# Neurodevelopmental Outcome of Young Children with Biliary Atresia and Native Liver: Results from the ChiLDReN Study

Vicky L. Ng, MD[1], Lisa G. Sorensen, PhD[2], Estella M. Alonso, MD[3], Emily M. Fredericks, PhD[4], Wen Ye, PhD[5], Jeff Moore, MS[5], Saul J. Karpen, MD, PhD[6], Benjamin L. Shneider, MD[7], Jean P. Molleston, MD[8], Jorge A. Bezerra, MD[9], Karen F. Murray, MD[10], Kathleen M. Loomes, MD[11], Philip Rosenthal, MD[12], Robert H. Squires, MD[13], Kasper Wang, MD[14], Ronen Arnon, MD[15], Kathleen B. Schwarz, MD[16], Yumirle P. Turmelle, MD[17], Barbara H. Haber, MD[11], Averell H. Sherker, MD[18], John C. Magee, MD[19], and Ronald J. Sokol, MD[20], and the Childhood Liver Disease Research Network (ChiLDReN)*

**Objectives** To assess neurodevelopmental outcomes among participants with biliary atresia with their native liver at ages 12 months (group 1) and 24 months (group 2), and to evaluate variables predictive of neurodevelopmental impairment.

**Study design** Participants enrolled in a prospective, longitudinal, multicenter study underwent neurodevelopmental testing with either the Bayley Scales of Infant Development, 2nd edition, or Bayley Scales of Infant and Toddler Development, 3rd edition. Scores (normative mean = 100 ± 15) were categorized as ≥100, 85-99, and <85 for $\chi^2$ analysis. Risk for neurodevelopmental impairment (defined as ≥1 score of <85 on the Bayley Scales of Infant Development, 2nd edition, or Bayley Scales of Infant and Toddler Development, 3rd edition, scales) was analyzed using logistic regression.

**Results** There were 148 children who completed 217 Bayley Scales of Infant and Toddler Development, 3rd edition, examinations (group 1, n = 132; group 2, n = 85). Neurodevelopmental score distributions significantly shifted downward compared with test norms at 1 and 2 years of age. Multivariate analysis identified ascites (OR, 3.17; $P = .01$) and low length z-scores at time of testing (OR, 0.70; $P < .04$) as risk factors for physical/motor impairment; low weight z-score (OR, 0.57; $P = .001$) and ascites (OR, 2.89; $P = .01$) for mental/cognitive/language impairment at 1 year of age. An unsuccessful hepatoportoenterostomy was predictive of both physical/motor (OR, 4.88; $P < .02$) and mental/cognitive/language impairment (OR, 4.76; $P = .02$) at 2 years of age.

**Conclusion** Participants with biliary atresia surviving with native livers after hepatoportoenterostomy are at increased risk for neurodevelopmental delays at 12 and 24 months of age. Those with unsuccessful hepatoportoenterostomy are >4 times more likely to have neurodevelopmental impairment compared with those with successful hepatoportoenterostomy. Growth delays and/or complications indicating advanced liver disease should alert clinicians to the risk for neurodevelopmental delays, and expedite appropriate interventions. *(J Pediatr 2017;■■:■■-■■).*

**Trial registration** Clinicaltrials.gov: NCT00061828 and NCT00294684.

Biliary atresia is the most common cause of chronic progressive liver disease in children, manifesting as cholestatic jaundice shortly after birth. It results from an inflammatory and fibrosing obstruction of extrahepatic bile ducts and abnormalities of the intrahepatic bile ducts.[1] The primary treatment is

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| Bayley-III | Bayley Scales of Infant and Toddler Development, 3rd edition |
| BSID-II | Bayley Scales of Infant Development, 2nd edition |
| ChiLDReN | Childhood Liver Disease Research Network |
| HPE | Hepatoportoenterostomy |
| PROBE | Prospective Database of Infants with Cholestasis |
| START | Steroids in Biliary Atresia Randomized Trial |
| TB | Total bilirubin |

Detailed affiliations available at www.jpeds.com (**Appendix 1**).

*List of additional members of the Childhood Liver Disease Research Network (ChiLDReN) is available at www.jpeds.com (**Appendix 2**).

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surgical hepatoportoenterostomy (HPE) performed as early as possible in an attempt to reestablish biliary flow.[2] Despite surgical treatment, most patients require liver transplant in childhood,[3] but survival with native liver into school age[4] and adulthood[5-8] is achievable, and understanding the challenges these patients may encounter at the earliest phase possible is key. A recent prospective study of infants with biliary atresia demonstrated that failure to achieve a serum total bilirubin (TB) level of <2.0 mg/dL in the first 3 months after HPE is associated with increased risk of various medical complications, including ascites, coagulopathy, and failure to thrive.[9] However, neurodevelopmental outcomes were not evaluated. Prior single-center reports describing neurodevelopmental functioning in infants with biliary atresia before liver transplantation[5-8] were limited by small samples. Neurodevelopmental data from a large, contemporaneous, multicenter cohort of young patients with biliary atresia with native liver followed longitudinally can better inform intervention strategies aimed at improving overall outcomes for this population.

The Biliary Atresia Research Consortium was established in 2002 by the National Institutes of Health to improve understanding of the etiology of biliary atresia, its natural history, and clinical outcomes, and to develop interventional strategies to improve outcomes. The Biliary Atresia Research Consortium was expanded into the Childhood Liver Disease Research Network (ChiLDReN) in 2009. In this prospective, multicenter study, neurodevelopmental outcomes at 1 and 2 years of age were assessed in a cohort of children with biliary atresia who were alive with a native liver and followed longitudinally in ChiLDReN. We hypothesized that patients with biliary atresia with their native livers at 1 and 2 years of age would exhibit significant neurodevelopmental delays and that specific demographic and clinical variables would be predictive of worse neurodevelopmental outcomes.

## Methods

Study participants were infants with biliary atresia enrolled in the ChiLDReN's Prospective Study of Infants and Children with Cholestasis (PROBE) Protocol (Clinicaltrials.gov: NCT00061828) between July 1, 2004, and November 1, 2012, who underwent HPE at a ChiLDReN site. Informed consent was obtained from parents or guardians and the protocol was carried out under institutional review board approval. A subset of these infants with biliary atresia with a birth weight of >2 kg was co-enrolled in the Steroids in Biliary Atresia Randomized Trial (START), a prospective, randomized double-blinded, placebo-controlled trial of corticosteroids as adjunctive therapy following HPE for biliary atresia (Clinicaltrials.gov: NCT00294684).[10] Exclusion criteria for this present study included a birth weight of ≤2000 g, acute liver failure, previous hepatobiliary surgery (other than HPE), sepsis, hypoxia, shock, malignancy, primary hemolytic disease, parenteral nutrition-associated cholestasis, extracorporeal membrane oxygenation–associated cholestasis, or liver transplantation.

### Data Collection

Data were collected prospectively and entered into a centralized database. Baseline data included patient demographics, medical history (age at HPE, the presence of biliary atresia splenic malformation syndrome [asplenia or polysplenia], family history, and laboratory studies).[9] START randomization group (START steroid or START placebo) or PROBE only assignment were also recorded. Research visits were scheduled 1, 2, 3, and 6 months after HPE, and then at 12, 18, and 24 months of age. Longitudinal data included anthropometry measures, liver biochemical values, and interval history of ascites, cholangitis, spontaneous bacterial peritonitis, gastrointestinal bleeding, and nasogastric feeding within the preceding year. Response to HPE was dichotomized into 2 groups based on serum TB levels in the first 3 months after HPE.[9] "Unsuccessful HPE" was defined for those patients never achieving a TB of <2.0 mg/dL (34.2 μmol/L) in the first 3 months after HPE. Successful HPE was defined for those patients having any TB of <2.0 mg/dL (34.2 μmol/L) within the first 3 months after HPE. neurodevelopmental testing was performed at 1 and 2 years of age (±2 months).

### Neurodevelopmental Assessment Measures

The Bayley Scales of Infant Development, 2nd edition (BSID-II), was used to assess neurodevelopmental outcomes through January 2010.[11] Starting in February 2010, all participants who were new to the study completed the updated Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III).[12] However, participants previously tested with the BSID-II at group 1, were retested with the BSID-II version at 2 years of age to be consistent. Both versions are normed for use between patients at 1 and 42 months of age, and involve a standard series of developmental play tasks that are organized into scales yielding standardized scores (mean = 100 ± 15). The Bayley-III improved on the BSID-II with significant changes in test structure, updated norms, and improved psychometrics. Participants assessed with the BSID-II completed the "mental" and "physical" scales; those assessed with the Bayley-III completed "cognitive," "language," and "motor" scales.

### Statistical Analyses

We used descriptive statistics to report continuous and categorical neurodevelopmental outcomes, and all demographic and other clinical characteristics. The 1-sample *t* test was used to determine whether the mean Bayley scores in our sample were lower than the test norms (100 ± 15). Domain scores for each Bayley version (BSID-II—physical/mental; or Bayley-III—motor/cognitive/language) were categorized as ≥100 (z-score ≥ 0), 85-99 (z-score between 0 and −1), and <85 (z-score < −1). The $\chi^2$ test was used to compare the distribution of Bayley scores in the study cohort in these 3 bins to the normal population. $P \leq .05$ was considered statistically significant.

Because of the significant changes to the construction and content of the scales, BSID-II and Bayley-III scores are only modestly correlated and are not equivalent. We combined results from the 2 Bayley versions to derive neurodevelopmental out-



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