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Published in:
Early Human Development

DOI:
10.1016/j.earlhumdev.2020.105167

Early Human Development 151 (2020) 105167

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

The quality of general movements in infants with complex congenital heart disease undergoing surgery in the neonatal period

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ARTICLE INFO

Keywords:
General Movements Assessment
Movement complexity
Complex congenital heart disease
Chronic hypoxaemia

ABSTRACT

Background: Advances in diagnostic technologies, surgical management, and perioperative care have increased survival for neonates with complex congenital heart disease (CCHD). The success of these advances exposed a heightened risk of brain injury and developmental disabilities. The General Movements Assessment, a non-invasive method, may detect early neurodevelopmental impairments in high-risk infants.
Aims: To examine whether infants with CCHD undergoing neonatal surgery have higher prevalence of atypical general movements (GMs) than a reference group, and whether single ventricle physiology with systemic oxygen saturations < 90% increases risk for atypical GMs.
Methods: Serial General Movements Assessment (GMA) in a cohort of infants with CCHD (n = 74) at writhing (term-6 weeks) and fidgety (7–17 weeks) GM-age. GMA focused on the presence of definitely abnormal GM-complexity and absent fidgety movements. Single GMAs at 3 months were available from a reference sample of Dutch infants (n = 300). Regression analyses examined relationships between cardiac characteristics and definitely abnormal GM-complexity.
Results: Higher prevalence of definitely abnormal GM-complexity in infants with CCHD compared to reference infants (adjusted OR 5.938, 95% CI 2.423–14.355), single ventricle CCHD increased the risk. Occurrence of absent fidgety movements was similar in infants with CCHD and reference infants (adjusted OR 0.475, 95% CI 0.058–3.876). Systemic postoperative oxygen saturations < 90% was associated with higher risk of definitely abnormal GM-complexity at fidgety (adjusted OR 16.445 95% CI 1.149–235.281), not at writhing age.
Conclusions: Infants with CCHD, especially those with single ventricle CCHD, are at increased risk of definitely abnormal GM-complexity. GMA at fidgety age is recommended.

1. Introduction

Congenital heart disease is the most common birth defect worldwide, affecting millions of newborns each year [1]. With advances in diagnostic technologies, surgical management, and postsurgical care, over 90% of children with complex congenital heart disease (CCHD) are expected to survive to adulthood in the current era. The significant success of these advances has exposed a heightened risk of brain injury and developmental disorders and disabilities [2]. Infants with CCHD have impaired circulation, reduced blood oxygen carrying capacity to the fetal and neonatal brain, and impaired brain growth in-utero compared to infants without CCHD [3,4]. A recent systematic review and meta-analysis [5] highlighted the increased risk of impaired developmental outcomes from birth through adolescence in newborns with CCHD who required surgery in early infancy, especially for those with single ventricle physiology.

Early detection of impaired development facilitates referral to early intervention services. Traditionally, most tests used in young infants evaluate muscle tone, so-called primitive reflexes, postural reactions, and motor responses to sensory input [6]. However, their use may be limited in infants with CCHD due to unstable physiological status, intolerance of handling, or sternal precautions. In infants with CCHD the technique of General Movements Assessment (GMA) offers an excellent alternative. The GMA is based on principles of movement variation and

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https://doi.org/10.1016/j.earlhumdev.2020.105167
Received 2 July 2020; Received in revised form 22 August 2020; Accepted 25 August 2020

complexity and assesses infant's spontaneous movements (GMs). It is used to evaluate the brain integrity in young infants [7]. GMA is highly predictive of cerebral palsy (CP) [8,9]. In addition, abnormal general movements (GMs) are associated with an increased risk of learning and behavioural problems at school age [10–12].

Knowing that infants with CCHD are at increased risk of developmental impairment, the aim of our study was to assess whether these infants show an increased prevalence of atypical GMs and whether a potentially increased prevalence of atypical GMs is related to ventricular physiology and the infant's systemic oxygen saturation (SpO2) in early life. In the literature the contribution of reduced oxygen saturation to the infant's developmental outcome is debated. The disparity in study outcomes most likely can be attributed to differences in the measurement of oxygen saturation in techniques (pulse oximetry, near infrared spectroscopy), timing (around surgery or at discharge from the hospital), and differences in developmental outcome parameters (developmental instruments or brain volumes) [13–15].

We addressed the following questions: (1) is GM quality at fidgety age of infants with CCHD worse than that of reference infants, in particular do infants with CCHD show increased GM-abnormalities that are clinically relevant (GMs with definitely abnormal complexity and absent fidgety movements); (2) do infants with single ventricle physiology show more atypical GMs at writhing age (0–6 weeks) and fidgety age (7–17 weeks) compared to infants with two ventricle physiology; and (3) is hypoxaemia, defined as SpO2 $<$ 90%, at birth or at discharge from hospital associated with a higher prevalence of atypical GMs at writhing and fidgety GM-age?

2. Material and methods

2.1. Study design

This was a longitudinal prospective cohort study involving consecutively eligible infants with CCHD who had surgery at Advocate Children's Hospital (ACH) between May 2015 and June 2019. The Institutional Review Board of Advocate Health Care approved the study; registered as NCT02781545. For reference, we had access to GMA data of a cohort infants representative of the Dutch population. The reference group was only assessed at fidgety age.

2.2. Participants

Inclusion criteria for the longitudinal study included: newborns (1) diagnosed with CCHD by echocardiography and (2) who had primary surgical palliation at ACH within the neonatal period (birth to 30 days). Infants were excluded if: (1) primary surgery was after 30 days and (2) had documented chromosomal, neurological, or genetic syndromes. Parents of eligible newborns were given information about the study and provided informed consent before data were collected. Clinical data were extracted on standardized data collection charts. The data included standardized recordings of SpO2 $<$ 90% at birth and at discharge by means of pulse oximetry.

Infants of the Dutch reference group were participants of the IMP-SINDA (Infant Motor Profile [16] and Standardized Infant NeuroDevelopmental Assessment [17]) project. The data of 1700 infants aged 2 to 18 months from a representative Dutch population in terms of social class and maternal ethnicity were collected 2017–2019. The IMP assessment is video-based and starts in young infants with an observation of spontaneous movements in supine position for at least 3 min. This allowed us to perform GMA in the 300 infants aged 2–4 months [18]. These infants formed our reference group. None of these infants had CCHD.

2.3. Developmental assessment

The GMA is a non-invasive, video-based infant assessment based on the infant's GMs. GMs are spontaneous movements, which involve all body parts, and are not related to external stimuli [19]. They emerge during early fetal life and disappear when goal-directed motor behaviour emerges around 4–5 months corrected age (CA). Typical GMs are characterized in particular by complexity and variation (in short: complexity), whereas atypical GMs exhibit a limited repertoire of movement complexity [20]. The nature of typical GMs changes as a result of developmental transformations of the nervous system. In the last phase, at 2–5 months CA, GMs have a 'fidgety' character. Fidgety movements occur irregularly over the body and consist of a continuous stream of tiny elegant movements. From early fetal life onwards, atypical GMs are primarily characterized by reduced complexity [20,21]. At fidgety age – the age at which GMA best predicts developmental outcome [8,9] – atypical GMs are also characterized by a reduction or absence of the age-specific fidgety movements. Therefore, Hadders-Algra suggested conducting GMA at 2–5 months CA (fidgety age) with a two-step procedure: (1) grading movement complexity and (2) assessing fidgety movements [20,21].

2.4. Procedures

Infants with CCHD were scheduled for longitudinal GMAs: before primary surgery, before hospital discharge, and at 1, 2, and 3–5 months CA. At the youngest ages, GMA took place in the hospital (critical care units, inpatient general floors). Older infant evaluations took place in the outpatient clinic or at infant's home. For the reference IMP-SINDA infants, only one assessment was recorded at the ages of 2–4 months CA.

Each GMA involved a 3–5 minute video recording of spontaneous movements in supine position. Care was taken to achieve an active awake, non-crying behavioural state. Infants with CCHD were stable, free from arterial lines, central catheters, and sedation medications during video recording. All videos were assessed according to Hadders-Algra protocol [7,21], which assesses GM complexity at all ages and fidgety movements at 2–5 months CA. GM complexity can be distinguished into 4 categories: normal-optimal (abundant complexity), normal-suboptimal (sufficient complexity), mildly abnormal (insufficient complexity; reflecting normal but non-optimal brain function) and definitely abnormal (very limited complexity reflecting brain dysfunction). Normal-optimal and normal-suboptimal complexity was pooled to form the category of normal complexity. For statistical analyses GM complexity was dichotomized into definitely abnormal, the clinically relevant category, and non-definitely abnormal category. Fidgety movements at fidgety age were divided into three categories: + clearly present (either continually present or intermittently present), +/− (sporadically present), and – (absent). For statistical analyses fidgety movements were dichotomized into absent and present (combination of two categories). Two authors (DH and MHA) assessed all videos of infants with CCHD independently. In case of disagreement, findings were discussed until consensus was reached. MHA was blinded to clinical background of infants with CCHD. MHA performed GMA of the IMP-SINDA cohort; she was masked to the infants' history.

2.5. Statistical analysis

Sample size of the CCHD cohort was based on the ability to demonstrate differences in outcome of infants with SpO2 $\geq$ 90% and those with SpO2 $<$ 90% on IMP scores at 18 months. The a priori sample size estimate with G*power 3.1 indicated two groups of 19 infants each resulted in 80% power ($\alpha = 0.05$) [22]. Attrition from death and family stress is a historical concern in studies of children with CCHD; therefore we aimed at having a minimum of 30 infants in each group.

Background factors between groups were compared with parametric or non-parametric tests where appropriate. For the latter we used the Mann Whitney *U* test, Chi square test, and Fisher's exact test. To

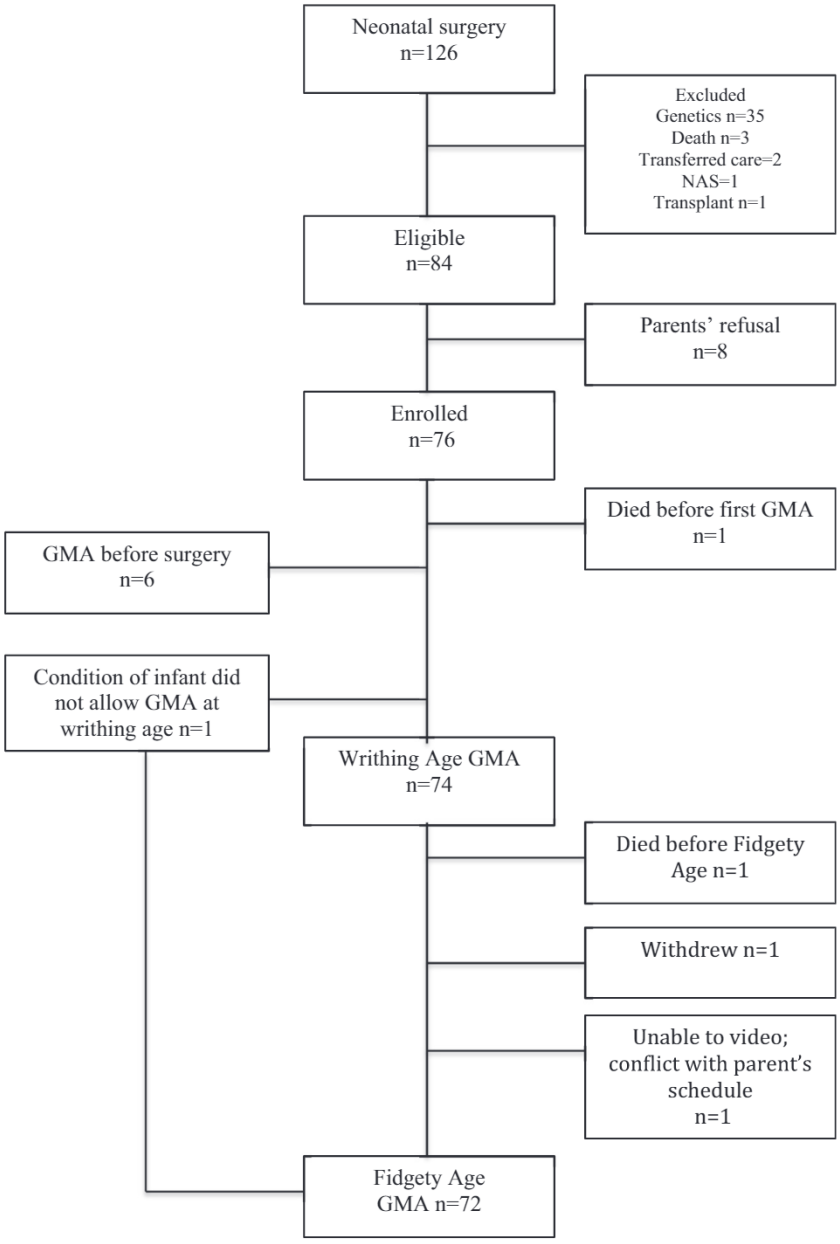

Fig. 1. Flow diagram of infants with CCHD.
CCHD, complex congenital heart disease; GMA, General Movements Assessment; NAS, neonatal abstinence syndrome.

estimate differences in outcome characteristics, univariable and multivariable statistics were used. In the multivariable logistic regression analyses comparing infants with CCHD with reference group, we adjusted for the following confounders: preterm birth, male sex, and maternal education. In the multivariable logistic regression comparing infants with single and two ventricle CCHD, we adjusted for preterm birth, male sex, maternal education, SpO2 $<$ 90% at birth and at discharge, mechanical ventilation $>$ 6 days and length of hospital stay $>$ 21 days. The confounders were selected on a-priori basis, in alignment with current literature [5]. Results are expressed as odds ratio (OR) with 95% confidence intervals (95% CI). All data were analysed using IBM SPSS Statistics for Mac version 24.0 (IBM Corp., Armonk, NY, USA).

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 whom 76 were enrolled. One infant died before first GMA and one infant was too ill to have GMA at writhing age, leaving 74 infants for GMA at writhing GM-age. Before fidgety age, another infant died and one was withdrawn from the study. One infant could not be assessed at fidgety age due to parental schedule complications. The infant, who was too ill at writhing age, was assessed at fidgety age. As a result, 72 infants had GMAs at fidgety age. Only six infants were adequately assessed prior to surgery; the others did not meet criteria for evaluation given medical condition.

Demographic and background characteristics of the CCHD and Dutch reference groups are demonstrated in Table 1. Infants with CCHD had lower gestational age than the reference group infants (p = 0.002). Maternal education in both groups was similar. Infants with single

Table 1
Background characteristics of infants with CCHD and infants of the Dutch reference group.

	Infants with CCHD			Dutch reference
	Infant with 1V CCHD *n* = 27	Infants with 2V CCHD *n* = 49	All infants with CCHD *n* = 76	*n* = 300
Male, *n* (%)	14 (52%)	32 (67%)	46 (61%)	162 (54%)
Gestational age in weeks, median (IQR)	38.0 (38.0–39.0)	39.0 (37.5–39.0)	**39.0 (38.0–39.0)**	**39.4 (38.3–40.6)***
Preterm birth (GA < 37 weeks), *n* (%)	3 (11%)	4 (11%)	7 (9%)	26 (8%)
Birth weight in grams, mean (SD)	3055 (454)	3251 (612)	**3288 (611)**	**3315 (621)***
Growth restriction at birth, *n* (%)				
< 10th percentile	2 (7%)	5 (10%)	7 (9%)	26 (9%)
Head circumference in centimeters, mean (SD)	**32.36 (1.57)**	**33.75 (1.84)**#	–	–
Maternal education: low/moderate/high, *n* (%)	5 (18%)/15 (56%)/7 (26%)	3 (6%)/28 (58%)/17 (36%)	8 (10%)/43 (57%)/25 (33%)	37 (12%)/144 (48%)/119 (40%)
Diagnosis, *n* (%)				
Coarctation of aorta	0 (0%)	3 (6%)	3 (4%)	n/a
Tetralogy of Fallot	0 (0%)	1 (2%)	1 (1%)	
Transposition of great arteries	0 (0%)	19 (39%)	19 (25%)	
Congenital pulmonary artery anomalies	1 (4%)	2 (4%)	3 (4%)	
Truncus arteriosus	0 (0%)	2 (4%)	2 (3%)	
Total anomalous pulmonary venous return	0 (0%)	7 (14%)	7 (9%)	
Unbalanced atrioventricular septal defect	1 (4%)	1 (2%)	2 (3%)	
Multiple complex congenital heart defects	7 (26%)	14 (29%)	21 (26%)	
Hypoplastic left heart syndrome	18 (66%)	0 (0%)	18 (25%)	
Prenatal diagnosis, *n* (%)	**22 (82%)**	**24 (49%)**#	46 (61%)	n/a
STAT category, *n* (%)				
2	0 (0%)	3 (6%)	3 (4.0%)	n/a
3	0 (0%)	14 (29%)	14 (18%)	
4	5 (18%)	30 (61%)	35 (46%)	
5	22 (82%)	2 (4%)	24 (32%)	
Surgical date after birth in days, median (IQR)	6 (5–8)	7.0 (5.5–10.5)	7 (5–9)	n/a
Cardiopulmonary bypass time in minutes, median (IQR)	136 (119–155)	134 (77–165.75)	135 (99–161)	n/a
Mechanical ventilation in days, median (IQR)	**10 (6–16)**	**4 (2–8)**#	6 (3 – 12)	n/a
Length of hospital stay after primary surgery in days, median (IQR)	**28 (21–35)**	**18 (14–26)**#	21 (16–28)	n/a
SpO2 at birth (< 90%), *n* (%)	**11 (24%)**	**34 (76%)**#	45 (59%)	n/a
SpO2 at discharge (< 90%), *n* (%)	**27 (100%)**	**14 (28%)**#	41 (54%)	n/a
Mode of feeding at discharge:				
PO only, *n* (%)	**0 (0%)**	**17 (35%)**#	17 (23%)	n/a
PO/NG tube, *n* (%)	17 (63%)	23 (48%)	40 (53%)	
NG tube only, *n* (%)	10 (37%)	8 (17%)	18 (24%)	
Gastroesophageal reflux medication at discharge, *n* (%)	**16 (59%)**	**16 (33%)**#	32 (43%)	n/a

Bold type indicates significant group differences.
Differences between infants with single versus two ventricle CCHD: # $p < 0.05$, tested with Mann Whitney or Fisher Exact test where appropriate.
Differences between infants with CCHD vs. Dutch reference group: * $p < 0.05$ with Mann Whitney test or *t*-test where appropriate.
Legends: ICU, Intensive Care Unit; IQR, Interquartile Range; NG, Nasogastric; PO, per os (oral); Maternal Education: Low, grade school, Moderate, high school, partial college, or trade school, High, College or University; SpO2, peripheral capillary oxygen saturation; STAT, The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery mortality risk score higher STAT category: greater risk of mortality associated with CHD procedure.
Growth restriction analysis based on values in Olsen et al. 2010 [31], for the Dutch infants in Wu et al. 2020 [18]

ventricle CCHD had smaller head circumference at birth ($p = 0.005$), higher rates of prenatal diagnosis ($p = 0.006$), longer intubation duration and need for mechanical ventilation during primary hospitalization ($p < 0.001$), longer length of hospital stay ($p < 0.001$), increased rate of hypoxaemia at discharge (p < 0.001), and increased need for gastroesophageal reflux medications ($p = 0.029$) when compared to infants with two ventricle CCHD.

GM complexity changed over time with substantial intra- and inter-individual variation (for details see Supplementary material file online). Six infants had GMA before and after surgery; their GM trajectories were also heterogeneous. Two infants showed normal GM complexity before surgery, but their GM complexity deteriorated thereafter to definitely abnormal (#4 and #16). GM complexity of two infants remained stable (#39 and #46). The remaining two infants demonstrated slightly improved GM complexity (#3 and #38). The time between surgery and GM assessments was not associated with GM-quality in infants with single ventricle CCHD. However, infants with two ventricle CCHD showed significantly more often definitely abnormal GM-quality at one week after surgery (adjusted OR: 14.023, 95% CI: 1.596–123.171) and two weeks after surgery (adjusted OR: 3.183, 95% CI: 1431–7.080) than GMAs at longer intervals after surgery.

Most infants had two assessments at writhing age and two assessments at fidgety age (Table 2). GM complexity at writhing age was stable in 50 infants, improved by one category in nine infants, and deteriorated by one category in 15 infants. GM complexity at fidgety age was stable in 53 infants, improved by one category in 14 infants, and deteriorated by one category in five infants. Fidgety movements were stable in 59 infants, improved by one category in 10 infants, and deteriorated by one category in three infants. For data reduction and to allow comparison with the reference group, the multiple GMAs were recoded into one GMA classification. 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 frequently occurring classification was assigned. Infants who had an equal number of a specific GMA classification were assigned the result of their last GMA.

3.2. GM quality in infants with CCHD and in the reference group

Table 2 summarizes GMA findings according to GM complexity and fidgety movements in infants with CCHD and the reference group. The prevalence of definitely abnormal GM-complexity was higher in infants

Table 2
GMA and crying in infants with CCHD and Dutch reference group.

	Infants with CCHD			Dutch reference
	Infant with 1V CCHD[a]	Infants with 2V CCHD[a]	All infants with CCHD[a]	*n* = 300
GM quality				
GM complexity				
Writhing age[a], *n* (%)				
Normal	2 (7%)	17 (35%)	19 (26%)	
Mildly abnormal	15 (58%)	20 (42%)	35 (47%)	–
Definitely abnormal	9 (35%)	11 (23%)	20 (27%)	–
Fidgety age[a], *n* (%)				
Normal	7 (27%)	11 (24%)	18 (25%)	235 (79%)
Mildly abnormal	11 (42%)	31 (67%)	42 (58%)	55 (18%)
Definitely abnormal	**8 (31%)**	**4 (9%)**[#]	**12 (17%)**	**10 (3%)**[*]
Fidgety movements				
Clearly present (+), *n* (%)	18 (69%)	38 (83%)	56 (78%)	227 (75%)
Sporadically present (±), *n* (%)	7 (27%)	8 (17%)	15 (21%)	65 (22%)
Absent (−), *n* (%)	1 (1%)	0 (0%)	1 (1%)	8 (3%)
Additional information				
Number of video assessments:				
Writhing age, median (range)	2 (1–2)	2 (1–2)	2 (0–5)	
Fidgety age, median (range)	2 (1–2)	2 (2–2)	2 (0–4)	1
Crying				
At writhing age *n* (%)	9 (35%)	24 (50%)	33 (45%)	n/a
At fidgety age, *n* (%)	**9 (35%)**	**3 (6%)**[†]	**12 (16%)**	**14 (4%)**[‡]

Bold type indicates significant group differences.
Reflux medication was not associated with crying at writing age, at fidgety age it was associated with crying in the univariate analysis: OR: 5.429, 95% CI: 1.324–22.261, $p = 0.019$, but not in the multivariate analysis OR: 3.641, 95% CI: 0.794–16.691, $p = 0.96$.
[a] Numbers of GMA in infants with CCHD: Writhing age: 1V $n = 26$; 2V $n = 48$; all CHD $n = 74$; Fidgety age: 1V n = 26; 2V $n = 46$; all CHD $n = 72$.
[#] Difference between infants with 1V CCHD and 2V CCHD: OR 4.667, 95% CI 1.245–17.489; adjusted OR 1.277, 95% CI 0.234–6.965.
[*] Difference between infants with CCHD and reference group infants: OR 5.800, 95% CI 2.396–14.040; adjusted OR 5.938, 95% CI 2.423–14.355.
[†] Difference between infants with 1V CCHD and 2V CCHD: OR 7.588, 95% CI 1.830–31.462; adjusted OR 5.937, 95% CI 1.371–25.714.
[‡] Difference between infants with CCHD and reference group infants: OR 4.086, 95% CI 1.800–9.274; adjusted OR 4.365, 95% CI 1.901–10.022.

with CCHD (17%) when compared to the reference group (3%; OR 5.800, 95% CI 2.396–14.040). When adjusting for potential confounders, the prevalence of definitely abnormal GM-complexity was higher in infants with CCHD (OR 5.938, 95% CI 2.423–14.355). The prevalence of GMs with normal GM complexity ($n = 18$, 25%) was significantly lower in infants with CCHD compared to that of the reference group ($n = 235$, 79%; adjusted OR 11.088, 95% CI 6.041–20.350). Prevalence of absent fidgety movements was comparable in both groups (3%; OR 0.500, 95% CI 0.062–4.061; adjusted OR 0.475, 95% CI 0.058–3.876).

3.3. GM quality in infants with single ventricle versus two ventricle CCHD

At writhing age, the prevalence of definitely abnormal GM-complexity did not differ significantly between infants with single ventricle CCHD ($n = 9$, 35%) and two ventricle CCHD ($n = 11$, 23%; for details see Tables 2 and 3). Prevalence of definitely abnormal GM-complexity was higher in the single ventricle group ($n = 8$, 31%) compared to the two ventricle group ($n = 4$, 9%; OR 4.667 95% CI 1.245–17.489; adjusted OR 1.277 95% CI 0.234–6.965) at fidgety age. The adjusted analyses revealed this higher risk could be attributed to the presence of hypoxaemia (SpO2 < 90%) at discharge (adjusted OR 16.445 95% CI 1.149–235.281; Table 3).

3.4. Additional findings: crying behaviour

During the analysis of GMA videos, we were struck by the relatively frequent occurrence of crying behaviour in the infants with CCHD. Crying made it time consuming to collect the minimum of 3 min of appropriate behavioural state required for GMA. Therefore, we sought to evaluate whether crying around the time of GMA would differ between the infants with CCHD and the reference group and whether it depended on ventricular physiology.

At fidgety age, infants with CCHD cried more frequently around the time of GMA ($n = 12$, 16%) compared to reference group ($n = 14$, 4%; OR 4.086, 95% CI 1.830–31.462; adjusted OR 5.937, 95% CI 2.423–14.355; see Table 2). At writhing age, 33 (45%) of the infants with CCHD cried around GMA, a frequency that was not significantly different from that at fidgety age (Chi-square $p = 0.075$). Importantly, crying was not associated with definitely abnormal GM-complexity (writhing: Chi-square $p = 0.203$; fidgety: Fisher Exact $p = 0.408$).

Ventricular physiology was not associated with crying around GMA at writhing age (Table 2). When adjusted for potential confounders (male sex, preterm birth, maternal education, SpO2 at discharge < 90%

Table 3
Risk factors associated with definitely abnormal GM complexity in infants with CCHD.

Risk factor	Writhing age		Fidgety age	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[*]
Single ventricle CCHD (versus two ventricle CCHD)	1.781 (0.622–5.097)	1.765 (0.385–8.087)	**4.667** (1.245–17.489)	1.277 (0.234–6.965)
SpO2 < 90% at discharge (versus SpO2 ≥ 90% at discharge)	1.500 (0.529–4.250)	1.013 (0.223–4.594)	**14.385 (1.744–118.629)**	**16.445 (1.149–235.281)**

[*] Analyses adjusted for preterm birth, male sex, maternal education, mechanical ventilation > 6 days, and length of hospital stay > 21 days; bold type indicates $p < 0.05$ in the regression analyses.

and need of reflux medication), crying at writhing age was not associated with ventricular physiology (adjusted OR 0.500, 95% CI 0.178–1.404). Yet, ventricular physiology was associated with crying around the time of GMA at fidgety age (Table 2; unadjusted OR 7.588, 95% CI 1.830–31.462; adjusted OR 5.937, 95% CI 1.371–25.714).

4. Discussion

The present study indicates that infants with CCHD, particularly those with single ventricle physiology and hypoxaemia measured by SpO2 < 90% at hospital discharge were at significantly higher risk of definitely abnormal GM-complexity at fidgety age than infants representative of the Dutch population. Our study indicated that reduced SpO2 at discharge was associated with the infant's developmental outcome at fidgety age, regardless if the SpO2 was reduced at birth. It is likely that SpO2 at discharge reflects the presence of chronic hypoxaemia, i.e., a condition that presumably started in fetal life and was not fully corrected within the initial surgical palliations. This corresponds to the notion of Mebius and colleagues [23] that conditions of chronic hypoxaemia, especially those that start in fetal life, are associated with less favourable developmental outcome.

GMA at fidgety age is considered one of the best predictors of later developmental outcomes, especially when the infant presents with the combination of definitely abnormal GM-complexity and absent fidgety movements. Absent fidgety movements are associated with a very high risk of CP, especially in preterm infants [8]. The same association has also been reported for infants with congenital anomalies requiring neonatal surgery [24]. The prevalence of absent fidgety movements in our CCHD cohort was comparable to that in the reference group. Only one infant with single ventricle CCHD presented with absent fidgety movements; her outcome was unfavourable, as she died at the age of four months so longitudinal follow-up was not possible. Yet, the rate of definitely abnormal GM-complexity in infants with CCHD was substantially higher than that in the reference group. It has been hypothesized that GM complexity is generated by the cortical subplate and around fidgety age by the cortical plate. Consequentially definitely abnormal GM-complexity has been attributed to impairments in these structures or their efferent connections running through the periventricular white matter [20]. The cortical subplate and the developing periventricular white matter are sensitive to hypoxaemia, especially to chronic or recurring episodes of hypoxaemia [25,26]. As a result neurodevelopment is disturbed, giving rise to altered circuitries, which is reflected on neuroimaging by reduced cortical and cerebellar volumes and impaired white matter [3,27]. Definitely abnormal GM-complexity is also associated with an increased risk of CP, especially when co-occurring with absent fidgety movements [21], but also with an increased risk of fine manipulative impairment and behaviour problems [12]. Therefore, it is conceivable that definitely abnormal GM-complexity is an early sign of the neurodevelopmental impairment frequently reported in children with CCHD, especially in those with single ventricle physiology. Our previous literature review [5] indicated that children with CCHD are at risk for impaired executive function, mildly impaired cognitive function, attention deficit hyperactive disorder, and autism spectrum disorder. In particular, children with single ventricle physiology are at highest risk for these impairments [2].

We found that the infant's age at the time of GMA mattered. Only definitely abnormal GM-complexity at fidgety age was associated with ventricular physiology and hypoxaemia at discharge, definitely abnormal GM-complexity at writhing age was not. It is conceivable that in the early post-surgical period, GM quality is not only affected by ventricular physiology and oxygen saturation, but also by the infant's current illness and physiologic instability [28]. The finding of frequent crying at writhing age supports the notion that these conditions may confound the associations between ventricular physiology and hypoxaemia and GM quality. The latter corresponds to reports of others that neonates with CCHD often have neurobehavioral difficulties related to state regulation, responses to stress, feeding, and irritability [29,30]. Our results suggest that when GMA in infants with CCHD is used for prognostic purposes, it is better to focus on the fidgety age.

The strengths of the study are the low attrition rate in the longitudinal CCHD cohort and the presence of a large reference group. The study had several limitations out of the author's control. The study did not include neuroimaging, which makes it hard to draw conclusions about the nature of potential organic impairments in the brain. In addition, we used pulse oximetry to measure hypoxaemia for group stratification and did not include near infrared spectroscopy measurements, which provide estimates of regional oxygen delivery. Nevertheless using a simple clinical tool has the advantage that the findings can be easily interpreted in terms of clinical relevance.

5. Conclusion

Our study confirms that infants with CCHD are at risk for developmental disorders, in particular the infants with single ventricle physiology and chronic hypoxaemia. Definitely abnormal GM-complexity and absent fidgety movements at fidgety age are associated with developmental impairments long term [8,12,21]. We found that definitely abnormal general movement quality in infants with CCHD is reflected in movement complexity rather than absent fidgety movements. The study indicates that GMA at fidgety age is a sensitive tool for detecting infants with the highest risk of developmental disorders that is tolerated by infants with CCHD and can be implemented easily in outpatient follow-up. Early detection of infants at highest risk of developmental disorders, including those with CCHD, allows the initiation of early intervention.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2020.105167.

CRediT authorship contribution statement

Darlene C. Huisenga: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing - original draft, Writing - review & editing. **Andrew H. Van Bergen**: Conceptualization, Methodology, Supervision, Writing - review & editing. **Jane K. Sweeney**: Conceptualization, Writing - review & editing. **Ying-Chin Wu**: Data curation, Writing - review & editing. **Mijna Hadders-Algra**: Conceptualization, Formal analysis, Methodology, Validation, Supervision, Writing - original draft, Writing - review & editing.

Declaration of competing interest

Mijna Hadders-Algra has provided courses on the assessment of GMs since 1993. The honorarium of the courses flows into the Research Fund of Developmental Neurology. She did not get an honorarium, grant, or other form of payment to produce the manuscript. Other authors declare no conflict of interest.

Acknowledgments

The authors gratefully acknowledge Christina Andriola, PT, DPT for assistance in GMA video recording.

Funding

No funding was received.

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