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Long-Term Neurodevelopmental Outcomes in Children with Biliary Atresia

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Objective To assess long-term neurodevelopmental outcomes in school-aged children with biliary atresia.
Study design All Dutch children (6-12 years of age) diagnosed with biliary atresia were invited to participate in this study. We used validated neurodevelopmental tests to assess motor skills and cognition, and questionnaires to assess behavior. Scores were compared with the Dutch norm population, by means of 1-sample tests. Results are given as number and percentage or mean ± SD.
Results We included 46 children, with a median age of 11 years (range, 6-13 years); 36 children had undergone a liver transplantation (78%). Twelve children (26%) received special education (vs 2.4% in the norm population; $P < .01$). Motor outcomes were significantly affected compared with the norm population ($P < .01$), with 25% normal (vs 85%), 25% borderline (vs 10%), and 50% low scores (vs 5%). Total IQ was lower in patients with biliary atresia, compared with the norm population (91 ± 18 vs 100 ± 15; $P < .01$). There were no significant differences in test scores between children with native liver and after liver transplantation.
Conclusions School-aged children with biliary atresia show neurodevelopmental impairments compared with the norm population, especially in motor skills. Our data strongly warrant evaluation of neurodevelopmental intervention programs to assess whether long-term outcomes could be improved. *(J Pediatr 2020;217:118-24)*.

Biliary atresia is characterized by obliteration and fibrosis of bile ducts, resulting in obstructive cholestasis. It is surgically treated by re-establishing the continuity between the portal bile ducts and the intestine via a Kasai portoenterostomy (KPE). Despite a successful operation, however, liver cirrhosis is inevitable in most patients, making biliary atresia the leading indication for liver transplantation in children.[1-3]

Adequate neurodevelopment is essential for daily functioning and school performance. Because early childhood is a time of critical brain growth, severe liver diseases during this specific age period could interfere with neurodevelopment.[4] In addition to the liver disease itself, other factors related to biliary atresia such as surgery, exposure to immunosuppressant treatments, and repeated general anesthesia in early childhood are possibly related to impaired neurodevelopment.[5-7] Moreover, growth deficits and impaired nutritional status may influence the developing brain.[4,8] This could result in impaired neurodevelopmental outcomes in several areas of neurodevelopment, such as cognition, behavior, and motor outcome.[4] Studies on the neurodevelopment of children with chronic disease are needed to understand the nature of these impairments.[9] Still, little is known about the neurodevelopmental sequelae of biliary atresia and possible risk factors for impaired neurodevelopmental outcomes. Results from the Childhood Liver Disease Research Network showed that infants with biliary atresia, surviving with native liver, had impaired neurodevelopmental outcomes at 12 and 24 months of age.[10] However, studies on long-term neurodevelopmental outcomes, exclusively including children with biliary atresia, are scarce. Especially data on school performance and motor skills are lacking. Therefore, the first aim of this study was to assess long-term neurodevelopmental outcomes in Dutch children with biliary atresia at school age: to determine which areas of neurodevelopment are affected and to what degree. The second aim was to identify risk factors associated with impaired neurodevelopmental outcomes.

Methods

In The Netherlands, the care for all infants with congenital liver disease is centralized in our center. Children were selected using the Dutch nationwide database known as Netherlands Study group of Biliary Atresia, the NeSBAR. All parents and guardians of school-aged children aged 6-12 years at time of invitation, who have been diagnosed with biliary atresia, were asked to participate in this

KPE	Kasai portoenterostomy
NeSBAR	Netherlands Study group of Biliary Atresia

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Portions of this study were presented at the International Liver Transplantation Society (ILTS) Annual International Congress, May 17, 2019, Toronto, Canada; at the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Annual Meeting, June 7, 2019, Glasgow, Scotland; and at the British Association of Paedatric Surgeons (BAPS) Congress, July 3, 2019, Nottingham, United Kingdom.

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study. We choose to include all eligible children with biliary atresia, including children with biliary atresia who were born prematurely and children with a history of intracranial hemorrhage, to provide a complete overview of this patient group. The inclusion period spanned from 2015 to 2018. All children had undergone a KPE between 2002 and 2012, in 1 of the 7 Dutch academic pediatric surgical centers that performed this type of surgery at that time. Exclusion criteria for this study were insufficient command of the Dutch language or no child assent. This study was carried out in accordance with the Declaration of Helsinki and approved by the ethics committee (METc UMCG 2011/185).

Data Collection

After obtaining written informed consent of both parents or guardians, and of children of 12 years of age, children were scheduled for a neurodevelopmental assessment. A history was taken for each child, including whether the child had study delay or attended special education and whether the child had received neurodevelopmental intervention (physiotherapy, speech language therapy, psychology). For each child, the following measures were reported: birth weight, history of intracranial hemorrhage, biliary atresia splenic malformation syndrome (yes/no), age at KPE, clearance (serum bilirubin concentration of <20 μmol/L within 6 months after KPE; yes/no), highest bilirubin level before KPE and during screening for liver transplantation, liver transplantation (yes/no), age at liver transplantation, major complication after liver transplantation, minimum total times of general anesthetics, already diagnosed psychomotor delay (yes/no), level of education, history of neurodevelopmental intervention, as well as history of growth failure (SD <2) and growth and weight Z-scores at time of test assessment. In addition, demographic information on parents was reported, such as ethnicity and level of education.

Neurodevelopmental Outcome Measures

We used a validated test battery for the patient, and parental questionnaires, to assess neurodevelopmental outcomes. The selected tests and questionnaires are widely used in neuropsychology, both in The Netherlands, as well as worldwide.[4] Multidimensional data on motor skills, cognition, behavior, and social-emotional development, were assessed by 2 trained test assistants. The Movement Assessment Battery for Children was applied to assess motor skills.[11] To assess cognitive outcomes, we used subtests of the Wechsler Intelligence Scale for Children, third edition, in Dutch, because the fourth edition was not available in Dutch (total IQ, verbal IQ, and performance IQ).[12] In addition, we used the Test of Everyday Attention for Children (selective attention and inhibition control), Auditory Verbal Learning Test (auditory memory), Beery-Buktenice Developmental Test of Visual-Motor Integration, 6th edition (visuomotor integration), Test of Visual Perceptual Skills, 3rd edition (visual-perceptual abilities), and for children >8 years of age also the Behavioural Assessment of the Dysexecutive Syndrome for Children (executive functioning; planning and strategy formation).[13-17] The psychometric qualities of all tests are satisfactory.[18-24] Moreover, to obtain additional information about behavior and executive functioning of the children, the following parental questionnaires were used: the attention deficit hyperactivity disorder (ADHD) questionnaire (ADHD-vragenlijst in Dutch), the Child Behavior Checklist for Children aged 6-18 (internalizing and externalizing problems), and the Behavior Rating Inventory of Executive Function questionnaire (executive functions).[25-27] Children with a known psychomotor delay, who were not able to perform neurodevelopmental tests, were included in categorical variables as a "low" score.

Statistical Analyses

Data on the measured parameters were investigated for their distribution using standard descriptive analyses. When data were not normally distributed, the parameter was described by either medians and its corresponding range of mininum to maximum, or percentiles for categorical data. Raw scores were transformed to age and sex adjusted percentiles or Z-scores based on norm data, as supplied by the test manuals.[11-17,25-27] To provide one outcome for the 2 subtests of the Test of Visual Perceptual Skills, 3rd edition, the mean Z-score was calculated. In addition, scores were classified as normal (IQ of >85; percentile >15), borderline (IQ of 70-85; percentile 6-16), or low (IQ of <70; percentile <6), based on the Dutch norm population, in accordance with the test manual.[9-18] IQ scores and Z-scores were compared with the norm population (IQ 100 $\pm$ 15; Z-score 0 $\pm$ 1) by means of either the 1-sample t test for normally distributed data, or the 1-sample Kolmogorov-Smirnov test for non-normally distributed data. The categorized outcomes were compared with the norm population using the χ^2 or the Fisher exact test.

To investigate the relation between total IQ or motor score percentile and risk factors, either the independent sample t test for dichotomous variables or correlation analysis for continuous variables was performed in addition to univariable regression analyses. Risk factors with a P value of <.20 were included in a multivariable backward stepwise regression analysis. Linear regression analysis was used for total IQ. Because data on motor skills did not fulfil assumptions for linear regression, a logistic regression model was built for low motor scores. Results were checked after multiple imputations (overall missing data 3%). Effect sizes were calculated by describing the mean difference in SD of children with biliary atresia with that of the general populations [$(\text{mean}^{\text{biliary atresia}} - \text{mean}^{\text{norm population}})/\text{SD}$].[28] Effect sizes and study power were calculated using the G*Power program, version 3 (Department of Psychology, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). An observed P value of <.05 was considered statistically significant. Data was analyzed using IBM SPSS version 23 (SPSS, Inc, Chicago, Illinois).

Results

Within a timeframe of 4 years (2015-2018), 59 school-aged children with biliary atresia in The Netherlands were contacted for inclusion after identification through the Netherlands Study group of Biliary Atresia database (**Figure 1**; available at www.jpeds.com). Of 59 contacted children, 46 (78%) were included. Reasons for exclusion were insufficient mastery of the Dutch language (n = 1), emigration (n = 1), currently being tested for a possible transfer to special education (n = 1), no show (n = 1), or no informed consent (n = 9). Of the 46 included children, 3 (7%) were not able to perform the neurodevelopmental tests owing to already diagnosed psychomotor delay. One of these children suffered from meningitis in the first months after birth; however, the cause of the psychomotor delay remained uncertain. Patient characteristics are listed in **Table I**. Five children were born preterm (11%), of whom 1 child was born at <35 weeks postmenstrual age.

Table I. Patient characteristics

Patient characteristics	n = 46	No. (%), mean ± SD, or median (range)
Male sex	46	27 (59)
Gestational age (weeks)	43	39 (30 to 42)
Caucasian	45	35 (78)
Highest household education	38	
High		24 (63)
Intermediate		10 (26)
Low		4 (11)
Follow-up		
Age at follow-up (years)	46	11 (6 to 13)
Median height (SD)	40	0.19 (−3.5 to 1.9)
Median weight for height (SD)	36	0.58 (−1.7 to 2.6)
Education child	46	
Formal education		27 (59)
Formal education with additional support		7 (15)
Special education		12 (26)
History of neurodevelopmental intervention	46	21 (46)
Medical history		
Intracranial hemorrhage	46	8 (17)
BASM	46	2 (4)
Diagnosed psychomotor delay	46	3 (7)
History of growth failure (SD<2)	42	20 (48)
KPE		45 (98)
Age at KPE (days)	45	60 ± 18
KPE <60 days of life	46	24 (52)
Total bilirubin serum level before KPE*	44	179 (78 to 339)
Direct bilirubin serum level before KPE†	42	135 (41 to 308)
Successful KPE‡	45	12 (27)
Liver transplantation		36 (78)
Age at liver transplantation (months)	35	11 (4 to 149)
Time since liver transplantation (years)	35	9 (1 to 12)
Living related liver transplantation	33	12 (36)
Hospitalization after liver transplantation (days)	32	33 (12 to 159)
Major complication§	33	23 (70)
Total bilirubin level at screening liver transplantation*	35	161 (12 to 584)
Direct bilirubin level at screening liver transplantation†	34	133 (4 to 427)

BASM, biliary atresia splenic malformation.
Normal values: *<17 μmol/L, †<5 μmol/L, ‡bilirubin level <20 μmol/L (1.17 g/dL) within 6 months after KPE, and §grade III-V of the Clavien-Dindo classification.

Eight children (17%) presented with an intracerebral hemorrhage secondary to vitamin K deficiency, before the diagnosis of biliary atresia.[29,30] At time of test assessment, 21 children (46%) had received neurodevelopmental interventions at some point in life, in the form of physiotherapy (n = 8 [17%]), speech language therapy (n = 10 [22%]), psychology (n = 7 [15%]), or other services (n = 3 [7%]). Up to 40% of these children received interventions for a duration of >1 year, of whom 25% received intervention for >2 years. Household education was somewhat higher in the study population than in the general Dutch population, although not statistically significant (63% high education vs 45% in the general population of Dutch working citizens aged 25-45; $P < .33$).[31]

School Performance

Of the 46 children, 27 (59%) received formal education, 7 (15%) received formal education with additional support, and 12 children received special education (26% vs 2.4% in the Dutch norm population; $P \leq .01$).[32] Of the 34 children receiving formal education, 8 children (24%) had a study delay of ≥1 years.

Motor Outcomes

Motor outcome was significantly lower ($P < .001$) compared with the norm population, with 25% normal (vs 85%), 25% borderline (vs 10%), and 50% low scores (vs 5%). All tested motor domains were significantly affected, ie, fine skills, ball skills, and balance. **Figure 2** shows the motor outcomes expressed in normal, borderline, and low scores. **Table II** (available at www.jpeds.com) provides effect sizes and study power.

Cognitive Outcomes

The mean total IQ of children with biliary atresia was 91 ± 18, and significantly lower ($P = .002$) than in the Dutch

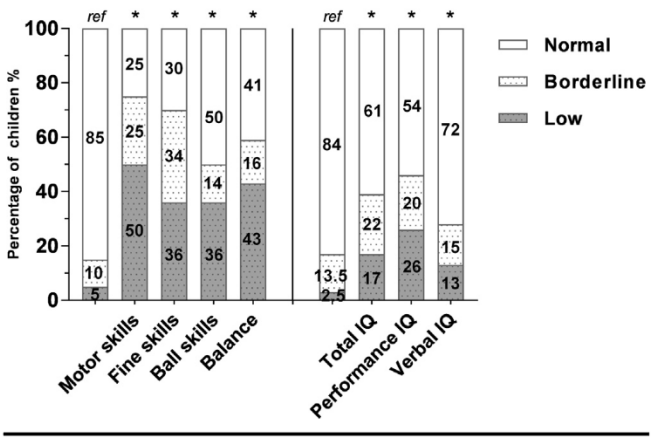

Figure 2. Distribution of motor scores (n = 44) and IQ (n = 46) in children with biliary atresia compared to reference values (ref) based on the Dutch norm population. *$P < .001$ using the Fisher exact test.

norm population (mean IQ, 100 ± 15). The mean performance IQ was 88 ± 18 ($P < .001$), and the mean verbal IQ was 96 ± 17 ($P = .09$). When divided into normal, borderline, and low scores, children scored significantly lower when compared with the norm population (**Figure 2**).

In other cognitive domains, children with biliary atresia scored significantly lower on both subtests of attention (selective attention, Z-score, −0.64; $P = .001$, and inhibition control, Z-score, −0.41; $P = .01$), visuomotor integration (Z-score, −0.59; $P < .001$), perceptual ability (Z-score, −0.40; $P = .01$), and planning (Z-score, −0.42; $P = .002$). There were no significant differences in verbal short- and long-term memory, or strategy formation. Age and sex adjusted Z-scores, based on the Dutch norm population, are displayed in **Figure 3**.

Behavioral Outcomes

The parent-reported questionnaires showed significantly more behavioral problems in biliary atresia children, compared with the norm population (**Table III**). Parents of children with biliary atresia reported a significantly higher prevalence of overall behavioral difficulties (23% vs 2%; $P < .001$), attentional problems (10% vs 5%; $P = .03$), and hyperactivity (18% vs 5%; $P = .003$). There were no significant differences in the impulsivity domain or in executive functioning.

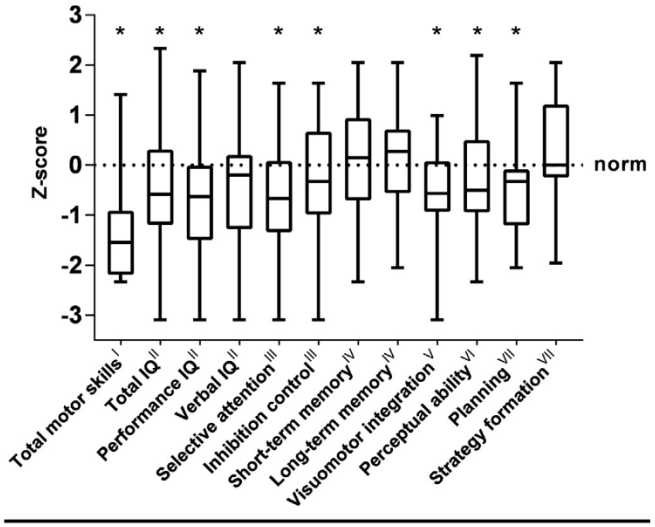

Figure 3. Boxplot of (age and sex adjusted) Z-scores of neurodevelopmental outcomes in children with biliary atresia compared with the Dutch norm population (Z-score, 0; SD, 1). *$P < .05$ using the 1-sample Kolmogorov Smirnov test. [I]Movement Assessment Battery for Children (n = 42), [II]Wechsler Intelligence Scale for Children, third edition, in Dutch (n = 43), [III]Test of Everyday Attention for Children (n = 42), [IV]Auditory Verbal Learning Test (n = 41), [V]Beery-Buktenice Developmental Test of Visual-Motor Integration, 6th edition (n = 42), [VI]Test of Visual Perceptual Skills, 3rd edition (n = 41), [VII]Behavioural Assessment of the Dysexecutive Syndrome for Children (n = 24).

Table III. Behavioral outcomes in children with biliary atresia

Questionnaire	No.	Normal	Borderline	Low	*P* value
CBCL	Ref	(93)	(5)	(2)	
Internalizing problems	39	18 (46)	6 (15)	15 (39)	<.001
Externalizing problems	38	28 (74)	3 (8)	7 (18)	<.001
Total behavioral problems	34	20 (59)	6 (18)	8 (23)	<.001
AVL	Ref	(90)	(5)	(5)	
Attentional problems	40	31 (78)	5 (12)	4 (10)	.03
Hyperactivity	39	29 (74)	3 (8)	7 (18)	.003
Impulsivity	39	35 (90)	3 (8)	1 (2)	.67
Total ADHD	38	29 (76)	8 (21)	1 (3)	.001
BRIEF	Ref	(50)	(43)	(7)	
Behavioral regulation	39	20 (51)	16 (41)	3 (8)	.97
Metacognition	37	20 (54)	13 (35)	4 (11)	.46
Global executive composite	37	19 (51)	14 (38)	4 (11)	.65

ADHD, attention deficit hyperactivity disorder; *AVL*, ADHD questionnaire (in Dutch); *BRIEF*, Behavior Rating Inventory of Executive Function; *CBCL*, Child Behavior Checklist.
Values are presented in numbers (%).
Distribution of behavioral outcomes in children with biliary atresia, in normal, borderline and low scores, compared with reference values (ref) based on the norm population, using the Fisher exact test.

Risk Factors

Data on the regression analyses of motor skills are shown in **Table IV** (available at www.jpeds.com). Univariable analysis revealed a significant effect of male sex (OR, 4.91; 95% CI, 1.33-18.21; $P = .017$) on low motor skills. The final model after multivariable analysis showed low odds for impaired motor skills in children with a history of intracranial hemorrhage, although not statistically significant (OR, 0.20; 95% CI, 0.03-1.30; $P = .09$), and high odds for male sex (OR, 5.74; 95% CI, 1.45-22.81; $P = .013$).

The regression model of total IQ is shown in **Table V** (available at www.jpeds.com). Univariable analysis showed a significant effect of selective attention abilities (mean difference [β], 0.25; 95% CI, 0.06-0.45; $P = .012$) and history of neurodevelopmental intervention (β, −15.60; 95% CI, −25.50 to −5.70; $P = .003$) on total IQ. Both variables remained significant after multivariable regression analysis. Results did not differ after multiple imputations of missing data (data not shown).

Overall, there were no significant differences between children with native liver and children after liver transplantation. Children with native liver had a mean total IQ of 94 ± 10 vs a mean total IQ of 90 ± 19 in children after liver transplantation ($P = .533$). All 8 children with a low IQ score had undergone a liver transplantation. In motor outcomes, 4 of 10 children (40%) with native liver scored low vs 18 of 34 children (53%) after liver transplantation ($P = .46$). Concerning school performance, 4 of 10 children (40%) with native liver received special education vs 8 of 36 children (22%) after liver transplantation ($P = .29$). Gestational age was not significantly associated with low IQ or motor skills.

Discussion

We found significantly impaired neurodevelopmental outcomes in children with biliary atresia compared with the

Dutch norm population. These impairments were present in all neurodevelopmental domains, that is, motor skills, cognition, and behavior. Motor outcomes were most affected, with even up to one-half of the children scoring low on motor skills. In addition, children scored significantly lower on total IQ, performance IQ, attention abilities, planning, visuomotor integration, and perceptual ability as compared with the norm population. Moreover, parents reported behavioral and attentional problems in children with biliary atresia. One in 4 children with biliary atresia received special education, a significantly higher percentage than the 2.4% in the general Dutch population.

Our second aim was to identify risk factors for impaired neurodevelopmental outcomes. Of the 46 children with biliary atresia, 36 (78%) had a history of liver transplantation. Children surviving with native liver did not score significantly higher on several subtests of cognition and motor skills compared with children after liver transplantation. However, there was a trend for higher scores on these subtests in survivors with native liver, but this difference did not reach statistical significance. We therefore refrained from scrutinizing the differences in specific neurodevelopmental subdomains between children with native liver and those who underwent liver transplantation. A note of caution is, however, due when interpreting these data considering the small proportion of children surviving with native liver. Nevertheless, our findings are in line with previous literature describing impaired neurodevelopmental outcomes in children with native liver and after liver transplantation.[10,33,34] These findings raise intriguing questions regarding the underlying pathophysiology of neurodevelopmental impairments in children with congenital liver disease. One could speculate that the neurodevelopmental delays were caused by exposure of the developing brain to cholestasis rather than, or in addition to, liver transplantation. Wayman et al showed that the neurodevelopmental outcomes of children with biliary atresia were in the low-average range before liver transplantation.[35] After liver transplantation, scores decreased significantly in the first months; however, they returned to the same level as the scores before liver transplantation 1 year after liver transplantation, but not exceeding the earlier liver transplantation scores.[35] Previous research showed a correlation between cholestasis and impaired cognitive outcomes.[36,37] Cholestasis might cause brain lesions, especially in the white matter, which is believed to be the neural foundation for general intelligence.[38] Talcott et al showed alterations in the brain biochemistry of children with liver disease, including children with asymptomatic liver disease.[37] All children with biliary atresia are faced with cholestasis before KPE surgery, and many also after KPE, making this a possible cause for neurodevelopmental impairments. Major surgery in young children itself may also be a possible risk factor for impaired neurodevelopment. Physiologic stress and anesthesia can be harmful in the period of early brain development.[5,39] In contrast, Davidson et al stated that general anesthesia in infants has no significant effect on neurodevelopmental outcomes at 2 years of age, although in relatively minor surgery.[6]

In line with previous studies, boys had higher odds of neurodevelopmental impairments, especially motor skills.[40-42] Both sex hormones and sex chromosome genes may influence brain function, for example, the Y-chromosome gene is suggested to be a male-specific risk factor for neurodevelopmental disorders.[41] Prematurity was not a risk factor for neurodevelopmental impairments at school age in our cohort. Moreover, our data showed no difference in IQ, and even better motor skills, in children with a history of intracranial hemorrhage, compared with children without a history of intracranial hemorrhage.

The exact pathophysiology and age at onset of the neurodevelopmental impairments remain unclear. Data on neurodevelopmental outcomes at earlier age are scarce, although required to further investigate age at onset and underlying pathophysiology of these impairments. Moreover, longitudinal follow-up is essential to explore the long-term neurodevelopmental trajectory in children with biliary atresia.

At the time of test assessment, 46% of children had already received some type of neuropsychological intervention. However, this treatment was not integrated in standard care. Children with a history of neuropsychological intervention had significantly lower scores on motor skills and IQ. The effectiveness of these neuropsychological interventions remains uncertain; however, we can conclude that they were not sufficient to fully recover the impairments. Previous studies have shown that, in preterm infants, early intervention programs have a positive effect on motor development in infancy, and cognitive development up to preschool age, compared with standard medical follow-up.[43] Early identification of infants with biliary atresia at risk for neurodevelopmental impairments may allow early targeting of intervention programs, focusing on infant development and parent-infant relationship, for example, in the form of physiotherapy, speech language therapy, and psychological intervention.

A chronic disease might also influence health-related quality of life. Existing data on quality of life in children with biliary atresia is contradictory, with some studies describing lower health-related quality of life compared with healthy children, whereas others describe similar quality of life.[44,45] Further research is needed to investigate whether impaired neurodevelopmental outcomes negatively affect the health-related quality of life in children with biliary atresia.

We are aware that our study has some limitations. Because biliary atresia is a rare disease, the sample size was relatively small, especially regarding children surviving with native liver. The sample size might have masked differences between subgroups of children, such as children with native liver and after liver transplantation, or some previously recognized associations between risk factors and neurodevelopmental outcomes. Furthermore, most of the children displayed problems with hyperactivity and attention. Regression analysis showed that selective attention abilities were associated with IQ scores, however, not with motor skills. Moreover, the cross-sectional study design limits exploration of neurodevelopmental outcomes over time. In addition, we did not receive informed consent from 11 of the invited children. It

is unknown whether these children reflect either the highest or lowest scoring children. Nevertheless, the inclusion ratio was high (78%) and, therefore, we feel that our cohort provides an adequate overview of children with biliary atresia from The Netherlands.

In conclusion, this study shows impaired outcomes in several very important fields of neurodevelopment in school-aged children with biliary atresia, such as motor skills, cognition and behavior. Moreover, 26% of children received special education. Our data strongly warrant evaluation of neurodevelopmental intervention programs to assess whether long-term outcomes could be improved. International collaboration and pooling of data is highly desirable to further investigate the underlying pathophysiology and risk factors for these neurodevelopmental impairments in children with biliary atresia. ■

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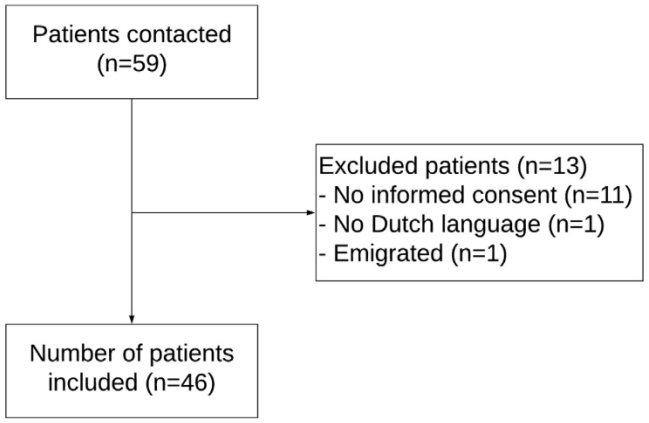

Figure 1. Flow chart of the inclusion process.

Table II. Effect sizes and study power

Outcomes	Effect size	Study power
	Cohen d	
Total motor skills	1.38	1.00
Total IQ	0.49	0.94
Performance IQ	0.72	1.00
Verbal IQ	0.37	0.77
Selective attention	0.64	0.99
Inhibition control	0.41	0.83
Short-term memory	0.02	0.06
Long-term memory	0.20	0.34
Visuomotor integration	0.59	0.98
Perceptual ability	0.40	0.81
Planning	0.42	0.64
Strategy formation	0.19	0.23
Multivariable model - IQ	f^2	
Total model	0.45	0.97
Multivariable model - motor skills	f^2	
Total model	0.45	0.92

Cohen effect sizes are interpreted as small (d = 0.20 or f^2 = 0.02), medium (d = 0.50 or f^2 = 0.15), and large (d = 0.80 or f^2 = 0.35). Effect sizes and study power were calculated using the G*Power program, version 3.

Table IV. The association between motor skills and risk factors (n = 43)

		Motor skills (percentile)	Low score motor skills (percentile < 5)	
		Descriptives	Univariable	Multivariable
Variables	No.	Median (range) or rho	OR [95% CI]	OR [95% CI]
Sex				
Girls	19	11 (2-92)	Ref	Ref
Boys	27	3 (1-25)*	4.91 [1.33-18.21]*	5.74 [1.45-22.81]*
Ethnicity				
Caucasian	32	6.5 (1-92)	Ref	
Non-Caucasian	9	4 (1-67)	1.80 [0.43-7.59]	—
Highest household education				
Low/intermediate	18	6.5 (1-92)	Ref	
High	23	6 (1-75)	1.00 [0.31-3.28]	—
Gestational age (weeks)	38	−0.05	1.05 [0.82-1.35]	—
Intracranial hemorrhage				
No	34	5 (1-92)	Ref	Ref
Yes	7	19 (1-67)†	0.27 [0.05-1.50]†	0.20 [0.03-1.30]†
History of growth failure (SD <2)				
No	20	7.5 (1-92)	Ref	
Yes	18	8.5 (1-75)	1.50 [0.43-5.25]	—
History of neurodevelopmental intervention				
No	22	9 (1-92)	Ref	
Yes	19	2 (1-67)*	2.10 [0.63-7.03]	—
Successful KPE‡				
No	28	6.5 (1-92)	Ref	
Yes	12	9 (1-75)	0.67 [0.17-2.57]	—
KPE <60 days of life				
No	19	10 (1-92)	Ref	
Yes	22	5 (1-67)	1.73 [0.53-5.72]	—
Age at KPE (days)	40	0.12	0.97 [0.94-1.01]†	—
Total bilirubin serum level before KPE§	41	−0.09	0.99 [0.99-1.01]	—
Direct bilirubin serum level before KPE¶	32	0.12	1.00 [0.99-1.01]	—
Liver transplantation				
No	10	6 (1-75)	Ref	
Yes	31	7 (1-92)	1.69 [0.40-7.07]	—
Selective attention (percentile)	42	0.19	0.99 [0.97-1.02]	—

Dichotomous risk factors and motor score percentiles were compared by using the Mann Whitney U test. The correlations between motor score percentiles and continuous risk factors were calculated by means of Spearman rho. ORs were calculated using logistic regression. Variables with a *P* value of <.2 were included in multivariable analysis, and the final model after backward regression is shown.

Normal values: ‡bilirubin level <20 μmol/L (1.17 g/dL) within 6 months after KPE, §<17 μmol/L, and ¶<5 μmol/L.

*$P < .05$.

†$P < .2$.

Table V. The association between total IQ and risk factors (n = 43)

		Total IQ (absolute number)		
		Descriptives	Univariable	Multivariable
Characteristics	No.	Mean ± SD or rho	β [95% CI]	β [95% CI]
Sex				
Girls	19	96 ± 12	Ref	
Boys	24	88 ± 21†	−8.04 [−18.85 to 2.77]†	—
Ethnicity				
Caucasian	34	94 ± 15	Ref	
Non-Caucasian	9	82 ± 24†	−11.92 [−24.95 to 1.10]†	—
Highest household education				
Low/intermediate	20	87 ± 15	Ref	
High	23	95 ± 19†	8.12 [−2.64 to 18.88]†	—
Gestational age	40	0.02	−0.11 [−2.52 to 2.30]	—
Intracranial hemorrhage				
No	36	91 ± 19	Ref	
Yes	7	93 ± 9	2.12 [−12.82 to 17.03]	—
History of growth failure (SD <2)				
No	22	92 ± 17	Ref	
Yes	18	86 ± 16	−6.01 [−16.62 to 4.60]	—
History of neurodevelopmental intervention				
No	23	98 ± 13	Ref	Ref
Yes	20	83 ± 19†	−15.60 [−25.50 to −5.70]*	−15.84 [−25.14 to −6.55]*
Successful KPE‡				
No	30	91 ± 19	Ref	
Yes	12	93 ± 12	1.72 [−10.27 to 13.71]	—
KPE <60 days of life				
No	20	85 ± 20	Ref	
Yes	23	96 ± 14†	10.55 [0.01 to 21.09]†	—
Age at KPE (days)	42	−0.12	−0.09 [−0.38 to 0.21]	
Total bilirubin serum level before KPE§	43	−0.17	−0.06 [−0.15 to 0.04]	—
Direct bilirubin serum level before KPE¶	34	−0.10	−0.06 [−0.16 to 0.04]	—
Liver transplantation				
No	10	94 ± 10	Ref	
Yes	33	90 ± 19	−4.05 [−17.04 to 8.94]	—
Selective attention (percentile)	42	0.39	0.25 [0.06 to 0.45]*	0.24 [0.07 to 0.41]*

Dichotomous risk factors and IQ were compared using the independent sample *t* test. The correlations between IQ and continuous risk factors were calculated by means of Spearman rho. Variables with a *P* value of <.2 were included in multivariable analysis, and the final model after backward regression is shown.
Normal values: ‡bilirubin level <20 μmol/L (1.17 g/dL) within 6 months after KPE, §<17 μmol/L, and ¶<5 μmol/L.
*$P < .05$.
†$P < .2$.