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Predictive value of General Movements Assessment for developmental delay at 18 months in children with complex congenital heart disease

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ABSTRACT

Background: Infants with complex congenital heart disease are at increased risk of impaired fetal brain growth, brain injury, and developmental impairments. The General Movement Assessment (GMA) is a valid and reliable tool to predict cerebral palsy (CP), especially in preterm infants. Predictive properties of the GMA in infants with complex congenital heart disease (CCHD) are unknown.
Aim: To evaluate predictive properties of the GMA to predict developmental outcomes, including cerebral palsy (CP), at 18-months corrected age (CA) in children with CCHD undergoing heart surgery in the first month of life.
Methods: A prospective cohort of 56 infants with CCHD (35 males, 21 females) was assessed with GMA at writhing age (0–6 weeks CA) and fidgety age (7–17 weeks CA) and the Bayley Scales of Infant Development at 18 months. GMA focused on markedly reduced GM-variation and complexity (definitely abnormal (DA) GM-complexity) and fidgety movements. Predictive values of GMA for specific cognitive, language and motor delay (composite scores <85th percentile) and general developmental delay (delay in all domains) were calculated at 18 months.
Results: At fidgety age, all infants had fidgety movements and no child was diagnosed with CP. DA GM-complexity at fidgety age predicted general developmental delay at 18 months (71 % sensitivity, 90 % specificity), but predicted specific developmental delay less robustly. DA GM-complexity at writhing age did not predict developmental delay, nor did it improve prediction based on DA GM-complexity at fidgety age.
Conclusions: In infants with CCHD and fidgety movements, DA GM-complexity at fidgety age predicted general developmental delay.

1. Introduction

Advances in medical and surgical management of infants with complex congenital heart disease (CCHD) have improved survival into adulthood. This success is, however, burdened with a heightened risk of brain injury in these infants resulting from impaired circulation, reduced blood oxygen capacity to the fetal and neonatal brain, and impaired brain growth in-utero compared to infants without CCHD [1]. The heightened risk is manifested throughout the developmental trajectory with an increased prevalence of neurodevelopmental impairments affecting motor, cognitive, behavioral and academic domains of development from birth through adolescence, particularly for children with single ventricle physiology [2,3]. These impairments include cerebral palsy (CP), but other less severe neurodevelopmental impairments also occur more frequently [4]. The insults that lead to CP in children with CCHD may result from the shared genetic origin, abnormal fetal or postnatal circulation, or adversities associated with postnatal cardiac surgeries or procedures [5]. The risk of CP in children with CCHD is 5 to 15 times higher than in the general population (overall prevalence of CP in the general population in high income countries: 0.1–0.3 % [6–8]; prevalence in children with CCHD in similar high income settings: 1.5 %) [5]. This means that the prevalence of CP in

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children with CCHD is in the similar range as that of infants born moderately to late preterm (33 to 36 weeks of gestation) [9], in whom GMA is often applied to monitor neurodevelopmental outcome [10].

The high risk of neurodevelopmental impairments demands early detection of these disorders for early intervention facilitating optimal infant development. An excellent tool for early detection of neurodisability is the General Movements Assessment (GMA) [11,12]. General movements (GMs) are the most often-occurring movement pattern at early age [12]. General movements are endogenously generated movements involving all body parts [13]. They appear during fetal life and disappear when goal-directed motor behavior develops around 4–5 months corrected age (CA). Typical GMs are always characterized by movement complexity and variation. Three GM-phases can be distinguished: 1) fetal/preterm phase (before 36–38 weeks postmenstrual age (PMA)); 2) writhing phase (between 36 and 38 weeks PMA and 6–8 weeks CA; a forceful component is added to the movements probably brought about by the increased motoneuronal excitability due to the transiently altered setting of various transmitter systems in the peri-term period [14,15]; and 3) fidgety phase from 2 months to 4–5 months CA [7]. During the latter phase, the forceful writhing component has disappeared, whereas the basic GM-melody consists of small, dancing movements occurring irregularly over the body (fidgety movements) [16,17].

In the assessment of the quality of GMs, two components may be distinguished, each attributed to a specific neural substrate [14]. At all GM-ages, GMA involves the assessment of movement complexity and variation (GM-complexity), also called the GM-repertoire [12]. Evidence suggests that GM-complexity reflects the integrity of the subcortical-cortical connectivity [14]. At fidgety age, also the presence of the age-specific fidgety movements is assessed. The emergence of fidgety movements is attributed to the maturation of the networks in the cortical plate [14]. At fidgety age, the presence of impairments in both GM-characteristics (movements with very limited GM-complexity and absent fidgety movements) is associated with a very high risk of CP [18]. When both markers of GM-quality are atypical, sensitivity and specificity levels for CP diagnosis reach values >90 % [19].

Atypical GMs at fidgety age do not only predict CP, but are also associated with an increased risk of cognitive and language delays at preschool ages and mental health disorders at school age [11,20–22]. In preterm infants, limited GM-complexity has consistently been associated with cognitive delay [23–25], whereas the association between absent fidgety movements and cognitive delay has not consistently been found [20,23].

Previous studies indicated that infants with CCHD have an increased prevalence of atypical GMs [26,27]. Atypical GMs at fidgety age have been associated with reduced prenatal cerebral perfusion, single ventricle physiology, and systemic postoperative oxygen saturations <90 % [26,28]. Interestingly, only reduced GM-complexity and not absent fidgety movements were associated with chronic hypoxemia, defined as systemic oxygen saturation of <90 % at hospital discharge [26], which suggests that chronic hypoxemia especially affects subcortical-cortical connectivity [14,26].

Little is known about the predictive value of GMA for neurodevelopmental outcome in infants with CCHD. Therefore, the aim of the present study is to evaluate the diagnostic accuracy of GMA for predicting developmental outcomes, including CP, at 18-months CA in children with CCHD undergoing surgery in the first month of life. The study is based on the ongoing follow-up of the cohort of infants with CCHD described by Huisenga et al. [26]. As only one of the 72 study infants had absent fidgety movements at fidgety age, we focused on the predictive value of GM-complexity only. We addressed the following questions: (1) What is the predictive power of very limited GM-complexity (definitely abnormal (DA)), during the fidgety phase for a developmental delay (i.e., score < 85th percentile) across all three composite scores of the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-3) [29] at 18 months? (2) What is the predictive power of DA GM-complexity for impaired development within specific domains: a) cognitive composite b) motor composite and c) language composite scores at 18 months? (3) Does the addition of GMA at writhing age improve the prediction of DA GM-complexity during the fidgety phase?

2. Material and method

2.1. Study design

The study was a longitudinal prospective cohort study involving consecutively eligible infants with CCHD who underwent surgery at Advocate Children's Hospital, Oak Lawn, Illinois, between May 2015 and June 2019 [26]. Advocate's Children's Hospital has a medium-sized surgical program that was consistently awarded a three star rating by the Society of Thoracic Surgeons public reporting system during the study period. Surgical volumes averaged around 265 per year, of which 40–50 were neonatal surgeries (excluding PDA procedures). Patients were cared for in a 9 bed dedicated pediatric cardiac critical care unit after surgery. The Institutional Review Board of Advocate Health Care approved the study (registered as NCT02781545).

2.2. Participants

Inclusion criteria included: newborn infants (1) diagnosed with CCHD by echocardiography and defined as structural defects that cause complex alterations in blood flow and hemodynamics;; (2) completed primary surgery or surgical palliation at Advocate Children's Hospital within 30 days of life. Exclusion criteria included: (1) primary surgery performed after 30 days of life; (2) presence of documented chromosomal, neurological, or genetic syndromes. Parents of eligible newborn infants received verbal and written information about the study and supplied written informed consent before data were collected.

2.3. Procedures

Infants received longitudinal assessments with the GMA: before surgery, before hospital discharge after primary surgery, and/or at writhing age (0–6 weeks), and fidgety age (7–17 weeks) CA as previously published [26]. In the present study only the assessments at writhing and fidgety age were used. At the youngest ages, GMA took place in the hospital (critical care units; inpatient general floors). Older infants' evaluations took place in the outpatient high-risk cardiology clinic or the infant's home. During video recording sessions, infants were hemodynamically stable and free from arterial lines, central catheters, and sedation medications. Infants were in an active, awake, non-crying behavioral state.

Longitudinal clinical monitoring of infant development at the Cardiac Neurodevelopmental Clinic on the Advocate Children's Hospital included an assessment with the BSID-3 at 18 months (CA) performed by experienced pediatric therapists (physical, occupational, and speech). Clinical follow-up also included assessment for the presence of CP, according to the criteria of the Surveillance of Cerebral Palsy in Europe [30].

2.4. Developmental assessments

2.4.1. General Movements Assessment (GMA)

The GMA is a non-invasive, video-recorded infant assessment based on the infant's spontaneous movements in supine. The video recording is required to evaluate the basic parameters of GM-quality, movement complexity (the independent exploration of all degrees of freedom in all participating body joints) and movement variation (the continuous exploration of complexity over time) [14] – in the current paper summarized as GM-complexity. The video recording can be completed in 3–5 min provided that the infant is in the required behavioral state

(active wakefulness). Off-line scoring and administration require another 5 to 10 min [12,20].

The assessment of the quality of GMs involves at all GM-ages the evaluation of GM-complexity. Four categories of GM-complexity have been distinguished: normal-optimal (abundant complexity), normal-suboptimal (sufficient complexity), mildly abnormal (insufficient complexity; reflecting typical but non-optimal brain function), and definitely abnormal (very limited complexity reflecting brain dysfunction) [16]. The DA-complexity has predictive value for developmental outcome, and GM-complexity was dichotomized into DA GM-complexity and non-DA GM-complexity.

At fidgety age GMA also involves the evaluation of the fidgety movements. Fidgety movements were classified as continually or intermittently present (+), sporadically present (±), or absent (−) [31]. For the calculation of predictive values fidgety movements were dichotomized into absent (−) and present (+ and ±). Two authors (DH and MHA) assessed all videos of the infants independently. In case of disagreement, findings were discussed until consensus was reached. MHA was blinded to the clinical background of the infants.

Most infants had multiple GM-recordings in the writhing and in the fidgety periods (see [26]). For data reduction, the multiple GMAs were recoded into one GMA classification for each period. Infants with stable GM-complexity within a period or one GMA kept the corresponding GM-complexity or fidgety movements classification. In infants with multiple GMAs the most often occurring classification was assigned. Infants with an equal number of a specific GMA classification were assigned the result of their last GMA.

Experienced assessors show a high reliability in the assessment of GM-complexity (inter-rater agreement: kappa 0.78–0.82) [24] and fidgety movements (kappa 0.88–0.91) [11]. As GMA reliability is experience-dependent, we determined reliability of GMA based on randomly selected videos (use of a random number generator) from the present study, assessed independently by DH and MHA. Cohen's kappa (κ) was used to calculate agreement; according to Fleiss [32], κ-Values of 0.40 to 0.75 are rated as fair to good, and values >0.75 as excellent.

2.4.2. Bayley Scales of Infant and Toddler Development, 3rd edition

The BSID-3 is an individually administered, norm-referenced instrument that assesses the developmental functioning of infants and young children between 1 month and 42 months of age across five domains of development: Cognitive, Language, Motor, Social-Emotional, and Adaptive. Its primary purposes are to identify children with developmental delays and to supply information for intervention planning [29]. Raw scores can be transformed into composite scores for each domain. The composite scores are scaled to a metric with a mean of 100 and a standard deviation (SD) of 15 [29]. We used the Cognitive, Language, and Motor composite scores and defined composite scores <85th percentile as developmental delay. We also used fine motor and gross motor subscale scores <7 to identify the specific motor delay. Our primary outcome was the presence of developmental delay (<85th percentile) in all three composite scores, which we labeled as general developmental delay.

2.5. Statistical analyses

We analyzed the data using the following procedures: 1) comparison of motor, cognitive, and language mean scores between children with DA GM-complexity and non-DA GM-complexity in each GM phase using two-sample independent *t*-test; 2) associations between DA GM-complexity and non-DA GM complexity and developmental delay at 18 months using multivariable logistic regression to calculate Odds Ratios (ORs) with 95 % confidence intervals (95 % CI), adjusted for the following confounders: male sex, preterm birth, and maternal education; and – most importantly - 3) prediction by calculating sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) including 95 % confidence intervals (CIs) for the various forms of developmental delay at 18-months. The confounders were selected on a-priori basis in alignment with current literature [2,33,34]. IBM SPSS Statistics for Mac version 24.0 (IBM Corp., Armonk, NY, USA) and MedCalc Software Ltd. [35] were used for statistical calculations.

3. Results

3.1. Cohort characteristics

Fig. 1 is a flow chart of infants with CCHD enrolled in the study. Eighty-four infants were eligible for the study, of which 76 were enrolled. One infant died before the first GMA and one infant was too ill to have a GMA at writhing age, leaving 74 infants for GMA at writhing age. Before fidgety age, another infant died, one withdrew from the study, and one parent had a scheduling conflict that prevented a GMA of their infant. The infant, who was too ill for a GMA at writing age, had a GMA at fidgety age. As a result, 72 infants had a GMA at fidgety age. Before the 18-month BSID-3 assessment, a total of three infants died, four had heart transplant referrals and followed elsewhere, one withdrew, four were lost to follow-up, and four canceled the developmental assessment appointment. Thus, 56 children were available for the evaluation of prediction of developmental outcome based on GMA at writhing age and 55 based on GMA at fidgety age. Of the final cohort that had a GMA at fidgety age and a developmental assessment at 18 months, 34 infants had a GMA at home, 20 infants had a GMA in an outpatient clinic, and 1 infant had a GMA as an inpatient in the hospital.

Study participant's neonatal characteristics, GM-quality at writhing and fidgety ages, and neurodevelopmental outcome at 18 months of age is found in Table 1. Thirty-five infants (63 %) were male, five infants (9 %) were born preterm, 45 had cardiopulmonary bypass during their primary surgery, and 44 infants (78 %) were categorized in the 4 and 5 Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) categories, which indicated greatest risk of mortality associated with a CHD surgical procedure. Twelve (21 %) infants had DA-complexity at writhing age and 10 (18 %) at fidgety age. Only one child had absent fidgety movements at fidgety age. She also had shown DA GM-complexity and unfortunately died at 16 weeks CA. General developmental delay was present in 7 children (13 %), motor delay in 13 children (23 %), cognitive delay in 18 children (32 %) and language delay in 20 children (36 %). Despite the proportion of children identified with a general developmental delay and motor delay, none of the children in our cohort were diagnosed with CP at 18 months.

3.2. Interrater reliability

Evaluation of inter-rater reliability was excellent for GM-complexity at both time points: The results of the interrater agreement were as follows: GM-complexity at writhing age: $n = 10$, $\kappa = 0.851$ (95 % CI: 0.577–1.12); fidgety age: $n = 30$, $\kappa = 0.786$ (95 % CI: 0.588–0.984). Fidgety movement results were $n = 60$, $\kappa = 0.826$ (95 % CI: 0.708–0.944).

3.3. GMA and neurodevelopmental outcome

Motor, cognitive, and language mean scores of infants with DA-complexity at writhing age were not significantly different from those with non-DA GM-complexity. However, infants with DA GM-complexity at fidgety age scored 15.82 points lower in mean cognitive scores ($p < 0.001$) than infants with non-DA GM-complexity. Motor and language scores at 18 months were not significantly different between infants with DA GM-complexity at fidgety age and those with non-DA complexity (Supplementary Material S1).

Table 2 shows the association between DA GM-complexity at writhing and fidgety ages and developmental delay at 18-months. It is clear that DA GM-complexity at writhing age was not associated with developmental delay at 18 months. However, there was a significant

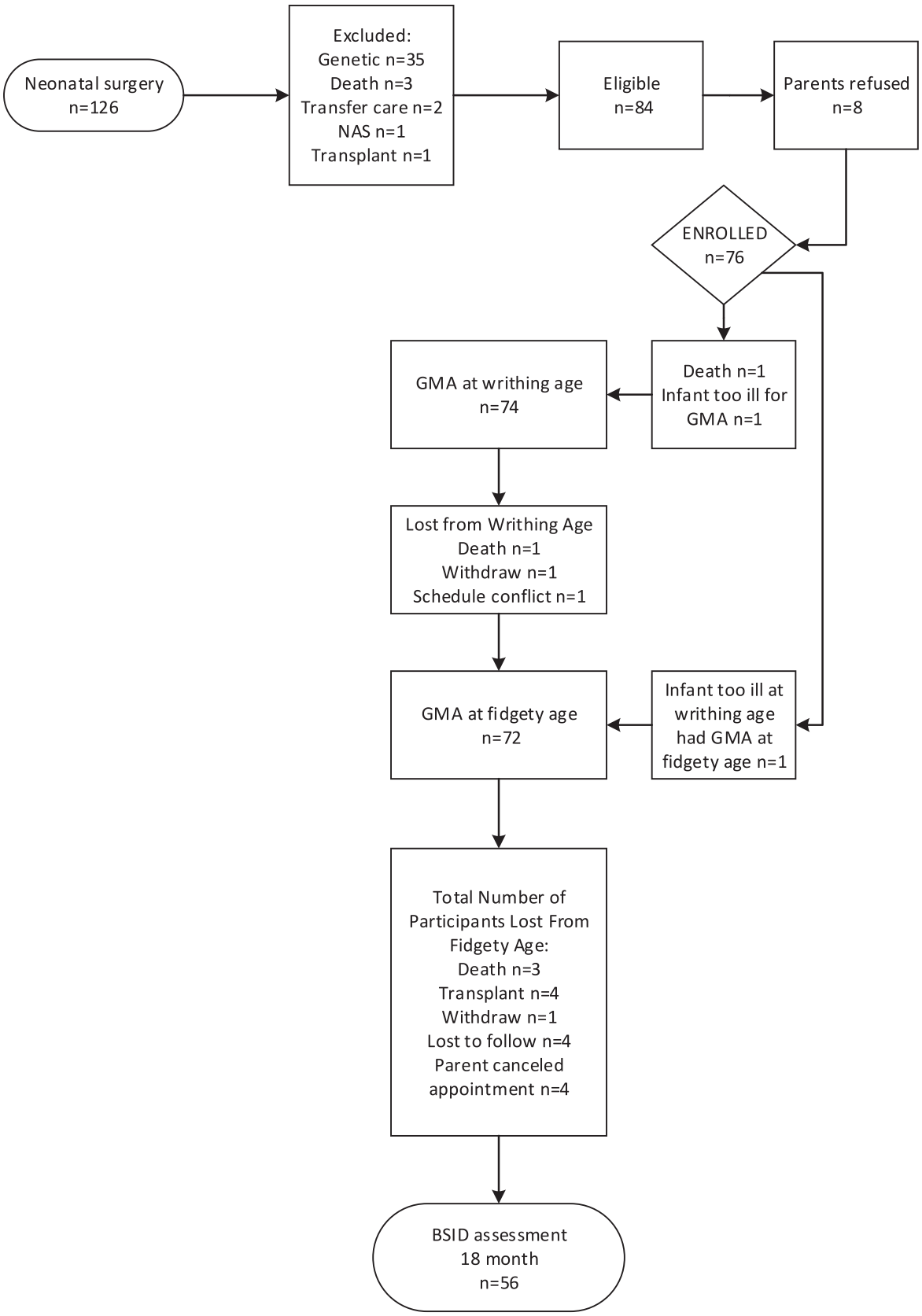

Fig. 1. Flow diagram of infants included in the study.
BSID = Bayley Scales of Infant and Toddler Development; GMA = General Movement Assessment; NAS = Neonatal Abstinence Syndrome; Transplant = heart transplant and followed elsewhere.

Table 1
Neonatal characteristics, GM-quality and neurodevelopmental outcome at 18 months CA of 56 infants studied.

Neonatal characteristics	
Male, *n* (%)	35 (63)
Gestational age (weeks), median weeks (IQR)	38.5 (38.0–39.0)
<30, *n* (%)	0 (0 %)
31–34, *n* (%)	1 (2 %)
35–37, *n* (%)	4 (7 %)
>37	51(91 %)
Preterm birth (GA < 37 weeks), *n* (%)	5 (9)
Birth weight (grams), mean (SD)	3233.6 (561)
Head circumference (centimeters), mean (SD)	33.4 (1.8)
CCHD diagnosis, *n* (%)	
Coarctation of aorta	2 (4 %)
Tetralogy of Fallot	1 (2 %)
Transposition of Great Arteries	14 (25 %)
Congenital pulmonary artery anomalies	3 (5 %)
Truncus arteriosus	2 (4 %)
Total Anomalous Pulmonary Venous Return	5 (9 %)
Unbalance Atrioventricular Canal	1 (2 %)
Multiple complex defects	16 (28 %)
Hypoplastic Left Heart Syndrome	12 (21 %)
STAT category, *n* (%)	
2	2 (4 %)
3	10 (18 %)
4	28 (50 %)
5	16 (28 %)
LOS after primary surgery (days), mean (SD)	23 (13.7)
Length of CPB, surgery within neonatal period (min), mean (SD); *n* = 45	138 (32.0)
ECMO *n* (%)	1 (2 %)
Maternal education: Low/Moderate/High, *n* (%)	6 (11)/31 (55)/19 (34)
General Movements Assessment categories	
GM-complexity at writhing age: *n* = 56	
NSO, *n* (%)	16 (29)
MA, *n* (%)	28 (50)
DA, *n* (%)	12 (21)
GM-complexity at fidgety age: *n* = 55	
NSO, *n* (%)	13 (24)
MA, *n* (%)	32 (58)
DA, *n* (%)	10 (18)
Neurodevelopmental outcome at 18 months CA	
Cerebral palsy, *n* (%)	0 (0)
BSID-3 composite scores 18 months, mean (SD)	
Motor	90.82 (11.83), range 52–115
Cognitive	89.38 (14.08), range 55–125
Language	87.79 (12.27), range 65–118
BSID-3 < 85th percentile at 18 months, *n* (%)	
Motor (n = 55)[a]	13 (23)
Fine motor subscale <7	7 (12)
Gross motor subscale <7	16 (29)
Cognitive (n = 56)	18 (32)
Language (*n* = 56)	20 (36)
All composite scores (n = 55)[a]	7 (13)

Legend: GM = general movements; CA = corrected age; IQR = Interquartile Range; GA = gestational age; CCHD = Complex Congenital Heart Disease; STAT = The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (no cases of STAT 1), higher STAT category = greater risk of mortality associated with CHD surgical procedure; Maternal Education: Low = grade school, Moderate = high school, partial college, trade school, High = College or University; LOS = length of stay; CPB = Cardiopulmonary bypass; GM-quality: NSO = normal suboptimal, MA = mildly abnormal; DA = definitely abnormal; BSID-3 = Bayley Scales of Infants and Toddler Development-3rd edition.

[a] 1 infant had no motor assessment at 18 months.

association between DA GM-complexity at fidgety age for general developmental delay (adjusted OR 18.11; 95 % CI 2.36–139.20), cognitive delay (adjusted OR 5.88; 95 % CI 1.13–30.47), and gross motor delay (adjusted OR 7.18; 95 % CI 1.36–37.98). No association was found between DA GM-complexity at fidgety age and fine motor delay and language delay (Supplementary Material S2).

3.4. Predictive validity of GMA

Predictive values of DA GM-complexity for developmental delay at 18-months are found in Table 3. DA GM-complexity at writhing age did not successfully predict developmental delay, as noted by the low sensitivity values. Yet, DA-complexity at fidgety age predicted general developmental delay well, with a sensitivity of 71 % and specificity of 90 %. Predictive values for delay in the specific domains were lower, especially due to lower sensitivity values. Prediction of gross motor delay was better than prediction of fine motor delay (Table 3). The presence of DA GM-complexity at writhing age did not improve the prediction based on DA GM-complexity at fidgety age (Table 3c).

4. Discussion

In the relatively small cohort of infants with CCHD of the current study, in infants demonstrating age-appropriate fidgety movements, DA GM-complexity had good predictive validity for general developmental delay at 18 months. The predictive power for detecting delay in a single developmental domain was less sensitive. Addition of information of GMA at writhing age did not improve prediction of general developmental delay based on GMA findings at fidgety age only.

Infants with DA GM-complexity and present fidgety movements have a clearly increased risk of CP, but the risk is less than infants demonstrating DA GM-complexity and absent fidgety movements [18]. It is the specific combination of both GMA-signs (DA GM-complexity and absent fidgety movements) that places the infant at very high risk of CP [18,19]. Butcher et al. [23] reported that in a study of preterm infants ≤33 weeks GM-complexity was associated with cognitive outcomes at school age, whereas absent fidgety movements were not. Van Dyke et al. 2018 [25] reported persistently DA GM-complexity trajectories were associated with delayed motor and cognitive outcomes at 18–24 months in preterm infants aged <30 weeks. Other studies in preterm infants have shown associations between reduced GM-complexity at fidgety age and cognitive impairment, attention deficit hyperactivity disorder, and minor neurological dysfunction [20–22]. The difference in prediction of GM-complexity at fidgety age and presence of fidgety movements corresponds to the hypothesized difference in neural substrate of both signs. Markedly reduced GM-complexity reflects compromised connectivity of complex cortico-subcortical networks, in which the periventricular white matter plays a dominant role, whereas the presence of fidgety movements reflects age-appropriate maturation of the cortical networks [14]. Neuroimaging studies showed that infants with CCHD are especially predisposed to impaired integrity of the white matter [36,37]. While there has been a decline in severe neurologic insults in children with CCHD, many children experience behavioral, emotional, cognitive, and motor impairments [2], suggesting nonspecific, widespread impairment of intracerebral connectivity [38]. The notion that DA GM-complexity reflects this impaired intracerebral connectivity would also explain why DA GM-complexity better predicts cognitive delay than motor delay. The results of this study indicate that GMA should not be restricted to the assessment of fidgety movements but must also include the evaluation of GM-complexity (the infant's motor repertoire).

We found that DA GM-complexity at writhing age did not predict developmental delay, nor did it improve predictive power of developmental delay based on GM-complexity at fidgety age. The recent systematic review of Casaer et al. [39] showed that in very preterm infants, GMA at writhing age had limited predictive power for developmental delay. The authors suggested that longitudinal trajectories of GMA in very preterm infants from preterm age up to and including fidgety age result in best prediction. Our data show that the situation in infants with CCHD may be different. We know that movement quality is not a fixed phenomenon and can be transiently and moderately affected by illnesses

Table 2
Associations between DA GM-complexity at: a) writhing age; b) fidgety age; c) writhing and fidgety ages combined and developmental delay based on BSID-3 composite scores <85th percentile at 18 months.

a) Writhing age

GM quality	General developmental delay		Total	OR (95 % CI)	Motor delay		Total	OR (95 % CI)	Cognitive delay		Total	OR (95 % CI)	Language delay		Total	OR (95 % CI)
	Yes	No			Yes	No			Yes	No			Yes	No		
DA GM-complexity	2	10	12	1.41 (0.19–10.32)	3	9	12	0.85 (0.18–4.06)	5	7	12	1.27 (0.30–5.45)	5	7	12	1.14 (0.27–4.77)
Non-DA	5	39	49	–	10	33	43	–	13	31	44	–	15	29	44	–
Total	7	49	56	–	13	42	55	–	18	38	56	–	20	36	56	–

b) Fidgety age

GM quality	General developmental delay		Total	OR (95 % CI)	Motor delay		Total	OR (95 % CI)	Cognitive delay		Total	OR (95 % CI)	Language delay		Total	OR (95 % CI)
	Yes	No			Yes	No			Yes	No			Yes	No		
DA GM-complexity	5	5	10	**18.11 (2.36–139.20)**	5	5	10	4.10 (0.84–19.71)	7	3	10	**5.88 (1.13–30.47)**	6	4	10	2.25 (0.48–10.53)
Non-DA	2	43	45		8	36	44		11	34	45		14	31	45	
Total	7	48	55		13	41	54		18	37	55		20	35	55	

c) Writhing and Fidgety ages combined

GM-complexity	General developmental delay		Total	OR (95 % CI)	Motor delay		Total	OR (95 % CI)	Cognitive delay		Total	OR (95 % CI)	Language delay		Total	OR (95 % CI)
	Yes	No			Yes	No			Yes	No			Yes	No		
Wri DA, Fid DA	2	2	4	9.51 (0.58–155.29)	2	2	4	3.15 (0.31–32.16)	3	1	4	4.69 (0.35–63.89)	3	1	4	3.90 (0.29–51.67)
Wri Non-DA, Fid Non-DA	5	46	51		11	39	50		15	36	51		17	34	51	
Total	7	48	55		13	41	54		18	37	55		20	35	55	

Bold: significant associations.
Legend: BSID-3 = Bayley Scales of Infant and Toddler Development, 3rd edition; Delay is identified as composite score < 85th percentile in all three domains (general delay), or in an individual domain; CI = confidence interval; DA = definitely abnormal; Fid = Fidgety phase; GM = general movements; OR = Odds Ratio, determined by multiple logistic regression analyses adjusted for male sex, maternal education, and preterm birth (GA < 37 weeks), as they contributed significantly to outcome (likelihood ratio tests); bold type indicates significant association; Wri = Writhing phase.

Table 3
Prediction of DA GM-quality at: a) writhing age, b) fidgety age, c) writhing and fidgety ages combined for developmental delay (BSID-3 composite scores <85th percentile at 18 months).

	Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)
a. Writhing age: presence of DA GM-complexity				
General developmental delay	28.57 % (3.67–70.96)	79.59 % (65.66–89.76)	16.67 % (5.19–24.07)	88.64 % (82.70–92.71)
Motor delay	23.08 % (5.04–53.81)	78.57 % (63.19–89.70)	25 % (9.55–51.26)	76.74 %% (70.20–82.21)
Cognitive delay	27.78 % (9.69–53.48)	81.58 % (65.67–92.26)	41.67 % (20.79–66.03)	70.45 % (63.30–76.73)
Language delay	25 % (8.66–49.10)	80.56 % (63.98–91.81)	41.67 % (20.66–66.21)	65.91 % (58.89–72.29)
b. Fidgety age: presence of DA GM-complexity				
General developmental delay	71.43 % (29.0–96.3)	89.36 % (76.90–96.45)	50 % (27.83–72-17)	95.45 % (84.53–99.44)
Motor delay[a]	38.46 % (13.86–68.42)	87.80 % (73.80–95.92)	50 % (25.52–74.48)	81.82 % (74.26–87.53)
Cognitive delay	38.89 % (17.30–64.25)	91.89 % (78.09–98.30)	70 % (40.56–88.86)	75.56 % (67.87–81.89)
Language delay	30.00 % (11.89–54.28)	88.57 % (73.26–96.80)	60 % (32.43–82.42)	68.89 % (61.88–75.13)
c. Writhing and Fidgety age: presence of DA GM-complexity in both age periods				
General developmental delay	28.57 % (3.67–70.96)	95.74 % (85.46–99.48)	50 % (4.76–93.24)	90.00 % (78.19–96.67 %)
Motor delay	15.38 % (1.92–45.45)	95.12 (83.47–99.40)	50 % (13.49–86.51)	78 % (73.57–81.87)
Cognitive delay	16.67 % (3.58–41.42)	97.30 % (85.84–99.93)	75 % (25.10–96.41)	70.59 % (65.97–74.82)
Language delay	15 % (3.21–37.89)	97.14 % (85.08–99.93)	75 % (25.03–96.42)	66.67 % (62.26–70.80)

Legend: DA = definitely abnormal; GM = general movements; BSID-3 = Bayley Scales of Infant and Toddler Development, 3rd edition; Sensitivity = true positives/(true positives + false negatives); Specificity = true negatives/true negatives + false positives); PPV (positive predictive value) = true positives/all positives; NPV (negative predictive value) = true negatives/all negatives.

[a] Prediction of DA-complexity at fidgety age of
- Fine motor delay: sensitivity 28.57 %, specificity 82.98 %, PPV 20.00 %, NPV 88.64 %.
- Gross motor delay: sensitivity 37.50 %, Specificity 89.47 %, PPV 60.00 %, NPV 77.27 %.

[40]. It is conceivable that writhing GM-quality during the early post-surgical period in infants with CCHD is affected by illness, medication, and physiologic instability and represents the structural integrity of the neonatal brain [26].

DA GM-complexity at fidgety age highly predicted general developmental delay and predicted isolated delays in specific developmental domains less robustly. Two explanations for this difference can be offered. First, the nonspecific, widespread impairment of intracerebral connectivity documented in infants with CCHD does not only give rise to DA GM-complexity, but also to general developmental delay. Second, it is conceivable that children with a qualitatively reduced motor repertoire successfully manage the motor and language milestones expected at 18 months, i.e., walking independently and walking up and down stairs, naming or pointing at familiar objects, people, or body parts [24]. It should be noted that the developmental outcomes in the present study correspond to those reported in a recent systematic review [2].

The strengths of this study included the longitudinal design. The study is, to the best of our knowledge, the first study to evaluate the predictive values of the GMA for developmental outcomes at 18 months in infants with CCHD. Limitations were the attrition to follow-up and the sample consisting of heterogeneous children with surgery in the neonatal period from a single institution that limited generalizability to all children with CCHD. We therefore recommend that future studies use a multi-center approach, as this allows for larger groups and analyses of developmental outcomes in specific subgroups of children with CCHD. An additional limitation is the lack of information on further procedures, including bypass, after initial palliative surgery that may have affected the associations between GMA and developmental delay. Conceivably such interference of further procedures would have made prediction worse.

5. Conclusion

The American Heart Association recommends a well-defined program of surveillance, screening, and evaluation of developmental delays in children with CHD as essential to obtain interventions appropriate to maximize the children's potential overall development. [41] GMA has as advantage that it is a non-invasive assessment, purely based on the infant's spontaneous movements, making it an attractive assessment for the vulnerable infants with CCHD. In line with the recommendation, our study showed that DA complexity and variation of GMs at fidgety age in infants with CCHD showing fidgety movements predicts delayed general development at 18 months. In infants with CCHD, GMA at writhing age does not improve predictive power for developmental delay, most likely related to their complex post-surgical condition and recovery period at an early, vulnerable age. Knowing that children with CCHD are at increased risk of neurodevelopmental impairments and that early detection of infants at high risk offers the opportunity for early intervention at an age with high neuroplasticity, we recommend GMA including the assessment of GM-complexity and fidgety movements at fidgety age, but not earlier.

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CRediT authorship contribution statement

Darlene C. Huisenga: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Sacha la Bastide-van Gemert:** Supervision, Validation, Writing – review & editing. **Andrew H. Van Bergen:** Conceptualization, Data curation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Jane K. Sweeney:** Conceptualization, Writing – original draft, Writing – review & editing. **Mijna Hadders-Algra:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Mijna Hadders-Algra has provided courses on the GMA since 1993. She did not get an honorarium, grant, or other form of payment to produce this manuscript. The other authors declare no conflict of interest.

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