		
N	46	—
Median (Q1, Q3)	0 (−2, 3)	—
Min, max	−87, 882	—
Sex, n (%)		
N	46	—
Male	30 (65.2)	—
Female	16 (34.8)	—
Race, n (%)		
N	45	—
White	42 (93.3)	—
Black	1 (2.2)	—
Other	2 (4.4)	—
Ethnicity, n (%)		
N	45	—
Hispanic	5 (11.1)	—
Non-Hispanic	40 (88.9)	—
AAT phenotype or genotype, n (%)		
N	46	—
ZZ	45 (97.8)	—
SZ	1 (2.2)	—
Co-enrolled in LOGIC, n (%)	37 (80.4)	—
LOGIC group, n (%)		
N	37	—
1	32 (86.5)	—
2	4 (10.8)	—
3	1 (2.7)	—
AAT level (mg/dL)		
N	41	—
Median (Q1, Q3)	33 (28, 39)	—
Min, max	21, 67	—
Total bilirubin (mg/dL)		
N	45	40
Median (Q1, Q3)	6.3 (4.4, 7.5)	6.0 (4.4, 8.0)
Min, max	0.3, 15.7	0.3, 15.7
Conjugated or direct bilirubin (mg/dL)		
N	44	39
Median (Q1, Q3)	3.6 (3.0, 4.4)	3.4 (2.7, 4.4)
Min, max	0.2, 6.6	0.1, 6.6
AST (U/L)		
N	43	38
Median (Q1, Q3)	139 (91, 190)	135 (83, 178)
Min, max	36, 298	36, 326
ALT (U/L)		
N	44	39
Median (Q1, Q3)	86 (51, 118)	87 (50, 114)
Min, max	3, 190	3, 190
GGT (U/L)		
N	39	35
Median (Q1, Q3)	669 (316, 985)	606 (297, 919)
Min, max	126, 2443	48, 2443
Height/length Z-score		
N	42	38
Median (Q1, Q3)	−1.46 (−2.17, −0.23)	−1.56 (−2.17, −0.65)
Min, max	−5.31, 2.16	−5.31, 2.16
Weight Z-score		
N	43	39
Median (Q1, Q3)	−1.60 (−2.53, −0.80)	−1.69 (−2.62, −0.98)
Min, max	−4.62, 0.56	−4.62, 0.56
Weight-for-height/length Z-score		
N	41	36
Median (Q1, Q3)	−0.85 (−1.59, −0.04)	−0.92 (−1.55, −0.06)
Min, max	−4.59, 3.30	−4.59, 3.30

Note: N = 46.

Abbreviations: AAT, alpha-1-antitrypsin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LOGIC, Longitudinal Observational Study of Genetic Intrahepatic Cholestasis; max, maximum; min, minimum; N, number; PROBE, Prospective Database of Infants with Cholestasis; Q, quartile.

coagulopathy (32%), and varices (26%), but others were less common, including gastrointestinal bleeding (8%), fractures (2%), xanthomas (1%), pruritus (11%), cholangitis (5%), encephalopathy (10%), hepatopulmonary syndrome (5%), and hepatorenal syndrome (1%). Laboratory data that preceded liver transplant in the incident group showed substantial TB elevations with a mean of 10.6 mg/dL and median of 2.9 mg/dL; median AST (209) was greater than ALT (129), which was similar to GGT elevations (108) for the data gathered closest to the date of transplantation. Growth parameters of the incident group were median −0.30 length Z-score and median −0.44 weight Z-score, but a small group was less than −2 Z-score for each, indicating a risk of significant growth retardation was present prior to liver transplant.

Longitudinal outcomes of the incident transplant cohort

Next, we examined factors related to transplant outcomes by analyzing data gathered longitudinally on the incident

TABLE 2 Clinical outcomes and ursodiol use

	Overall N = 46
Follow-up time (y)	
N	46
Median (Q1, Q3)	3.9 (1.8, 6.9)
Min, max	0.0, 14.0
Death, n (%)	2 (4.3)
Age at death (y)	
N	2
Median (Q1, Q3)	1.9 (0.5, 3.3)
Min, max	0.5, 3.3
Transplant, n (%)	7 (15.2)
Age at transplant (y)	
N	7
Median (Q1, Q3)	4.1 (2.5, 7.0)
Min, max	0.4, 7.0
Transplant/death, n (%)	9 (19.6)
Age at transplant/death (y)	
N	9
Median (Q1, Q3)	3.3 (2.5, 6.1)
Min, max	0.4, 7.0
dpCEPH, n (%)	19 (41.3)
Time to dpCEPH (y)	
N	19
Median (Q1, Q3)	0.4 (0.1, 3.6)
Min, max	0.0, 11.5
Resolution of cholestasis (total bilirubin ≤ 1.2 mg/dL)	40 (87.0)
Age at resolution of cholestasis (mo)	
N	40
Median (Q1, Q3)	5 (3, 6)
Min, max	2, 12
Urso use at baseline, n (%)	
N	22
Yes	19 (86.4)
Urso use ever	
N	46
Age at first urso use (mo)	39 (84.8)
N	39
Median (Q1, Q3)	3 (2, 4)
Min, max	1, 37

Note: N = 46.
Abbreviations: dpCEPH, definite or possible clinically evident portal hypertension; urso, ursodiol; max, maximum; min, minimum; N, number; Q, quartile.

cohort. There was a median of 1.5 years of pretransplant participant data and a median of 4 years of post-transplant follow-up (Table 4). We, therefore, compared participants with and without neonatal cholestasis regarding liver transplant and related outcomes (Table 5). Eleven participants without a history of neonatal cholestasis received liver transplants, while 29 transplanted participants had previous neonatal cholestasis. Those without neonatal cholestasis were diagnosed significantly later ($p = 0.003$), at a median age of 7 months (range 0–90) compared with 2 months for those with neonatal cholestasis. Age at liver transplant was also significantly later in the no neonatal cholestasis group ($p = 0.04$) at a median of 7.8 years, compared with 4.1 years in the cholestasis group (Figure 1). After further analysis, we found it was not possible to develop a useful algorithm predictive of severe disease based on cholestasis parameters at diagnosis with the data available (Figure 1). Likewise, Kaplan-Meier curves of time to transplant or death for those with and without neonatal cholestasis are not different (Figure 2, $p = 0.409$). There were no differences in the rate of liver-related complications prior to transplant between the with and without cholestasis groups, with ascites, pruritus, and varices being the most common, as noted above. Both groups showed a similar large male predominance. Likewise, there were no differences between the groups in total or conjugated bilirubin, AST, ALT, or GGT levels at the time of transplant. However, weight Z-score was statistically significantly lower ($p = 0.022$) at transplant in the group with previous neonatal cholestasis, although length and weight-for-length were not statistically different.

DISCUSSION

Here, we report outcomes in a large cohort of young subjects with AAT deficiency from multiple centers in North America. It is especially noteworthy to review data from the PROBE study in which subjects were enrolled and data gathered from the time of presentation with neonatal cholestasis, even before the AAT deficiency diagnosis was made. First, we document how rapidly the diagnosis was made. In most participants, it was at less than 3 months of age, which is consistent with clinicians sending specific testing for the disease early in the workup, as recommended in various pediatric guideline documents, but not always as seen in adult studies.[12] It seems likely that the desire to quickly identify infants with biliary atresia, and to separate them from those that would usually not need a cholangiogram for diagnosis or surgery for treatment was driving testing. Another finding is the male predominance in the population with AAT deficiency neonatal cholestasis. A male predominance, approximately double the number of males to females with severe liver injury in this study, is described in several liver diseases and has been reported previously in some, but not all AAT deficiency cohorts.[2,13–15] This includes more males with overt liver abnormalities in the unbiased birth cohort from Sweden.[16,17]

Other characteristics of interest in the neonatal cholestasis group include the wide range of GGT elevations, with a few subjects with remarkably high levels. Our previous recent report showed that higher GGT was associated with an increased risk of

TABLE 3 Demographics and baseline characteristics by transplant timing

	Incident transplant[a] (N = 41)	Prevalent transplant[a] (N = 78)	All transplants (N = 119)
Demographics			
Age at diagnosis (mo)			
N	41	75	116
Mean (SD)	8 (18)	21 (50)	17 (42)
Median (Q1, Q3)	2 (1, 5)	3 (2, 15)	2 (1, 9)
Min, max	0, 90	0, 244	0, 244
Age at transplant (y)			
N	41	73	114
Median (Q1, Q3)	6.1 (2.2, 9.8)	2.8 (1.3, 5.9)	3.6 (1.3, 7.3)
Min, max	0.3, 16.6	0.4, 16.0	0.3, 16.6
Sex, n (%)			
N	41	77	118
Male	28 (68.3)	49 (63.6)	77 (65.3)
Female	13 (31.7)	28 (36.4)	41 (34.7)
Race, n (%)			
N	40	77	117
White	37 (92.5)	71 (92.2)	108 (92.3)
Black	1 (2.5)	2 (2.6)	3 (2.6)
Other	2 (5.0)	4 (5.2)	6 (5.1)
Ethnicity, n (%)			
N	40	77	117
Hispanic	2 (5.0)	4 (5.2)	6 (5.1)
Non-Hispanic	38 (95.0)	73 (94.8)	111 (94.9)
A1AT phenotype, n (%)			
N	37	74	111
ZZ	35 (94.6)	70 (94.6)	105 (94.6)
SZ	2 (5.4)	4 (5.4)	6 (5.4)
Complications prior to transplant, n (%)			
Bone fractures			
N	28	63	91
Yes	1 (3.6)	1 (1.6)	2 (2.2)
Xanthomatosis			
N	28	63	91
Yes	0	1 (1.6)	1 (1.1)
Pruritus			
N	28	63	91
Yes	6 (21.4)	4 (6.3)	10 (11.0)
Ascites			
N	33	63	96
Yes	20 (60.6)	47 (74.6)	67 (69.8)
Cholangitis			
N	33	63	96
Yes	1 (3.0)	4 (6.3)	5 (5.2)
Coagulopathy			
N	33	63	96
Yes	9 (27.3)	22 (34.9)	31 (32.3)
Varices			
N	33	63	96
Yes	8 (24.2)	17 (27.0)	25 (26.0)

TABLE 3. (*continued*)

	Incident transplant[a] (N = 41)	Prevalent transplant[a] (N = 78)	All transplants (N = 119)
GI bleed			
N	33	63	96
Yes	1 (3.0)	7 (11.1)	8 (8.3)
Encephalopathy			
N	33	63	96
Yes	4 (12.1)	6 (9.5)	10 (10.4)
Hepatopulmonary syndrome			
N	33	63	96
Yes	3 (9.1)	2 (3.2)	5 (5.2)
Hepatorenal syndrome			
N	33	63	96
Yes	1 (3.0)	0	1 (1.0)
Labs prior to transplant			
Total bilirubin (mg/dL)			
N	38	—	38
Median (Q1, Q3)	2.9 (1.7, 17.4)	—	2.9 (1.7, 17.4)
Min, max	0.5, 46.0	—	0.5, 46.0
Conjugated bilirubin (mg/dL)			
N	16	—	16
Median (Q1, Q3)	0.8 (0.0, 5.0)	—	0.8 (0.0, 5.0)
Min, max	0.0, 16.7	—	0.0, 16.7
Direct bilirubin (mg/dL)			
N	16	—	16
Median (Q1, Q3)	5.8 (1.7, 20.0)	—	5.8 (1.7, 20.0)
Min, max	1.0, 28.1	—	1.0, 28.1
Conjugated or direct bilirubin (mg/dL)			
N	31	—	31
Median (Q1, Q3)	2.3 (0.6, 13.3)	—	2.3 (0.6, 13.3)
Min, max	0.0, 28.1	—	0.0, 28.1
AST (U/L)			
N	36	—	36
Median (Q1, Q3)	209 (120, 309)	—	209 (120, 309)
Min, max	31, 7960	—	31, 7960
ALT (U/L)			
N	36	—	36
Median (Q1, Q3)	129 (83, 159)	—	129 (83, 159)
Min, max	21, 3074	—	21, 3074
GGT (U/L)			
N	34	—	34
Median (Q1, Q3)	108 (62, 255)	—	108 (62, 255)
Min, max	16, 726	—	16, 726
Height/length Z-score			
N	33	—	33
Median (Q1, Q3)	−0.30 (−1.98, 0.73)	—	−0.30 (−1.98, 0.73)
Min, max	−3.98, 3.69	—	−3.98, 3.69
Weight Z-score			
N	38	—	38
Median (Q1, Q3)	−0.44 (−1.42, 0.76)	—	−0.44 (−1.42, 0.76)
Min, max	−3.14, 3.06	—	−3.14, 3.06

TABLE 3. (*continued*)

	Incident transplant[a] (N = 41)	Prevalent transplant[a] (N = 78)	All transplants (N = 119)
Weight-for-height/length Z-score			
N	18	—	18
Median (Q1, Q3)	0.17 (−0.15, 0.93)	—	0.17 (−0.15, 0.93)
Min, max	−1.68, 2.22	—	−1.68, 2.22

Note: N = 119.
[a]Incident transplants are defined as occurring during the LOGIC or PROBE study longitudinal observation period. Prevalent transplants are defined as occurring prior to the subject's entry into the LOGIC study.
Abbreviations: A1AT, alpha-1-antitrypsin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; GI, gastrointestinal; LOGIC, Longitudinal Observational Study of Genetic Intrahepatic Cholestasis; max, maximum; min, minimum; N, number; PROBE, Prospective Database of Infants with Cholestasis; Q, quartile; SZ, S and Z alleles; ZZ, Z alleles.

dpCEPH.[9] We will continue to follow the entire native liver LOGIC cohort to better understand the variables involved in early versus late development of end-stage liver disease.[15] We note with concern the impact on the growth of neonatal cholestasis, which may result from impaired fat digestion, a systemic phenomenon of disease and inflammation, or other factors. More studies will be needed, and awareness raised on this risk in this population.

The cohort of liver-transplanted participants is also of interest. Those who did not have neonatal cholestasis follow the same course to transplant, with similar complications as the group that had neonatal cholestasis, but they do so many years later in childhood.[18,19] This questions whether there are other disease-modifying factors at work, such as childhood infections or exposures, that have not yet been identified. There is evidence from model systems of AAT liver disease that episodes of systemic inflammation and medications such as nonsteroidal anti-inflammatory drugs, increase AAT mutant Z protein accumulation in the liver and thereby exacerbate liver disease. A lack of understanding of these factors may pose a problem for how to design clinical trials in this age group.[20] It would be wise for enrollment to consider a history of neonatal cholestasis or a lack thereof. We see that the impact on delay of weight gain is again documented in the transplanted participants with preceding neonatal cholestasis but is not commonly seen in those without preceding neonatal cholestasis, who were significantly older. Weight and growth might also impact trial design or response to therapy. Finally, we note the many participants with documented evidence of PHT who have not progressed to liver transplant (28% of the subjects who presented with neonatal cholestasis). Clinicians should be alert for this type of patient, even though they may have minimal symptoms, and continue to follow them closely to minimize possible PHT-related complications. This group, with no current options other than transplantation, might become a focus of future clinical trials.

TABLE 4 Outcomes and follow-up post-transplant

	Incident transplant[a] (N = 41)
Pretransplant follow-up (y)	
N	41
Median (Q1, Q3)	1.5 (0.3, 3.0)
Min, max	0.0, 7.8
Post-transplant follow-up (years)	
N	25
Median (Q1, Q3)	4.0 (2.4, 6.3)
Min, max	0.0, 8.3
Death, n (%)	1 (2.4)
Time from transplant to death (d)	
N	1
Median (Q1, Q3)	1 (1, 1)
Min, max	1, 1

Note: N = 41.
Incident cohort.
[a]Incident transplants are defined as occurring during the LOGIC or PROBE study longitudinal observation period.
Abbreviations: max, maximum; min, minimum; N, number; Q, quartile.

Despite this large number of participants and much of the data being systematically and longitudinally gathered, our study has important limitations. First, we have used retrospective data from the subject's medical records to study the prevalent liver transplant group, which introduces a higher possibility of missing data due to loss, recall bias, or other factors compared with the longitudinal data gathered during the study for the incident group. Also, there is likely a bias to the tertiary-quaternary sites being referred more severe patients. The high rate of dpCEPH (41%) and liver transplant (15%) in the PROBE participants enrolled when they presented with neonatal cholestasis is higher than in reports of patients with AAT deficiency from other countries and probably more than twice as high as the rate in subjects with neonatal cholestasis from the unbiased Swedish AAT deficiency birth cohort from the 1970s.[16,17] We know from population-based genetic studies that likely most patients with AAT deficiency remain well and undiagnosed in

TABLE 5 Demographics and baseline characteristics by neonatal cholestasis. Incident transplant cohort. N = 40[a]

Characteristics	No neonatal cholestasis (N = 11)	With neonatal cholestasis (N = 29)	Group difference (95% CI)[b]	p[c]
Demographics				
Age at diagnosis (mo)				
N	11	29	—	—
Mean (SD)	20 (27)	4 (10)	16.5 (2.6, 34.1)	0.003
Median (Q1, Q3)	7 (3, 35)	2 (0, 2)	—	—
Min, max	0, 90	0, 56	—	—
Age at transplant (y)				
N	11	29	—	—
Mean (SD)	9.7 (4.7)	6.0 (5.6)	3.7 (0.3, 7.1)	0.04
Median (Q1, Q3)	7.8 (6.0, 14.5)	4.1 (0.9, 8.3)	—	—
Min, max	3.2, 16.6	0.3, 16.5	—	—
Sex, n (%)				
N	11	29		
Male	9 (81.8)	18 (62.1)	2.7 (0.5,15.1)	0.29
Female	2 (18.2)	11 (37.9)	—	—
Race, n (%)				
N	11	28	—	—
White	11 (100.0)	25 (89.3)	[d]	1.00
Black	0	1 (3.6)	—	—
Other	0	2 (7.1)	—	—
Ethnicity, n (%)				
N	10	29	—	—
Hispanic	0	2 (6.9)	[d]	1.00
Non-Hispanic	10 (100.0)	27 (93.1)	—	—
A1AT phenotype or genotype, n (%)				
N	11	29	—	—
ZZ	10 (90.9)	29 (100.0)	[d]	0.27
SZ	1 (9.1)	0	—	—
Complications prior to transplant				
Bone fractures				
N	9	18	—	—
Yes	0	1 (5.6)	[d]	1.00
Xanthomatosis				
N	9	18	—	—
Yes	0	0	[d]	—
Pruritus, n (%)				
N	9	18	—	—
Yes	1 (11.1)	5 (27.8)	3.1 (0.3, 31.3)	0.63
Ascites, n (%)				
N	9	23	—	—
Yes	5 (55.6)	14 (60.9)	1.2 (0.3, 5.9)	0.78
Cholangitis, n (%)				
N	9	23	—	—
Yes	1 (11.1)	0	[d]	0.28
Coagulopathy, n (%)				
N	9	23	—	—
Yes	3 (33.3)	6 (26.1)	0.7 (0.1, 3.7)	0.69
Varices, n (%)				

TABLE 5. (*continued*)

Characteristics	No neonatal cholestasis (N = 11)	With neonatal cholestasis (N = 29)	Group difference (95% CI)[b]	*p*[c]
N	9	23	—	—
Yes	2 (22.2)	5 (21.7)	1.0 (0.2, 6.2)	0.98
GI bleed, n (%)				
N	9	23	—	—
Yes	0	1 (4.3)	[d]	1.00
Encephalopathy, n (%)				
N	9	23	—	—
Yes	1 (11.1)	3 (13.0)	1.2 (0.1, 13.3)	0.88
Hepatopulmonary syndrome, (%)				
N	9	23	—	—
Yes	0	3 (13.0)	[d]	0.54
Hepatorenal syndrome, n (%)				
N	9	23	—	—
Yes	1 (11.1)	0	[d]	0.28
Labs at transplant, n (%)				
Total bilirubin (mg/dL)				
N	11	26	—	—
Mean (SD)	10.0 (13.0)	11.2 (14.2)	−1.2 (−9.7, 8.5)	0.82
Median (Q1, Q3)	2.8 (1.8, 17.6)	3.8 (1.7, 17.4)	—	—
Min, max	1.0, 42.1	0.5, 46.0	—	—
Conjugated bilirubin (mg/dL)				
N	5	11	—	—
Mean (SD)	6.9 (8.5)	2.1 (3.1)	4.8 (−1.8, 11.8)	0.28
Median (Q1, Q3)	2.2 (0.0, 15.6)	0.6 (0.0, 3.0)	—	—
Min, max	0.0, 16.7	0.0, 9.0	—	—
Direct bilirubin (mg/dL)				
N	4	12	—	—
Mean (SD)	8.2 (12.5)	11.4 (10.0)	−3.2 (−13.4, 9.9)	0.61
Median (Q1, Q3)	2.4 (1.5, 14.9)	8.0 (2.7, 20.0)	—	—
Min, max	1.0, 26.9	1.1, 28.1	—	—
Conjugated or direct bilirubin (mg/dL)				
N	9	22	—	—
Mean (SD)	7.5 (9.8)	7.1 (8.9)	0.4 (−6.3, 7.6)	0.92
Median (Q1, Q3)	2.2 (1.0, 15.6)	2.7 (0.6, 9.6)	—	—
Min, max	0.0, 26.9	0.0, 28.1	—	—
AST (U/L)				
N	11	24	—	—
Mean (SD)	929 (2337)	230 (173)	698.3 (−82.0, 215.0)	0.64
Median (Q1, Q3)	207 (128, 380)	208 (108, 309)	—	—
Min, max	91, 7960	31, 877	—	—
ALT (U/L)				
N	11	24	—	—
Mean (SD)	401 (890)	142 (108)	259.6 (−52.2, 819.0)	0.72
Median (Q1, Q3)	126 (79, 168)	124 (80, 153)	—	—
Min, max	64, 3074	21, 496	—	—
GGTP (U/L)				
N	11	22	—	—
Mean (SD)	156 (97)	176 (200)	−19.6 (−124.2, 72.6)	0.43

TABLE 5. (*continued*)

Characteristics	No neonatal cholestasis (N = 11)	With neonatal cholestasis (N = 29)	Group difference (95% CI)[b]	p[c]
Median (Q1, Q3)	120 (77, 266)	95 (49, 215)	—	—
Min, max	25, 294	16, 726	—	—
Height/length Z-score				
N	10	22	—	—
Mean (SD)	0.45 (1.59)	−0.79 (1.82)	1.2 (−0.1, 2.6)	0.07
Median (Q1, Q3)	0.46 (−0.77, 1.12)	−0.57 (−1.99, 0.13)	—	—
Min, max	−1.98, 3.69	−3.98, 3.21	—	—
Weight Z-score				
N	11	26	—	—
Mean (SD)	0.43 (1.20)	−0.66 (1.28)	1.1 (0.2, 1.0)	0.02
Median (Q1, Q3)	0.45 (−0.55, 1.21)	−0.75 (−1.54, 0.06)	—	—
Min, max	−1.06, 3.06	−3.14, 2.13	—	—
Weight-for-height/length Z-score				
N	3	14	—	—
Mean (SD)	0.94 (0.83)	0.24 (0.91)	0.7 (−0.5, 1.9)0.24	—
Median (Q1, Q3)	0.93 (0.12, 1.78)	0.12 (−0.15, 0.69)	—	—
Min, max	0.12, 1.78	−1.68, 2.22	—	—

[a]One subject with incident transplant has neonatal cholestasis status missing.
[b]Chi-square or Fisher exact test for categorical variables and two-sample *t* or Wilcoxon test for continuous variables.
[c]For continuous variables, group difference = mean in no neonatal cholestasis group − mean in neonatal cholestasis group. Bootstrap resampling method to estimate the SEM difference when normality assumption is not met. For categorical variables, group difference = OR from a logistic model (reference group = no neonatal cholestasis).
[d]Not calculated due to small cells.
Abbreviations: A1AT, alpha-1-antitrypsin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGTP, gamma-glutamyl transpeptidase; GI, gastrointestinal; max, maximum; min, minimum; N, number; Q, quartile; SZ, S and Z alleles; ZZ, Z alleles.

childhood. Still, our report is representative in many ways of the patients that clinicians in North America commonly care for, and given these data, it seems wise to continue to follow all ZZ and SZ patients regularly for symptoms and signs of progressive liver disease and possible impending PHT.[13]

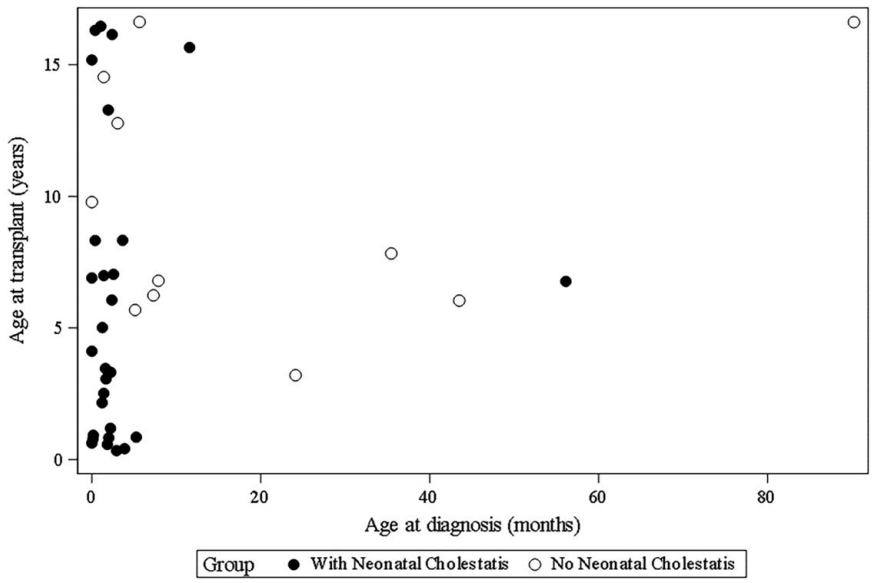

FIGURE 1 Incident transplant cohort: age at diagnosis (months) by age at transplant (years).

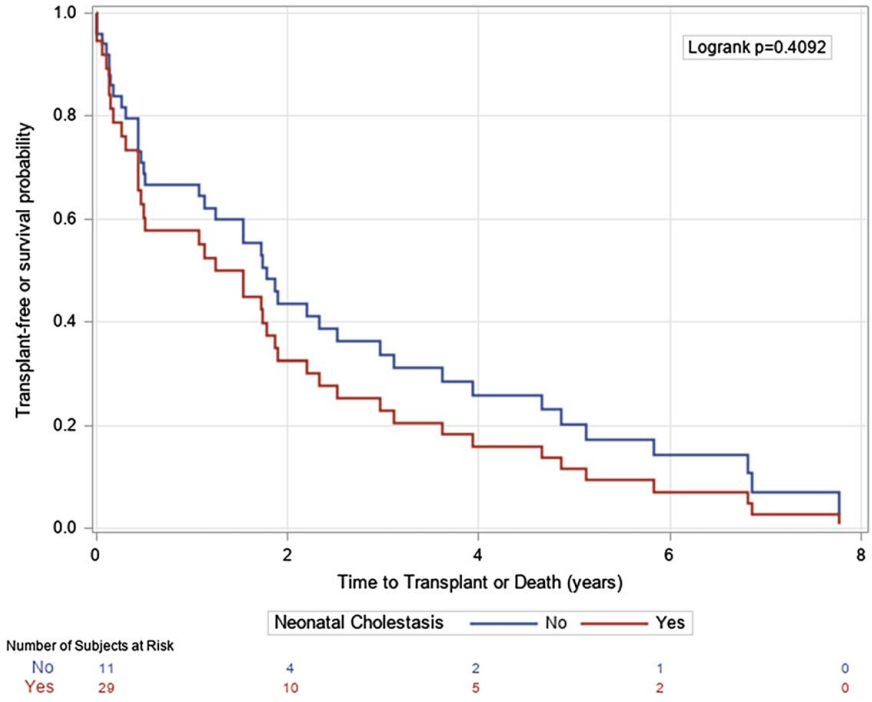

FIGURE 2 Kaplan-Meier curve for time to transplant or death, incident transplant, N = 40.

CONCLUSIONS

We studied 2 specific groups of participants with AAT from ChiLDReN, on which our previous reports have not focused: a unique and extensively documented group of infants with cholestasis enrolled prior to diagnosis and followed longitudinally, and a large group of young participants' status post-liver transplant. We documented a male predominance in those with end-stage liver disease and noted a higher rate of progression to end-stage in those followed at the ChiLDReN centers than in past reports. We also saw that while those with and without preceding neonatal cholestasis are at risk of future PHT, those with neonatal cholestasis can progress more rapidly, and there is a risk of growth disturbance. We will continue to gather longitudinal data on the participants with native livers, with the aim of further defining factors associated with progression to end-stage liver disease. Many new therapeutic trials are pending in adults with this disease, and these data will be useful in designing future studies in younger patients.

AUTHOR CONTRIBUTIONS

Jeffrey Teckman, Philip Rosenthal, Lee M. Bass, JCM, Rosalinda V. Ignacio, and Cathie Spino were involved with study conception, study design, and analysis and interpretation of data; all authors were involved with acquisition of data, drafting the article, and critically revising the article for important intellectual content; and all authors were involved with final approval of the version to be published.

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TR000130 (Children's Hospital Los Angeles, University of Southern California), DK062436 and UL1 TR000150 (Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University), DK103140 (University of Utah), DK103135 (Hospital for Sick Children, Toronto).

CONFLICTS OF INTEREST

Jeffrey Teckman consults and received grants from BioMarin, KorroBio, NeuBase, Takeda, Vertex, and UniQure. He consults for Arrowhead and Intellia. Philip Rosenthal consults and received grants from Albireo. He consults for Audentes, BioMarin, Dicerna, Encoded, and MedinCell and received grants from AbbVie and Gilead. Lee Bass consults and is on the speakers' bureau for Mirum. He consults for AstraZeneca and Albireo and is on the speakers' bureau for Mead Johnson Nutrition. Simon Horslen consults and received grants from Albireo. He consults for iECURE and Alexion and received grants from Mirum. Saul Karpen consults for Albireo/Ipsen, Mirum, Hemoshear and Intercept. Binita Kamath consults and received grants from Mirum and Albireo. She consults for Audentes. Kathleen Loomes consults and received grants from Mirum and Albireo. She consults for Travere. Ronald Sokol advises Mirum, Albireo, and Astellas. Jean Molleston received grants from Cf Foundation, Mirum, Albireo, AbbVie, and Gilead. The remaining authors have no conflicts to report.

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