Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome

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Objectives To assess health-related quality of life (HRQOL) in children with Alagille syndrome (ALGS) in comparison with healthy and other liver disease cohorts, and to identify determinants of HRQOL in patients with ALGS.

Study design Within the Childhood Liver Disease Research Network prospective study of cholestasis, Pediatric Quality of Life Inventory (PedsQL) questionnaires were administered to 70 children with ALGS, 95 children with alpha-1-antitrypsin deficiency (A1ATD), and 49 children with other causes of chronic intrahepatic cholestasis (IHC) aged 5-18 years. Parent proxy PedsQL scores were recorded for children aged 2-18 years (98 ALGS, 123 A1ATD, and 68 IHC).

Results Mean ages and total bilirubin (mg/dL) were ALGS 9.4 years; 4.4, A1ATD 9.5 years; 0.7, and IHC 10.3 years; 2.9. ALGS child PedsQL scores were lower than in healthy children and children with A1ATD (mean 73 vs 83; $P = .001$). Children with ALGS and IHC were similar, except in physical scores (73 vs 79; $P = .05$). Parents of children with ALGS perceived their children to have worse HRQOL than A1ATD ($P \leq .001$) and marginally lower compared with IHC. Univariate analysis revealed ALGS child-reported scores were positively associated with better growth and inversely with total bilirubin. Growth failure, elevated international normalized ratio, and an intracardiac defect were predictive of poor parental scores ($P \leq .05$). In multivariate analysis, only weight z-score remained significant for child- and parent-reported scores.

Conclusions HRQOL is impaired in children with ALGS compared with healthy and children with A1ATD, similar to children with IHC and is associated with growth failure, which is a potentially treatable cause of impaired HRQOL. *(J Pediatr 2015;167:390-6)*.

Alagille syndrome (ALGS) is an autosomal dominant disorder that affects the liver, heart, eyes, face, skeleton, kidneys, and vasculature.[1,2] Children with chronic disease in any one of these systems alone may have impairment of their health-related quality of life (HRQOL), however, investigations of HRQOL in ALGS, as well as other causes of chronic pediatric liver disease, have been limited. Most studies have focused on HRQOL in recipients of liver transplant (LT)[3-9] or biliary atresia[10] and have demonstrated that pediatric recipients of LT have lower HRQOL outcomes than healthy children. There is scant literature regarding HRQOL in specific pediatric liver diseases and very few patients with ALGS have been captured in the transplant studies.

ALGS has unique manifestations that may affect HRQOL. The cholestasis-related pruritus of ALGS is among the most severe of all liver disease resulting in cutaneous mutilation and disrupted sleep and school activities. Children with cholestasis and ALGS often have disfiguring xanthomas, and linear growth

A1ATD	Alpha-1-antitrypsin deficiency
ALGS	Alagille syndrome
HRQOL	Health-related quality of life
ICC	Intraclass correlation coefficient
IHC	Chronic intrahepatic cholestasis
INR	International normalized ratio
LOGIC	Longitudinal Study of Genetic Causes of Intrahepatic Cholestasis
LT	Liver transplant
PedsQL	Pediatric Quality of Life Inventory
PFIC	Progressive familial intrahepatic cholestasis
QOL	Quality of life

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retardation, poor weight gain, and decreased bone mineral density are common. Finally, significant cardiac involvement or renal dysfunction may independently impact exercise tolerance and school attendance. As each of these factors may impact HRQOL across multiple domains, there is a rationale for studying HRQOL in ALGS.

One prior study of HRQOL in ALGS utilized the Child Health Questionnaire - Parent Form 50 questionnaire. This documents parental responses only[11] but provides preliminary insight into the problem. Parents of children with ALGS reported substantially lower HRQOL than parents of healthy children. Significant cardiac disease, a mental health diagnosis, and sleep problems were associated with lower Child Health Questionnaire scores. These data reinforce the need to systematically characterize HRQOL in ALGS.

The objectives of the current study were to capitalize on a large ongoing prospective multicentered study of childhood cholestatic liver diseases, further characterize HRQOL in ALGS, and identify its determinants. We compared HRQOL in children with ALGS with liver disease to previously published normative data, and to 2 other groups of pediatric liver diseases, one with minimally cholestatic chronic liver disease, alpha-1-antitrypsin deficiency (A1ATD), and one that included children with other forms of chronic intrahepatic cholestasis (IHC) including patients with progressive familial intrahepatic cholestasis (PFIC). The significance of understanding HRQOL and its determinants in ALGS lies in identifying treatable causes of impaired HRQOL.

Methods

This is a cross-sectional study of HRQOL in a cohort of patients with ALGS with liver disease. Subjects in this study were enrolled in the Longitudinal Study of Genetic Causes of Intrahepatic Cholestasis (LOGIC) protocol organized under the Childhood Liver Disease Research Network, a National Institute of Diabetes and Digestive and Kidney Diseases/National Institutes of Health-funded network of 16 pediatric academic medical centers across North America. This study was approved by Institutional Review Boards at each center, and informed consent was obtained from parents/guardians or subjects 18 years or older, and assent from children 7 years and older.

LOGIC is a longitudinal observational study of the natural history of several genetic causes of intrahepatic cholestasis, including ALGS, A1ATD, and PFIC. Defined data elements are collected in a prescribed fashion at yearly intervals for up to 10 years, or until death. Pertinent data about past history including major illness, hospitalizations, and surgery, along with growth parameters and standard laboratory evaluations are recorded annually. Upon enrollment into the study, and annually thereafter, the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scale is administered to children ages 5 and older and to the parents of children 2-18 years of age.[12]

Study subjects were between 2 and 18 years of age, had not undergone liver transplantation, had confirmed ALGS, A1ATD, or IHC by set diagnostic criteria, and had evidence of liver disease. Cholestasis was defined by either fasting total serum bile acid greater than 3 times the upper limit of normal for age; direct bilirubin >2 mg/dL; fat-soluble vitamin deficiency otherwise unexplainable; gamma glutamyl transpeptidase greater than 3 times the upper limit of normal for age; and/or intractable pruritus explainable only by liver disease.

Subjects were confirmed as ALGS by standard clinical criteria and/or the presence of a disease-causing mutation in *JAGGED1* or *NOTCH2*. The clinical criteria were at least 3 of the following: bile duct paucity on liver biopsy, heart murmur, or cardiac anomaly; posterior embryotoxon or other anterior chamber defect; butterfly vertebrae; and characteristic facial features and renal anomalies. Patients with A1ATD had low alpha-1 antitrypsin concentrations, and PIZZ or PISZ phenotype or genotype, and evidence of liver disease. Patients with IHC were defined by biochemical evidence of cholestasis for greater than 6 months, or 2 mutant alleles of *ATP8B1*, *ABCB11*, or *ABCB4*, without another definable cause of cholestasis. By definition, this group of patients was heterogeneous with broad inclusion criteria to capture those with unknown causes of PFIC and others with chronic cholestasis for which the genetic cause was yet to be identified. At the time of data analysis, the total number of patients for each disease in LOGIC were ALGS: n = 146; IHC: n = 126; and A1AT: n = 169.

Measurement of HRQOL

The PedsQL 4.0 Generic Core Scale (PedsQL) is a validated, 23-item modular instrument designed to measure HRQOL in children and adolescents. The PedsQL includes parallel child self-report and parent proxy report versions. The PedsQL assesses child HRQOL across 4 domains: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning. The PedsQL also yields 3 summary scores: Total Scale Score, Physical Health Summary, and Psychosocial Health Summary.[12] Items are reverse scored and linearly transformed to a scale of 0-100, with higher scores indicating better HRQOL. The published validation study identified a value 1 SD below the population mean for the PedsQL Total Scale Score (69.7 for child self-report and 65.4 for parent proxy) as a threshold score for an at-risk status for impaired HRQOL relative to the population sample.[13] HRQOL scores were examined by age group and in aggregate for both child self-report and parent proxy report.

Statistical Analyses

Mean and median PedsQL 4.0 Generic Core Scale and summary scores were calculated for the ALGS, A1ATD, and IHC cohorts. Wilcoxon 2-sample tests were used to compare scores between patients with ALGS and A1ATD, and then between patients with ALGS and IHC. Differences in mean scores and effect sizes were calculated to determine the magnitude of difference by subtracting the ALGS mean from the A1ATD or IHC mean and then dividing by the pooled SD.[14] Aggregate data including mean and SD for the healthy population were cited from the literature.[13] Effect sizes were calculated by subtracting the ALGS mean from the