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Neurodevelopment in patients with biliary atresia up to toddler age: Outcomes and predictability

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ABSTRACT

Aim: To assess neurodevelopment in young patients with biliary atresia (BA) and to determine the predictive value of General Movement Assessment (GMA) at infant age for neurodevelopmental impairments at toddler age.
Method: Infants diagnosed with BA were prospectively included in a longitudinal study. Neurodevelopmental status was previously assessed before Kasai porto-enterostomy (KPE) and one month after KPE using Prechtl's GMA, including motor optimality scores. At 2–3 years, neurodevelopment was assessed using the Bayley Scales of Infant Development, and compared to the Dutch norm population. The predictive value of GMA at infant age for motor skills and cognition at toddler age was determined.
Results: Neurodevelopment was assessed in 41 BA patients. At toddler age (n = 38, age 29 ± 5 months, 70 % liver transplantation), 13 (39 %) patients scored below-average on motor skills, and 6 (17 %) patients on cognition. Abnormal GMA after KPE predicted both below-average motor skills and cognitive score at toddler age (sensitivity, 91 % and 80 %; specificity 83 % and 67 %; negative predictive value, 94 % and 94 %; and, positive predictive value, 77 % and 33 %, resp.).
Interpretation: One-third of toddlers with BA show impaired motor skills. GMA post-KPE has a high predictive value to identify infants with BA at risk of neurodevelopmental impairments.

Children with biliary atresia (BA) are at risk of impaired outcomes in motor skills, cognition, and behavior [1,2]. BA patients are exposed to disease-related factors that have the potential to adversely affect neurodevelopment. Cholestasis, growth deficits, multiple hospitalizations and major surgery in early childhood may all adversely affect the developing brain [2–6]. As BA manifests in the first weeks after birth, patients are faced with several of these risk factors in early infancy.

Previously, we described that approximately half of BA patients showed an abnormal early motor repertoire at time of diagnosis [7]. The quality of the early motor repertoire is a reliable indicator for brain dysfunction in infants and a predictor of long-term neurodevelopmental outcomes [8–10].

Early infancy and childhood are critical periods of brain development [11]. Therefore, targeted intervention programs to improve neurodevelopmental outcomes seem to be most beneficial in early childhood [11]. Early identification of infants who are at risk of neurodevelopmental impairments would allow for timely starting targeted intervention programs [11].

Our primary aim was to investigate the neurodevelopmental trajectory of infants with BA up to toddler age, and to determine the predictive

Abbreviations: BA, Biliary Atresia; FMs, Fidgety Movements; GM, General Movements; GMA, General Movement Assessment; GMOS, General Movements Optimality Score; MOS, Motor Optimality Score; LTx, Liver Transplantation.

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value of the early motor repertoire for the neurodevelopmental status at toddler age. Our secondary aim was to identify disease-related factors that are associated with below-average scores on motor skills and cognition.

1. Methods

From November 2015 to November 2019, the caregivers of all BA patients were approached for inclusion in a Dutch national prospective cohort study. A proportion of this cohort overlaps with the infants participating in our previously published study [7]. Infants with a birth weight $\leq$ 2000 g, a diagnosis other than BA, who received a primary LTx, or with concurring neurological diseases were excluded from this study. This study was conducted in accordance with the national laws and regulations and approved by the local Medical Ethics Committee of the University Medical Center Groningen (METC 2011/185). The caregivers of all included infants gave written informed consent. The guideline of the Equator network was used in conducting this study.

1.1. Study population

A flowchart of the inclusion process is shown in Fig. 1. All 41 children underwent neurodevelopmental testing during at least one of the three timepoints. Pre-KPE data of 35 infants, as previously published, was added in this paper to demonstrate the individual trajectories [7].

1.2. Data collection

Caregivers were asked to fill out a demographic questionnaire. Additional information was collected from the infants' medical files. The mean upper arm circumference (MUAC) was collected as measure of the child's nutritional status. The Pediatric End-Stage Liver Disease (PELD) score at time of screening for LTx was included to explore the relation between disease severity pre-LTx and neurodevelopmental outcomes [13]. If children underwent a LTx, data regarding their LTx was collected. Complications were registered according to the Clavien Dindo classification, with grade III and above defined as a major complication [12].

The early motor repertoire was assessed in accordance with GMA according to Prechtl [14]. At time of diagnosis (previously published data), and during the first out-patient visit after KPE, approximately 4 weeks after surgery, the motor repertoire of infants was recorded on video [7].

Children were scheduled for follow-up assessment around 24 months of age. In case of missing data on motor development and recent assessment by a physical therapist in our centre at a minimum age of 12

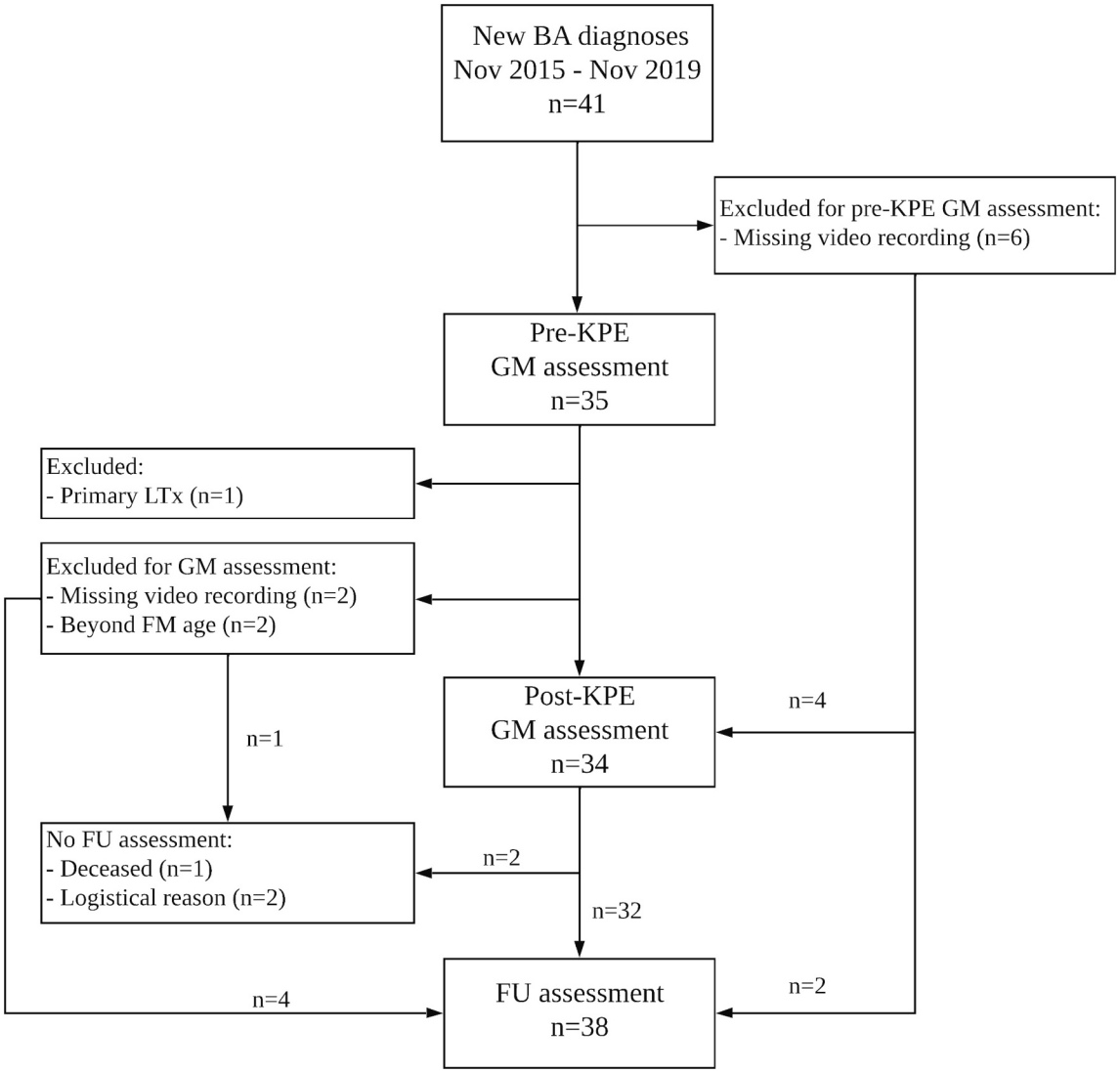


Fig. 1. Flowchart of the inclusion process.

months, we extracted those scores from the patient's medical file (n = 5).

1.3. Early motor repertoire in biliary atresia

We assessed the early motor repertoire using validated and age-appropriate GM scoring forms [15,16]. At birth, GMs are called writhing movements. At approximately two months of age writhing disappear and fidgety movements (FMs) emerge [16,17]. Apart from these FMs, the early motor repertoire in this age period consists of other movement patterns which may occur together with FMs, such as visual scanning, leg lift and wiggling-oscillating arm movements [16,17].

Infants with predominantly writhing movements were scored using the standard form 'Detailed assessment of General Movements during preterm and term age'. [15] Per infant, a GM optimality score (GMOS, min-max 5–42 points) was computed [15]. In accordance with our previous paper, a GMOS of 35 or lower was defined as atypical and considered as abnormal [15].

The motor optimality score (MOS-R, min-max 5–28 points) was scored if infants showed predominantly FMs during the recording, independently of their post menstrual age [16]. Per infant, a motor optimality score was calculated [16]. A MOS-R of 24 or lower was defined as atypical and considered as abnormal.

All video recordings were evaluated in blinded fashion by two certified observers (LR and JB). One of the observers (LHR) was a junior (certified) observer at the beginning of the study. Therefore we choose to judge the video-recording both by a junior and senior observer, for both training purpose and for the most reliable results. In case of a discrepancy, video recordings were re-evaluated by LR and JB together and, if necessary, a third observer (AB), was contacted.

1.4. Neurodevelopmental outcomes in toddlers with biliary atresia

The validated Bayley Scales of Infant Development, 3th edition (BSID-III), was used to assess motor skills and cognition [18]. In accordance with the test manual, domain scores for motor skills and cognition can be transformed to age-matched index scores (population mean 100 ± 15). Total motor skills can be subdivided in fine and gross motor skills and transformed to age-matched scaled scores based on norm data (population mean 10 ± 3) [18]. Index or scaled scores of more than one SD below the population mean (resp. <85 and ≤7) were categorized as 'below average'. The assessments were performed by one trained investigator LHR and on indication supervised by our neuropsychologist (AEdH). LHR also assessed the GMs post-Kasai and was therefore aware of the clinical status at that time, however not about the overall status at the time of follow-up.

Behavioural problems were assessed using the parent-reported Child Behaviour Checklist (CBCL 1.5-5). The CBCL determines internalizing and externalizing behavioural problems. The CBCL manual provides age- and gender-matched norm values from the general population and cut-off values for normal, borderline clinical and clinical range.

1.5. Data analysis

Outcomes are reported as number (%), mean ± SD for normally, or otherwise as median (min, max) for non-normally distributed data. Data were checked for distribution and missing values. In case of missing data, the subject was excluded for that particular analysis. Missing data was not imputed because of low accuracy of imputation in small samples.

Data was compared to norm values from the general population, by means of a Chi-square or Fisher exact analysis for proportions, the one-sample *t*-test for normally distributed data or the one-sample Wilcoxon signed ranked test for non-normally distributed data.

To determine the predictive value of an abnormal early motor repertoire for below-average scores (index scores <85) on motor skills and cognition in toddlers, we calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), using standard formulas. The relation between patient-related factors and neurodevelopmental outcomes was assessed using Chi-square or Fisher exact analysis for dichotomous variables, and independent sample *t*-tests or Mann-Whitney U analysis for continuous variables. A p value <0.05 was considered as statistically significant. Statistical analyses were performed by using SPSS 23.0 (SPSS Inc., Chicago, IL).

2. Results

Patient characteristics are reported in Table 1. Twenty-eight children (70 %) had received a LTx before the FU assessment. One child died of a variceal bleeding 3 months after KPE. All caregivers gave consent.

Table 1
Patient characteristics.

Patient characteristics	N	Number Mean Median	% ±SD Min, max
Female gender (n, %)	41	29	71 %
Gestational age (weeks)	39	39	36, 42
Birth weight (grams)	39	3384	±470
Caucasian ethnicity (n, %)	40	23	58 %
T0: Diagnosis			
BASM	41	3	7 %
H/o intracranial haemorrhage (n, %)	40	0	0
Age at first hospital admission (days)	38	47	7, 131
Highest serum level at diagnosis			
- Total bilirubin (μmol/L)[a]	41	159	87, 364
- ALAT (U/L)[b]	41	161	46, 923
- Ammonia (μmol/L)	29	62	32, 132
MUAC (Z-score)	39	−1.80	−3.00, −0.20
T1: Four weeks post-KPE			
Age at KPE (days)	41	56	27, 143
KPE <60 days of life (n, %)	41	26	63 %
Major complication post-KPE[c]	41	2	5 %
Serum level post-KPE			
- Total bilirubin (μmol/L)[a]	40	109	8, 201
- ALAT (U/L)[b]	40	157	65, 527
- Ammonia (μmol/L)	28	65	37, 107
MUAC (Z-score)	38	−1.20	−2.5, 0.80
T2: Toddlers			
Successful KPE[d] (n, %)	41	17	42 %
Age at screening for LTx (months)	32	3	1,15
Liver transplantation (n,%)	41	28	68 %
- post-mortem donor graft	28	6	21 %
- living donor graft	28	22	79 %
Age at LTx (months)	28	7	4, 22
PELD score	32	10	0, 32
Time since LTx (months)	27	21	6, 37
Major complication after LTx[c]	28	11	39 %
Current serum level			
- Total bilirubin (μmol/L)[a]	38	6	3, 286
- ALAT (U/L)[b]	38	41	18, 289
- Ammonia (μmol/L)	29	39	20, 76
MUAC (Z-score)	25	−1.00	−2.60, 2.50

Normal values: [a] < 17 μmol/L, [b] < 60 U/L, [c]grade III or higher of Clavien-Dindo Classification (surgical intervention under general anaesthesia), [d]bilirubin level < 20 μmol/L (1.17 g/dL) within 6 months after KPE. The MUAC Z-score is an age-matched, standardized score based on growth charts from the general population.

Abbreviations: ALAT, alanine-aminotransferase; BASM, biliary atresia splenic malformation syndrome; KPE, Kasai portoenterostomy; LTx, liver transplantation; MUAC, mean upper arm circumference; PELD, Pediatric End-Stage Liver Disease; SD, standard deviation.

2.1. Early motor repertoire

The results of the early motor repertoire pre-KPE were previously reported [7]. At time of diagnosis, at a PMA of 47 weeks [42–60], 16/35 infants (46 %) scored below the cut-off value for a typical early motor repertoire. After KPE, at a PMA of 53 ± 4 weeks, 15/34 infants (44 %) scored below the cut-off value for an atypical early motor repertoire, which was significantly ($p < 0.001$) more than in the reference group of healthy peers (*i.e.* 18 %). Detailed scores of the infant's early motor repertoires are reported in Table 2.

2.2. Neurodevelopmental outcomes in toddlers

Thirty-eight children (age 29 ± 5 months, 70 % LTx) were scheduled for follow-up assessment. In nine toddlers (22 %) not all neurodevelopmental tests could be completed due to attentional problems or problems with language comprehension (n = 8) or logistic reason (n = 1). Caregivers of 32/38 toddlers (84 %) completed the behavioural questionnaires.

On total motor skills, toddlers with BA obtained a median index score of 89 (67–129, n = 33), which was significantly lower than the population median of 100 ($p = 0.001$). Thirteen of 33 toddlers (39 %) scored >1 SD below the population mean (index score < 85), and 4/33 (12 %) scored >2 SD below the population mean (index score < 70). When divided into fine and gross motor skills, the median scaled score for fine motor skills was 9 (3–15) and for gross motor skills 6 (3–17). Thirteen of 37 toddlers (35 %) scored >1 SD below the population mean (scaled score ≤ 7) on fine motor skills and 22/34 toddlers (65 %) on gross motor skills.

As for cognition, toddlers with BA obtained a median index score of 96 (63–129, n = 35), which was not significantly ($p = 0.38$) lower than the population median of 100. 6/35 toddlers (17 %) scored >1 SD below the population mean (index score < 85), and 2/35 (6 %) scored >2 SD below the population mean (index score < 70).

Regarding behavioural outcomes, 5/32 toddlers (16 %) scored in the borderline range and 1/32 toddlers (3 %) scored in the clinical range for total behavioural problems. One out of 32 toddlers (3 %) scored in the clinical range for internalizing problems and 2/32 toddlers (6 %) scored in the clinical range for externalizing problems.

Table 2
Early motor repertoire after KPE.

Early motor repertoire after KPE	Number Median	% Min, max
Total group	n = 34	
Atypical early motor repertoire	15	44 %
GMOS	n = 2	
GMOS total score (max 42)	32	29, 35
GMOS score ≤ 35 (atypical)	2	100 %
Poor repertoire	1	50 %
MOS-R	n = 32	
MOS-R total score (max 28)	26	21, 28
MOS-R score ≤ 24 (atypical)	13	41 %
General assessment: normal FMs	32	100 %
Observed movement patterns (N > A)[a]	32	100 %
Postural patterns (N > A)[a]	29	91 %
Age-adequate movement repertoire:		
- Present	18	56 %
- Reduced or absent	14	44 %
Movement character:		
- Smooth and fluent	9	28 %
- Abnormal, all categories	23	72 %
- Abnormal, monotonous	12	38 %

Abbreviations: KPE, Kasai portoenterostomy; GMOS, general movement optimality score; max, maximum; min, minimum; MOS-R, motor optimality score-revised; FMs, fidgety movements; N, normal; A, abnormal.

2.3. Predictive value of the early motor repertoire

The early motor repertoire was previously assessed, either pre-KPE, post-KPE or both, in 36 of the 38 toddlers who were assessed at follow-up, *i.e.* cognition (n = 29) and/or motor skills (n = 29). In 26 infants, neurodevelopment was assessed at three timepoints (pre-KPE, post-KPE, toddler age). The individual trajectories are shown in Fig. 2.

Notably, the majority of infants remain in the same category at all time-points (11/26 for motor skills, 9/26 for cognition) or change category (normal/below-average) peri-KPE and subsequently remain in the same category during follow-up (12/26 for motor skills, 9/26 for cognition).

The early motor repertoire post-KPE had a higher predictive value for outcomes at toddler age than the early motor repertoire pre-KPE. An abnormal early motor repertoire pre-KPE predicted below-average motor skills in toddlers with a sensitivity of 40 % (95 % CI 12–74), and a PPV of 31 % (95 % CI 15–52). The specificity for motor skills was 50 % (95 % CI 26–74) and the NPV 60 % (95 % CI 43–74). As for cognition, all but two children stayed on the normal level for both early motor repertoire and cognition (14 out of 16) and most of the infants with an abnormal motor repertoire improved to normal at toddler age (12 out of 14). Therefore, an abnormal motor repertoire predicted below-average cognitive development with a sensitivity of 88 % (95 % CI 62–98), and a PPV of 54 % (95 % CI 47–61). The specificity was 14 % (95 % CI 2–43) and the NPV 50 % (95 % CI 14–86). An abnormal early motor repertoire post-KPE predicted below-average motor skills in toddlers with a sensitivity of 91 % (95 % CI 59–100), and a PPV of 77 % (95 % CI 54–91). The specificity for motor skills was 83 % (95 % CI 59–69) and the NPV 94 % (95 % CI 70–99). As for cognition, all but one child stayed on the normal level for cognition (16 out of 17) and most of the infants with an abnormal motor repertoire improved to normal at toddler age (8 out of 12). Therefore, an abnormal motor repertoire predicted below-average cognitive development with a sensitivity of 80 % (95 % CI 28–99), and a PPV of 33 % (95 % CI 20–51). The specificity was 67 % (95 % CI 45–84) and the NPV 94 % (95 % CI 73–99).

One child with a previously normal motor repertoire moved to the abnormal category for both motor skills and cognition. This child experienced major complications in the post-surgery period after liver transplantation (Clavien-Dindo grade IVa).

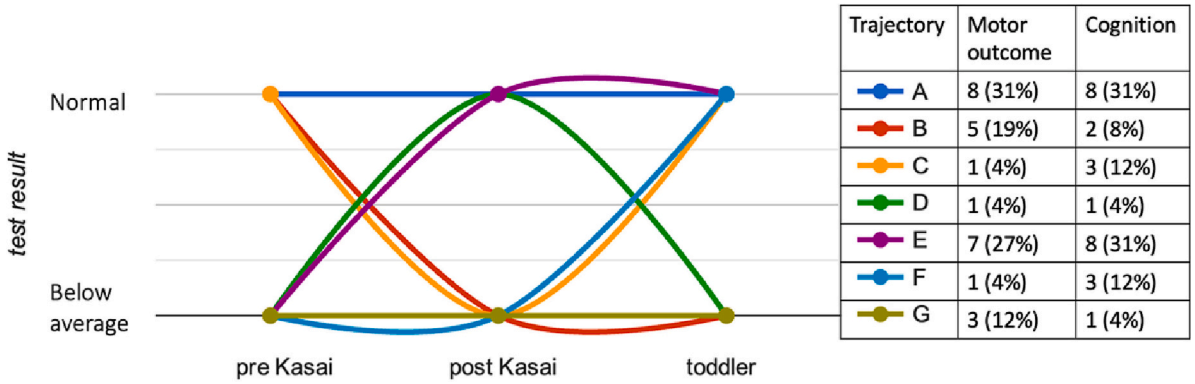
No significant relationship was found between normal and abnormal results of pre-KPE assessment and index scores at toddler age (Fig. 3). Infants who showed an abnormal early motor repertoire post-KPE scored on average 20 points lower on motor skills (resp. median of 78 *vs* 98, $p = 0.002$) and 12 points (resp. 89 *vs* 101, $p = 0.02$) lower on cognition at toddler age, compared with infants who showed a normal early motor repertoire (Fig. 4).

2.4. Risk factors for neurodevelopmental outcomes

There were no disease-related factors that were significantly associated with below-average scores on motor skills and cognition (Supplemental Tables 1, 2). However, in our cohort, a high amount of BA patients had a history of poor nutritional status (Table 1). Approximately half of the infants had a MUAC of 2 SD below the population mean. Although the Z-score of the MUAC increased over time, still half of the BA patients had a MUAC of 1 SD below the population mean at toddler age, and 16 % even had a MUAC of 2 SD below the population mean.

3. Discussion

Our aim was to assess neurodevelopmental outcomes in infants and toddlers with BA and to determine the predictive value of GMA at infant age for neurodevelopmental impairments at toddler age. At toddler age, patients with BA scored considerably lower on motor skills, compared with their healthy peers, albeit on average still within the normal range.



Trajectory	Motor outcome	Cognition
A	8 (31%)	8 (31%)
B	5 (19%)	2 (8%)
C	1 (4%)	3 (12%)
D	1 (4%)	1 (4%)
E	7 (27%)	8 (31%)
F	1 (4%)	3 (12%)
G	3 (12%)	1 (4%)

Fig. 2. Individual trajectories of motor and cognitive outcomes in BA patients over time.

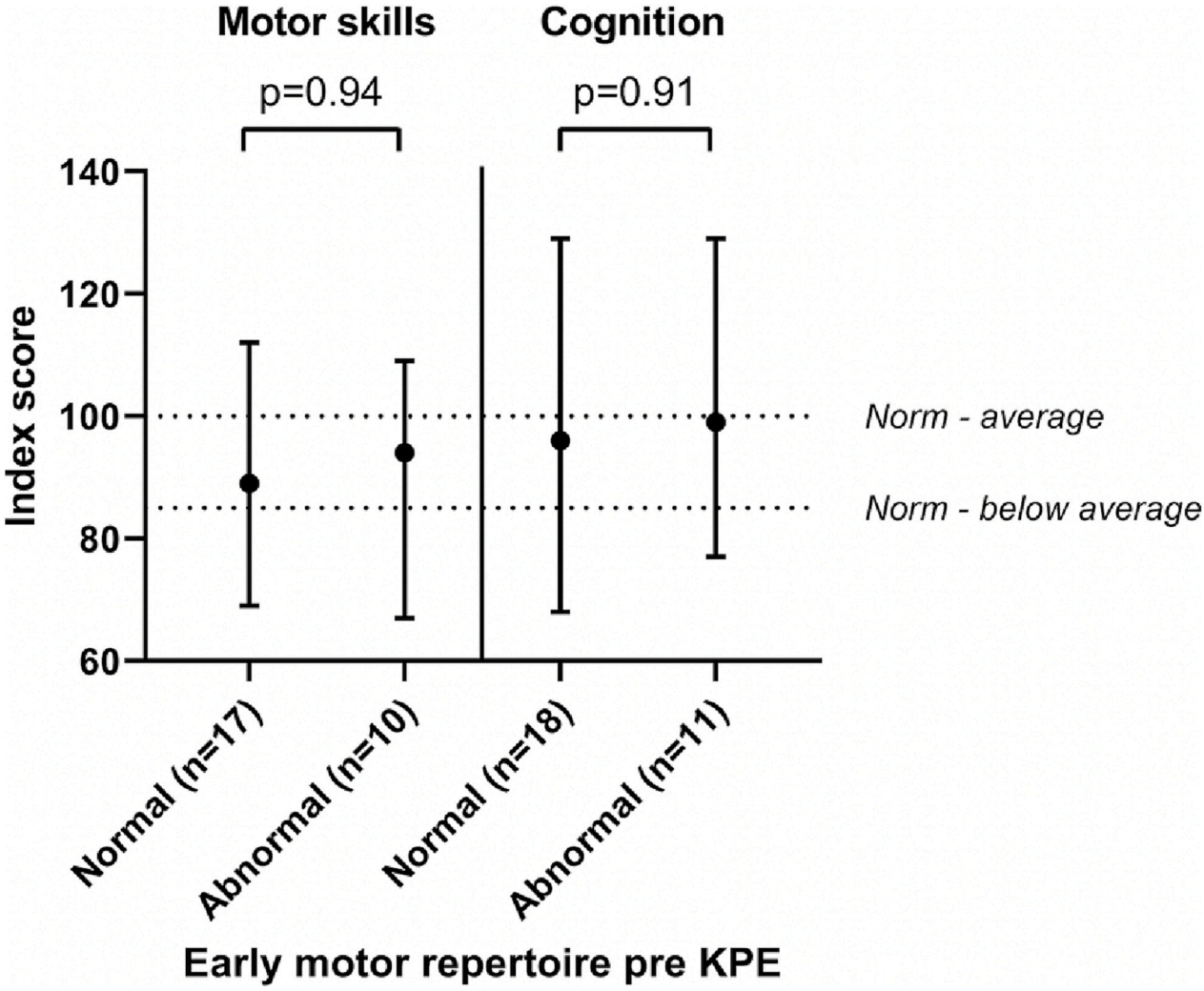


Fig. 3. Median and range of age and gender adjusted index scores (population mean 100 ± 15) of cognition and motor skills in toddlers with BA, stratified for toddlers who had a normal or abnormal early motor repertoire at *pre-KPE assessment.*

We also demonstrated that the quality of the early motor repertoire post-KPE had a high predictive value for neurodevelopmental impairments at toddler age and, therefore, may be used for early detection of infants with BA who are at increased risk of neurodevelopmental impairments. Furthermore this study showed the additional value of the use of the MOS-R. Although in our study all infants had normal fidgety movements, the MOS-R as part of the GMA turned out to be beneficial for identifying those children at risk for neurodevelopmental problems. This underscores the importance for clinicians of including the MOS-R in the assessment of the early motor repertoire, rather than judging the general assessment of fidgety movements only. Over the past decade, several research groups have recognized the neurodevelopmental problems that accompany BA [2,19–21]. In our cohort motor skills were delayed in more than a third of the toddlers having below-average motor skills.

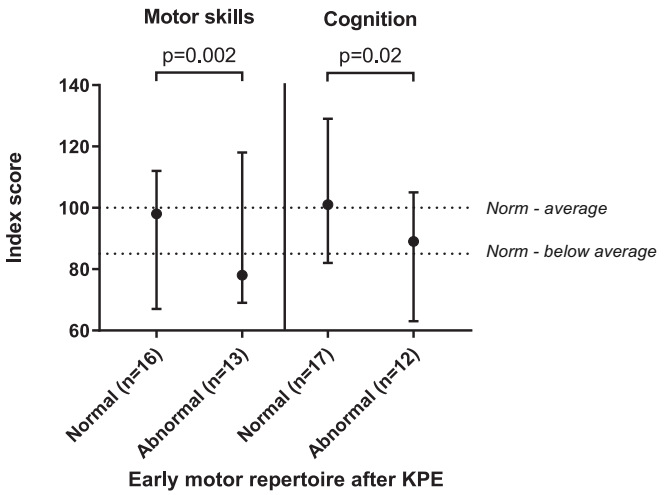


Fig. 4. Median and range of age and gender adjusted index scores (population mean 100 ± 15) of cognition and motor skills in toddlers with BA, stratified for toddlers who had a normal or abnormal early motor repertoire at *post-KPE assessment.*

Especially gross motor skills were severely impaired, with almost two-third of these toddlers scoring below average. These findings are in line with previous studies in school-aged BA patients reporting that especially motor skills are affected [1,21]. Cognitive skills were less affected in our cohort.

Knowledge on risk factors for neurodevelopmental impairments might further contribute to the early identification of high-risk infants. Therefore, we attempted to identify those risk factors. First, we found somewhat higher serum bilirubin levels in toddlers with impaired cognitive outcome, although the relevance of this finding is to be speculated as median bilirubin levels were within the normal range for both groups. However, the negative relation between cognition and bilirubin has been previously described in literature [3,21].

Second, adequate nutritional status has been related to, and considered important for, optimal neurodevelopment [22]. Growth deficits have been reported to be associated with lower neurodevelopmental outcomes [2,6,19,23–27]. In our cohort, an alarming proportion of BA patients had a history of poor nutritional status. These findings demonstrate the urgent need for more attention for growth measures and nutritional intervention in children with BA.

Third, it has been speculated that major surgery with general anaesthesia might influence neurodevelopment [28]. Neurodevelopmental deficits have been reported in other paediatric patients who undergo major surgery in infancy [28]. Although neurological impairments were already visible before surgery, BA patients undergo at least one major surgery, in the form of a KPE, and most patients will undergo a LTx. The early motor repertoire 4 weeks post-KPE was probably not influenced by the post-surgical condition because the high predictive value of the motor repertoire for impaired motor scores at toddler age supports the concept that the lower score is due to ongoing injury rather than due to transient pain or wound healing.

Furthermore in our cohort we found no significant differences between toddlers with a history of LTx compared to children who still had their native liver. This is in line with a previous study from Finland [21]. Factors related to LTx, such as age at LTx and the PELD score were not statistically related to the neurodevelopmental outcomes. Data from a follow-up study of children with BA who still had their native liver, showed that pre-school and school-aged children did not demonstrate a higher prevalence of cognitive impairments compared to the norm population [29]. We believe that is because those patients reflect a subgroup of BA patients with limited exposure to lengthy cholestasis because of successful KPE. This finding also suggests that neurodevelopmental impairments in early infancy might be partly reversible, as the neurodevelopmental outcomes in those patients with stable liver disease improved over time [2,29]. On the contrary, neurodevelopmental impairments have also been described for infants with BA who did not undergo a LTx [2,19]. In our previous study, half of the infants with BA already showed an impaired early motor repertoire [7]. This supports our hypothesis that the neurodevelopment in BA patients is affected more by factors directly related to the liver disease, rather than surgery.

As early childhood is a crucial period of brain development, with high brain plasticity, it seems reasonable to start neurodevelopmental intervention as early as possible [12]. Our results suggest that GMA is a valid method for the identification of infants with BA who are most at risk of an impaired motor development and therefore might benefit most from early intervention. Our findings are in line with a previous study showing a predictive value of the quality of the early motor repertoire in infants who underwent early neonatal surgery, for neurodevelopmental outcomes at one year of age [30]. By the implementation of standard GMA post-KPE surgery, physical therapy can already be started at infant age, followed by targeted intervention for an adequate motor development in toddlers. Infants with a normal early motor repertoire have a lower risk of neurodevelopmental delays, however, should be tested again at toddler age to determine whether intervention is indicated.

We acknowledge that our study has several limitations. During neurodevelopmental testing (according to the BSID-III manual), gross motor skills are always the last domain to be assessed. Children often tire and lose concentration which may influence the test results.

As BA is a rare disease, the sample size in our study is small. This affects the precision of the predictive value of GMA and the identification of risk factors for impaired neurodevelopmental outcomes in toddlers. We feel that international collaboration is warranted to confirm the predictive value of GMs in a second, larger, cohort of BA patients and to further investigate risk factors for neurodevelopmental impairments. Especially because all caregivers in our cohort participated in this study, which emphasizes their worries and needs in taking care of infants with BA.

In conclusion, patients with BA are at increased risk of neurodevelopmental deficits, particularly motor skills. Almost half of patients with BA showed an abnormal early motor repertoire at infancy and over one-third showed below-average motor skills at toddler age. These data are alarming and warrant the development of a targeting intervention program to improve long-term outcomes. Our data suggest that the quality of the early motor repertoire has a high predictive value for neurodevelopmental impairments in toddlers with BA. We propose that early neuropsychological screening, by means of GMA at infant age, should be implemented in the clinical care of BA patients. This will allow early identification of those infants who are at increased risk of impaired neurodevelopment, to start targeted intervention at an early stage.

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CRediT authorship contribution statement

Ms. Dibbits collected data, performed neurodevelopmental tests, carried out analyses and revised the manuscript.

Drs. Rodijk conceptualized and designed the study, coordinated inclusion of participants and data collection, performed neurodevelopmental tests, carried out analyses, wrote the first version of the manuscript and revised the manuscript.

Drs. den Heijer designed the study, supervised the neurodevelopmental test assessments and data collection process, and critically reviewed and revised the manuscript.

Dr. Alizadeh supervised data analyses and critically reviewed and revised the manuscript.

Dr. Bos, Dr. Hulscher, Dr. Verkade and Drs de Kleine conceptualized the study and critically reviewed and revised the manuscript.

Dr. Bruggink conceptualized and designed the study, supervised data collection, and critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Declaration of competing interest

AF Bos is a tutor of the GM Trust, teaching the various patterns of general movements.

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