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► **To cite this version:**

Samantha Butler, Anjali Sadhwani, Valerie Rofeberg, Adam Cassidy, Jayne Singer, et al.. Neurological features in infants with congenital heart disease. *Developmental Medicine and Child Neurology*, 2022, 64 (6), 10.1111/dmcn.15128 . hal-03504472

HAL Id: hal-03504472

<https://hal.science/hal-03504472v1>

Submitted on 30 May 2022

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Neurological features in infants with congenital heart disease

Samantha C. Butler^{1,2} | Anjali Sadhwani^{1,2} | Valerie Rofeberg³ | Adam R. Cassidy^{1,2} |
Jayne Singer^{1,2} | Johanna Calderon^{1,2} | David Wypij^{3,4,5} | Jane W. Newburger^{3,4} |
Caitlin K. Rollins^{6,7} | Cardiac Neurodevelopmental Program at Boston Children's Hospital Group*

¹Department of Psychiatry, Boston Children's Hospital, Boston, MA

²Department of Psychiatry, Harvard Medical School, Boston, MA

³Department of Cardiology, Boston Children's Hospital, Boston, MA

⁴Department of Pediatrics, Harvard Medical School, Boston, MA

⁵Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA

⁶Department of Neurology, Boston Children's Hospital, Boston, MA

⁷Department of Neurology, Harvard Medical School, Boston, MA, USA

Correspondence

Samantha C. Butler at 1 Autumn Street Room 335, Boston Children's Hospital, Boston, MA 02115, USA. E-mail: samantha.butler@childrens.harvard.edu

Funding information

Kenrose Kitchen Table Foundation; National Institute of Neurological Disorders and Stroke, Grant/Award Number: K23 NS101120

Aim: To report neurological examination findings at 5 to 12 months of age in infants with congenital heart disease (CHD) and to identify predictors of abnormal neurological examination.

Method: This retrospective observational study included infants who required cardiac surgery at less than 3 months of age and underwent a standard neurological examination from a neurologist in the cardiac neurodevelopmental outpatient clinic between age 5 months and 12 months. Predictors for abnormal neurological examination (concerns on structured developmental history, demographic factors, medical history, and newborn neurodevelopmental assessment) were considered for multivariate regression.

Results: The sample included 127 infants (mean age 7mo 2wks), who underwent first cardiac surgery at 7 days (4–49 interquartile range [IQR]) of age and were seen for a neurological examination in the cardiac neurodevelopmental clinic. Neurological abnormalities were common; 88% of infants had an abnormal neurological examination in at least one domain assessed. The most common abnormalities were abnormal axial (48%) and extremity (44%) tone, mostly hypotonia. Abnormal neurological examination was associated with concerns on the concurrent structured developmental history, genetic condition, extracardiac anomaly, longer length of stay, more than one cardiac surgery, ongoing early intervention services, and abnormalities on newborn neurodevelopmental assessment.

Interpretation: Neurological examination abnormalities are common in infants with CHD after infant heart surgery, supporting the need for early and ongoing therapeutic developmental services and adherence to American Heart Association recommendations for developmental follow-up for children with CHD.

Congenital heart disease (CHD) is the most common birth defect, affecting approximately 40 000 infants born each year in the USA.¹ Mortality rates for children with CHD have significantly declined but associated developmental disabilities are increasingly apparent in survivors.^{1–5} Children with CHD often present with deficits in multiple developmental

domains including motor and visual spatial skills, executive functioning, language, social cognition, and adaptive behavior.^{6–9} Approximately 75% of children with CHD will show delay in at least one developmental domain by 3 years of age.¹ Children with CHD are more likely than children without CHD to require early intervention and special education

Abbreviations: CHD, Congenital heart disease; LOS, Length of hospital stay.

services, which result in a significant economic and psychosocial impact on families and society.¹⁰

Developmental and neurological concerns may be detected early in infancy. Just before discharge home, infants with CHD who underwent open-heart surgery as newborn infants demonstrated atypical autonomic regulation, attention, and motor organization, along with challenges in state regulation, feeding, and sleeping.¹¹⁻¹³ Among term newborn infants with complex CHD, 15% to 40% show brain injury on MRI before surgery, most commonly white matter injury.^{14,15} Neurological events (e.g. seizures, stroke) in infants with CHD are associated with a higher risk for long-term cognitive, motor, language, and emotional/behavioral problems, as well as social difficulties and inattention.¹⁶ Finally, medical factors such as severity of heart condition, age at surgery, and length of hospital stay (LOS) are associated with long-term neurodevelopmental concerns.^{2,5,8,17-20}

The known neurodevelopmental challenges for children with CHD spurred the American Heart Association to recommend routine evaluation of neurodevelopment in high-risk patients with CHD. The American Heart Association statement suggests that the first visit, before 12 months, incorporates a neuromotor examination assessing muscle tone, primitive and deep tendon reflexes, sensory status, and gross motor skills.¹⁰ While many children with CHD now undergo a neurological examination based on this recommendation, these examinations and their results have not yet been described. Moreover, factors that predict abnormal neurological examination have not been identified. Improving our understanding of the findings at this routinely recommended neurological evaluation enhances the ability to detect abnormalities and thereby optimize support for children with CHD and their families.

The present study aimed to (1) describe the neurological examination findings in a clinic-referred population of infants with CHD at 5 to 12 months of age, and (2) identify early medical and neurodevelopmental predictors of an abnormal neurological exam in these infants. We hypothesized that infants whose families report developmental concerns, infants with greater medical morbidity (i.e. longer LOS, severe heart disease such as single ventricle, and genetic diagnosis), and infants with neurodevelopmental abnormalities noted during the newborn period would be more likely to demonstrate abnormal neurological examination at 5 to 12 months than those without these risks.

METHOD

Participants

Participants in this retrospective observational cohort study were drawn from a clinic-based convenience sample of infants whose data are part of a single-center clinical registry. At our hospital, newborn infants who receive open-heart surgery systematically undergo an inpatient newborn neurodevelopmental assessment after surgery and are then

What this paper adds

- Neurological examination abnormalities are common in infants who undergo open-heart surgery.
- Medical complications in infancy increase risk for neurological abnormalities.
- Family-reported concerns on structured developmental history may predict abnormal neurological examination at 5 to 12 months of age.
- Abnormal newborn neurodevelopmental assessment may predict abnormal neurological examination at 5 to 12 months of age.

referred for an outpatient neurological examination before 12 months of age. The family receives instructions to schedule the outpatient visit in their discharge instructions and via a letter mailed home. Data from these visits are included in a clinical registry.

Inclusion criteria for the current sample from this registry were: underwent cardiac surgery with cardiopulmonary bypass at less than 3 months of age at Boston Children's Hospital and returned for an outpatient neurological examination at 5 to 12 months of age between December 2011 and June 2017. The Boston Children's Hospital Institutional Review Board approved data to be included in the registry by obtaining informed consent from the family and a waiver for use of archival data was granted by the Institutional Review Board.

Demographic, medical, and neurodevelopmental history

Demographic information was collected via a family intake interview including child sex and ethnicity along with primary caregiver education.

The study team's cardiac research nurse reviewed the medical records and collected information on birthweight, gestational age at birth, presence of any known genetic diagnosis associated with a neurodevelopmental disorder, extracardiac congenital anomaly, number of cardiac catheterizations, incidence of stroke or seizure, and mode of feeding at hospital discharge. Data regarding infant heart surgery was obtained from the Society of Thoracic Surgeons Congenital Heart Surgery Database,²¹ a central hospital database, including cardiac anatomy, age at operation, number of cardiac surgeries, and LOS during inpatient admission for cardiac surgery. The family indicated whether their child was receiving early intervention services at the present time or in the past.

Newborn neurodevelopmental assessment was conducted on infants less than 3 months of age when inpatient after their first surgical intervention. Infant behavior

was assessed by a developmental and clinical psychologist using a clinical adaptation of the Newborn Behavioral Observation, a measure derived from the Brazelton Neonatal Behavioral Assessment Scale.^{22,23} Details of the newborn assessment and the variables collected were presented in a previous manuscript.¹¹ Systems of infant developmental functioning assessed included autonomic, motor, attention, and state organization along with the degree of examiner facilitation required to support subsystem balance. Assessment also measured the amount of examiner facilitation which included the degree of environmental and examiner support to bring the infant to organization such as breaks during the assessment, use of a pacifier, and slowly pacing the assessment. Each variable was classified as normal versus abnormal for age. Infant inclusion criteria included complete neurodevelopmental assessment before discharge home and absence of prescribed sedative medications at time of discharge.

Neurological evaluation

A board-certified pediatric neurologist conducted the outpatient neurological evaluation at 5 to 12 months of age, which included a structured developmental history and a standard neurological examination. The structured developmental history was obtained from the family via a clinical interview including open-ended questions about language and motor development, feeding, sleep patterns, and hand preference. The neurologist categorized responses that were then classified for analysis as 'normal for age' or 'of concern'. After the structured developmental history, neurological examination was performed using an adaptation of a standardized neurological exam previously used in infants born preterm.²⁴ Adaptation included expansion of the motor section to capture axial tone and hypotonia. The neurological examination components were mental status (state, visual attention, expressive communication, and receptive communication), cranial nerves (pupillary responses, extraocular movements, facial symmetry, palate rise, suck), motor system (muscle bulk, tone, strength axially and in the extremities), and reflexes (deep tendon and primitive) with each item categorized then classified as normal versus abnormal. Communication items were stratified because of age of assessment (Table S1, online supporting information).

Statistical analysis

The primary outcome variables were the outpatient neurological examination at 5 to 12 months of age. The predictors evaluated included concerns noted on structured developmental history at the time of outpatient neurological evaluation, demographic factors, and medical history. In the subset of infants who underwent inpatient newborn neurodevelopmental assessment, these newborn variables were also evaluated as predictors.

For concerns noted on the structured developmental history, sensitivity, specificity, positive predictive value, and negative predictive value in predicting abnormal neurological examination were evaluated. For demographic and medical factors, logistic regression was used to evaluate associations with neurological examination abnormalities. Univariable logistic regression was used to identify significant predictors of abnormal neurological examination items. Candidate variables included sex, ethnic group, primary caregiver education, birthweight, gestational age in weeks, Apgar score at 5 minutes, single ventricle anatomy, genetic diagnosis, cardiac catheterization, LOS at first hospitalization in weeks, age in months at assessment (adjusted for preterm birth, for those gestational age <37wks), and current use of early intervention services. Variables with limited variability (less than 10% of the participants affected) or substantial missing data (>10%) were not included. Predictors with a *p*-value <0.20 were then considered for bidirectional stepwise model building with significant improvement in the Akaike information criterion and a *p*-value <0.05 required for a variable to remain in the multivariable models.

A similar approach was used to evaluate associations of newborn neurodevelopmental assessment variables with results from the infant neurological examination in the subset of infants with newborn assessment. Newborn assessment variables included items from the autonomic, motor, and state organization scales, as well as a composite of attention organization items. The multivariable models retained any demographic characteristic or medical morbidity found to be previously significant. Analyses were performed using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of the patient population

Demographic and medical characteristics of the 127 infants who returned for neurological examination between 5 months and 12 months of age are presented in Table 1. The majority of the sample was male (61%), white (87%), and the primary caregiver had at least a college education (64%). Sixteen percent of the sample had single ventricle heart disease and 13% of the sample had a genetic diagnosis. Most were orally fed at hospital discharge (94%) and two-thirds were receiving early intervention at the time of the neurological evaluation (66%).

Structured developmental history

Concerns were noted in gross and fine motor skills (48%), oral feeding (32%), sleeping (25%), and expressive or receptive communication (27%), but few concerns for social/emotional skills (2%). Early hand preference was reported in 20% of infants.

TABLE 1 Demographic and medical characteristics of study population (n=127)

Variable	n (%), mean SD, or median [IQR]
Demographic characteristics	
Female	50 (39)
Male	77 (61)
Hispanic, black, other	16 (13)
White	111 (87)
Primary caregiver college degree or higher	81 (64)
Medical background	
Birthweight (kg)	3.1, SD 0.7
Gestational age (wks) ^a	38.4, SD 1.9
Gestational age <37wks	16 (13)
Apgar score at 5min	9 [8–9]
Single ventricle anatomy	20 (16)
Prenatal CHD diagnosis	74 (58)
Genetic diagnosis ^b	16 (13)
Non-cardiac congenital anomaly ^c	20 (16)
Events before neurological examination	
Age at first operation (d)	7 [4–49]
>1 cardiac operation	25 (20)
Cardiac catheterization	38 (30)
ECMO	2 (2)
Stroke/seizure	2 (2)
Feeding at initial hospital discharge	
Mixed oral and tube	120 (94)
Nasogastric tube only	8 (6)
Nasojejunal tube only	1 (1)
Gastrostomy tube only	5 (4)
Length of stay (d)	
Receiving EI at time of neurological examination	84 (66)
Never received EI	36 (28)
Discharged from EI	4 (3)
Adjusted age at neurological examination (mo)	
5–6	31 (24)
7–9	76 (60)
10–12	20 (16)
Time from last cardiac surgery to neurological examination	
7mo–1wk [5mo–3wks]	3wks–8mo
	3wks]

All variables with <10% missing.

^aRange of gestational age was 29–41 weeks, IQR 38–40 weeks.

^bMost frequent genetic diagnoses include: Kabuki syndrome, Mosaic Trisomy X syndrome, Townes-Brocks syndrome, CHARGE syndrome, Jacobsen syndrome, Trisomy 18, and 22q11.2 deletion.

^cMost frequent non-cardiac congenital anomalies include: brain, renal, orthopedic, cleft lip/palate, and gastrointestinal.

IQR, interquartile range; CHD, congenital heart disease; ECMO, extracorporeal membrane oxygenation; EI, early intervention services.

Neurological examination

On standard neurological examination, 112 infants (88%) had abnormality in at least one domain assessed. Of those infants with an abnormality, most patients had abnormality in either mental status (state, visual attention, expressive communication, and receptive communication) or motor domains (Fig. 1). Seventy-two infants (64%) showed abnormalities in more than one domain and 33 (29%) showed abnormalities in more than two domains. Abnormalities on the neurological examination are presented in Table 2. Abnormalities included reduced expressive (37%) or receptive communication (22%) in the mental status exam of the neurological examination. Forty-eight percent had abnormal axial tone, mostly hypotonia (47%); 44% had abnormal extremity tone, mostly hypotonia (31%). Diffuse hypotonia (both axial and extremity) was seen in 27%. Weakness was also common in upper (32%) and lower (19%) extremities.

Newborn neurodevelopmental assessment

Of the 127 patients seen for neurological examination, 63 (50%) were also seen in the newborn period for neurodevelopmental assessment, off sedative medications at time of assessment and included in our data registry (Table 3). The median adjusted age at the newborn assessment was 21 days (IQR 13–32). Common abnormalities on the newborn assessment were noted in autonomic (68%), motor (81%), attention (63%), and state (43%) organization.

Predictors of neurological examination

Structured developmental history was moderately predictive of concurrent abnormalities on the neurological exam

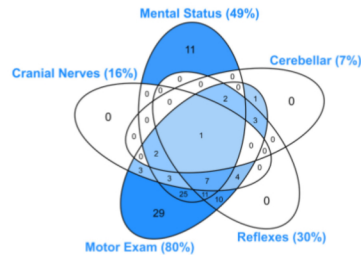


FIGURE 1 Overlap of abnormalities present across the five domains assessed on the neurological examination. Numbers in the figure denote the number of individual infants with abnormalities and numbers outside of the figure note percent of infants with abnormalities.

TABLE 2 Abnormalities on neurological examination (n=127)

Neurological examination item	Abnormal n (%)
Mental status	62 (49)
Exam state	3 (2)
Visual interaction	2 (2)
Receptive communication	27 (22)
Expressive communication	47 (37)
Cranial nerves	20 (16)
Visual field	1 (1)
Pupillary response	1 (1)
Extraocular movement	4 (3)
Visual interest	4 (3)
Facial symmetry	5 (4)
Hearing	5 (4)
Suck	2 (2)
Motor	101 (80)
Head control	23 (24)
Axial tone	61 (48)
Extremity tone	55 (44)
Grasp precision	6 (6)
Extremity strength	38 (33)
Symmetry of movement	23 (18)
Reflexes	38 (30)
Strength of deep tendon reflexes	23 (18)
Symmetry of deep tendon reflexes	10 (8)
Cerebellar	9 (7)
Dysmetria	8 (6)
Extraneous movement	2 (2)

(Table S2, online supporting information). For example, expressive communication concerns in the structured developmental history were associated with expressive communication findings on the neurological exam with a sensitivity of 78% and specificity of 76%. Gross motor concerns in the structured developmental history were associated with axial tone abnormality on the neurological exam with a sensitivity of 74% and specificity of 77%.

Univariable and multivariable associations of demographic and medical characteristics with neurological examination findings are presented in Table 4 and Table S3 (online supporting information). Receiving early intervention services at the time of neurological evaluation was associated with abnormal receptive communication on the mental status portion of the neurological examination. Younger age at exam, primary caregiver college degree, and presence of a non-cardiac congenital anomaly were associated with abnormal expressive communication on the mental status portion of the neurological examination. Infants with a known genetic diagnosis and those who underwent more than one cardiac surgery were more likely to demonstrate abnormal axial tone. Infants with a non-cardiac congenital anomaly

TABLE 3 Predischarge newborn neurodevelopmental assessment findings (n=63)

Behavioral system	Abnormal n (%)
Autonomic organization	43 (68)
Autonomic regulation	30 (48)
Need for facilitation	27 (44)
Consolability	12 (19)
Activity level	38 (62)
Crying	38 (60)
Motor organization	51 (81)
General tone—upper extremities	37 (64)
General tone—lower extremities	36 (62)
Asymmetry	14 (23)
Rooting	26 (44)
Sucking	23 (38)
Hand grasping	30 (50)
Attention organization	38 (63)
Animate visual	33 (55)
Animate visual and auditory	36 (60)
Inanimate visual	30 (50)
Inanimate visual and auditory	28 (47)
State organization	
State regulation	27 (43)

All variables with <10% missing.

and those with longer LOS were more likely to demonstrate abnormal extremity tone.

When adding the newborn neurodevelopment variables for the subset of infants who underwent this assessment, abnormal rooting in the newborn period was associated with abnormal expressive communication. Increased need for examiner facilitation in the newborn period was associated with abnormal axial tone. Increased crying in the newborn period was associated with abnormal extremity tone. Surprisingly, children with better attention in the newborn period were more likely to show abnormal receptive communication on the neurological examination.

DISCUSSION

This study reported neurological examination findings in 5- to 12-month-old infants with CHD who previously underwent surgical repair and identified predictors of neurological examination abnormality. The majority of children had abnormal findings on neurological examination, most commonly axial and extremity hypotonia, extremity weakness, and delayed expressive and receptive communication. Abnormalities in cranial nerves and cerebellar function were less prevalent than other abnormalities, similar to past research.²⁵ These findings indicate that neurological

TABLE 4 Multivariable associations of medical variables and newborn neurodevelopmental assessment with selected neurological exam findings

Neurological abnormality	Predictor variables	Model including only medical and demographic variables (n=127)	Model including medical, demographic, and newborn assessment variables (n=63)
		Odds ratio (95% confidence interval)	
Receptive communication	Early intervention services at any time	3.63 (1.16, 11.4) ^a	2.41 (0.44, 13.2)
	Abnormal newborn attention organization		0.26 (0.07, 0.99) ^a
Expressive communication	Primary caregiver college degree or higher	2.53 (1.02, 6.29) ^a	2.50 (0.58, 10.8)
	Non-cardiac congenital anomaly	3.70 (1.16, 11.8) ^a	2.12 (0.40, 11.2)
	5–6mo at assessment	Reference	Reference
	7–9mo at assessment	0.34 (0.14, 0.84) ^a	0.53 (0.12, 2.39)
	10–12mo at assessment	0.16 (0.04, 0.64) ^b	0.22 (0.03, 1.80)
	Abnormal newborn rooting		3.85 (1.05, 14.2) ^a
Axial tone	Genetic diagnosis	6.87 (1.80, 26.2) ^b	5.85 (0.95, 36.0)
	>1 cardiac operation	4.17 (1.56, 11.2) ^b	4.48 (0.93, 21.6)
	Abnormal newborn need for facilitation		5.78 (1.60, 20.9) ^b
Extremity tone	Non-cardiac congenital anomaly	4.60 (1.52, 13.9) ^b	4.26 (0.85, 21.4)
	Length of stay in wks	1.18 (1.01, 1.39) ^a	1.10 (0.73, 1.65)
	Abnormal newborn crying		4.96 (1.39, 17.7) ^a

^ap<0.05.

^bp<0.01.

abnormalities previously found in older children with CHD, including hypotonia, gross motor delay, and language delay, are also common under 1 year of age.^{18,25–29} Neurological abnormalities were strongly associated with family-reported concerns on a concurrent structured developmental history, medical risk factors, and abnormalities on an inpatient newborn neurodevelopmental assessment.

We found that information gathered from the structured developmental history was generally consistent with findings on the neurological examination. Previous research in typically developing school-age children noted a strong relationship between family concern and developmental status, especially for motor and language concerns.^{30,31} However, our study is the first to delineate the relationship between infant neurological examination and family-reported developmental concerns. These findings highlight the importance of pursuing further evaluation when the family of an infant with CHD expresses neurodevelopmental concern.

Several additional factors predicted neurological abnormality. Similar to previous research on neurodevelopment in CHD, the current study identifies an association between children with complex medical needs (longer LOS, genetic diagnosis, non-cardiac congenital anomalies) and neurological abnormality.^{12–15,25} These associations between children with complex developmental disability, neurodevelopmental delay, and neurological examination highlight the need for close follow-up of children with complex medical status.

Observations during the newborn period predicted later neurological abnormality. Specifically, increased

need for facilitation, which reflects either infant overstimulation or reduced state regulation, predicted later abnormalities in axial and extremity tone on the neurological exam, and abnormal newborn rooting and a high rate of crying predicted abnormalities in communication and tone. Whereas past research showed a strong association between concurrent neurobehavioral newborn testing and neurological examination findings in infants with CHD, these findings are the first to indicate the predictive value of newborn neurodevelopmental assessment for neurological abnormalities later in infancy.¹³ Recently there are data to promote developmental care and protecting the newborn brain in newborn infants with CHD, the current data support neurodevelopmental assessment as a primary step to implementing developmental services before discharge home and referral to outpatient developmental therapy services, such as physical therapy, occupational therapy, and feeding therapy.^{11,32–35}

The Individuals with Disabilities Education Act³⁶ mandates that every state provide early identification programs for infants and toddlers with developmental delays, established medical conditions, and biological risk factors that are highly associated with developmental delay. In addition, the American Heart Association guidelines for children with CHD recommend that all high-risk infants with CHD receive early intervention in early infancy.¹⁰ Furthermore, early intervention is available in every state and territory in the USA and is publicly funded to provide services for free or at reduced cost for any child who is eligible. All the

infants in our sample were referred to early intervention before their hospital discharge. Two-thirds of children seen for the outpatient neurological examination were followed by early intervention, and in general we did not find a relationship between current receipt of early intervention and neurological abnormalities on exam, except in the domain of receptive communication. Children not receiving early intervention were just as likely to have abnormalities in their neurological examination as those receiving early intervention. Conducting a clinical neurology visit in infancy helps to educate families on their child's specific developmental needs, provide guidance on means of supporting development, and facilitate referral to therapeutic services. Given the high risk for neurological abnormality at 5 to 12 months of age, the current study suggests that all children with complex CHD and open-heart surgery in infancy should receive developmental therapeutic services, such as early intervention, beginning very early in infancy. In addition, future investigations should systematically clarify the reasons for lack of early intervention involvement to determine social inequities, understanding of need, or other variables that might impact acquisition of early intervention, especially for infants for such high risk for neurological impairment.

The current study has limitations. While all children at our center who undergo CHD surgery in the first year after birth are referred for outpatient neurological examination before 12 months of age, the study could only assess those children who returned for the outpatient visit and therefore had data in the registry. Our sample may be subject to selection bias, based upon medical severity or social factors that influence likelihood of a family attending the outpatient neurology visit and may not be generalizable to the broader population with CHD. Second, as this is an observational study of patients seen clinically, there is no control or comparison group. Third, because of the clinical nature of the visit, the neurologist could not be blinded to the infant's medical history. Additionally, while there are other standardized neurological examination instruments for infants,^{37,38} this study recorded a standard neurological examination using an existing tool previously found to be reliable in infants born preterm³⁴ and modified to capture hypotonia, which is commonly found in infants with CHD. The tool included prespecified categories to systematically document examination findings and enable comparison between different examiners. Similarly to other assessment tools, some of the domains (e.g. tone) are subjective, and the clinical nature of the examination could potentially create observer bias. Fourth, the sample, while like other studies performed at our institution,^{6,7,9,11,39} was mostly white, with higher primary caregiver education level, and thus not socio-demographically representative of the broader US population. Future studies should investigate potential disparities in follow-up care for children with CHD. Our sample was also derived from a single center where patients receive neurodevelopmental education before hospital discharge; the predictive validity of the structured developmental history may not be generalizable to other settings as our families were primed to monitor development. Finally,

our data on neurological examination was limited to the infant period, thus we cannot determine the persistence and evolution of these neurological abnormalities over time. It is known that early childhood evaluations have low sensitivity for detecting future neurodevelopmental concerns. This is not a failing of the assessment tools themselves, but a function of both neural plasticity in early childhood accounting for compensatory development and that some neurodevelopmental functions are not typically expressed until after early childhood and thus not detectable until those skills are measurable.^{40,41} Therefore, children with CHD require ongoing neurodevelopmental evaluations which begin in infancy.

Broadly, our findings indicate high rates of neurological abnormality on outpatient follow-up in a clinically derived sample of children with CHD and support adherence to recommended ongoing neurodevelopmental evaluation. The identification of a neurological abnormality in the first year allows for early targeted interventions, such as physical therapy, occupational therapy, speech therapy, and feeding therapy early in development. We also noted the importance of soliciting the concerns of family members as a means of identifying children in need of support. Lastly, our results highlight the potential of a newborn neurodevelopmental assessment before discharge to identify patients at highest risk for future neurological abnormality. These findings underscore the need for early and ongoing therapeutic neurodevelopmental services and support the American Heart Association recommendations for neurodevelopmental follow-up throughout the life span for children with severe CHD.

ACKNOWLEDGEMENTS

Members of the Cardiac Neurodevelopmental Program at Boston Children's Hospital Group are as follows: David C Bellinger, Catherine Clark, Kristina Espinosa, Brandi Henson, Catherine Ullman Shade, and Janice Ware. The research work was supported by the Kenrose Kitchen Table Foundation and National Institute of Neurological Disorders and Stroke of the NIH under award number K23 NS101120. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors stated that they had no interests that might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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