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Neurodevelopmental Outcomes for Children With Hypoplastic Left Heart Syndrome at the Age of 5 Years

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Abstract

This study aimed to determine the neurodevelopmental (ND) outcome for children with hypoplastic left heart syndrome (HLHS) at early school age. English-speaking patients who underwent the Norwood procedure between 2000 and 2005 were eligible at 4–6 years of age for ND testing. Of the 72 eligible patients, 44 (61 %) agreed to participate, and 37 completed ND testing before the close of the study. Three subjects were excluded from analyses due to late stroke. The ND testing included intelligence, visual motor integration, memory and motor and language skills. Parents and teachers completed measures of behavior and attention problems. Subjects' scores and parent/teacher ratings were converted to z-scores and compared with test norms. Higher scores on child measures represent better outcomes, whereas higher scores on parent and teacher rating scales indicate more problems. The average ND performance of the tested cohort fell within one standard deviation of the test norms for all measures. However, the subjects performed significantly lower than the test norms on measures of visual-motor

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integration, fine motor skills, memory, and word structure ($z = -0.42$ to -0.54 ; $p < 0.005$). On the parent and teacher completed measures, the subjects scored higher than the test norms on attention problems ($z = 0.40$ – 0.62 ; $p < 0.005$). Although the overall ND performance of the cohort was normal, the subjects showed relative weakness in visual motor and attention skills. Ongoing developmental monitoring of these children is recommended to guide interventions that may improve individual outcomes and to assess the impact of changes in clinical management strategies on functional outcomes.

Keywords

Congenital heart disease/defects; Developmental outcomes; Hypoplastic left heart syndrome

Advances in diagnostic and surgical techniques as well as perioperative management strategies have increased survival rates for children with hypoplastic left heart syndrome (HLHS) and other forms of univentricular heart disease (UVH) [31, 33, 34]. The favorable early survival rates for children with HLHS have coincided with increasing recognition of associated neurodevelopmental (ND) problems.

In infants and preschool-aged children, delays in gross motor and adaptive behavior skills are common [2, 12, 23, 26, 27, 29, 30, 32]. Older children with HLHS have been found to have intelligence quotient (IQ) scores within the low average range but to have higher rates of attention and learning problems, behavioral and emotional problems, visual-motor/visual-spatial deficits, and language difficulties than the normal population [6, 8, 10, 11, 14, 21, 22, 28, 38]. Because of these deficits, many of these children require special education services within the school setting.

Whereas many centers have reported on 1- and 2-year ND outcomes for this population, less is known about longer-term ND outcomes for children with HLHS who have undergone surgery in the most recent era. The current study aimed to summarize the ND outcomes for a recent cohort of early school age children with HLHS and variants and to determine what factors predict variability in ND outcomes.

Methods

Patient Population

English-speaking children 4–6 years of age who had undergone the Norwood procedure were eligible for participation in the study. The sample for this study included a consecutive series of 93 patients who underwent the Norwood procedure for HLHS or variants of UVH between December 2000 and August 2005. All the children received their surgical care at Children's Hospital of Wisconsin. In this cohort, early survival (survival 30 days after the primary procedure or before discharge from surgical hospitalization) was 95 % (88/93). Before eligibility for testing, five late deaths occurred [one during the interstage period, three after bidirectional Glenn (BDG), and one after Norwood], and six patients underwent heart transplantation (one death afterward). The final sample eligible for testing during this time period included 77 children. The study was approved by the Institutional Review Board at Children's Hospital of Wisconsin.

Of the 77 children eligible for testing, two were excluded due to a language barrier, two relocated out of state, and one was excluded due to a known genetic abnormality thought to contribute independently to ND outcome. The remaining 72 families were contacted by mail for participation in the study. Of these, 44 families (61 %) agreed to have their children

participate. Before close of the study, 34 subjects were able to complete the full ND testing battery.

Neurodevelopmental and Behavioral Evaluation

The parents completed a demographic information questionnaire that also included questions about early intervention services that their child had received or was currently receiving. Socioeconomic status (SES) was calculated based on the parental report using the Hollingshead Four-Factor Index of Social Status [16].

A prospective perioperative database together with a chart review yielded additional medical variables and treatment characteristics including pre- versus postnatal diagnosis, history of prematurity (defined as gestational age younger than 37 weeks), age at Norwood, preoperative high-risk status (defined as gestational age of 35 weeks or younger, birth weight lower than 2.5 kg, or presence of additional cardiac or noncardiac anomalies), history of extracorporeal membrane oxygenator (ECMO) support, hospital length of stay (LOS) after the Norwood procedure, history of growth failure (defined as height or weight at less than the 5th percentile) or feeding problems, age at BDG, cumulative lifetime inpatient hospitalization days (to the time of the study visit), cardiopulmonary bypass (CPB) time, and deep hypothermic circulatory arrest (DHCA) time. Additional physiologic data on a subset of the patients were available. This information is presented in a separate report [15].

All ND testing was conducted by a pediatric psychologist (C.B.) within the clinic setting. Appointments were scheduled at the families' convenience and lasted approximately 90–120 min. Due to time constraints, a complete neuropsychologic battery could not be administered. However, because IQ tests do not assess more subtle neuropsychological problems [3], a number of well-validated measures were administered based on the deficits commonly seen in these children [38]:

Cognitive—An estimate of the child's IQ was calculated using the Word Reasoning and Matrix Reasoning subtests of the Wechsler Preschool and Primary Scale of Intelligence—Third Edition (WPPSI-III) [36] (mean, 100 ± 15). This two-subtest short form has a correlation of 0.94 with the WPPSI-III Full-Scale IQ score. An estimate of the parent's IQ was calculated using the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) [35] (mean, 100 ± 15). This two-subtest short form has a correlation of 0.87 with the Wechsler Adult Intelligence Scale—III Full-Scale IQ score. These two-subtest short forms were used because they provide a reliable general summary of an individual's cognitive functioning and can be administered in a much shorter time than an entire IQ test.

Visual Motor—The Developmental Test of Visual Motor Integration (VMI) [4] was used to assess visual spatial and visual motor integration ability (mean, 100 ± 15).

Fine Motor—The Finger Tapping and Imitating Hand Positions subtests of the NEPSY (A Developmental Neuropsychological Assessment) [19] were used to assess fine motor skills (mean, 10 ± 3).

Attention—The Vigilance subtest (commission score) from the Gordon Diagnostic System (GDS) [13] and the Visual Attention subtest of the NEPSY [19] were used to assess attention skills (raw score compared with the score for the normative sample on Gordon; mean for Visual Attention subtest, 10 ± 3). The Conners' ADHD Index subscale of the Conners' Parent Rating Scale—Revised [7] (completed by the parent), the Conners' Teacher Rating Scale—Revised [7] (completed by the teacher/daycare provider), the Attention

Problems subscale of the Child Behavior Checklist (CBCL) [1] (completed by the parent), and the Caregiver/Teacher Report Form (CTRF) [1] (completed by the teacher/daycare provider) also were used as additional sources of information regarding the child's attentional functioning (mean T scores, 50 ± 10). Notably, a formal degree in education is not required to complete the teacher forms. These measures are valid for use by personnel who work with children in a group setting. Respondents must be able to read English and should know the child for at least 2 months before completing the measures. All the respondents in the study met these criteria.

Memory—The Narrative Memory subtest from the NEPSY [19] and the Recall of Objects subtest from the Differential Ability Scales (DAS) [9] were used to assess memory skills (mean, 10 ± 3).

Language—The Naming Vocabulary subtest from the DAS [9] and the Word Structure and Sentence Structure subtests of the Comprehensive Evaluation of Language Fundamentals Preschool, Second Edition (CELF Pre 2) [39] were used to assess language skills (mean, 10 ± 3).

Behavioral/Emotional—The Internalizing, Externalizing and Total Problems subscales of the CBCL [1] and the CTRF [1] were used as measures of child emotional/behavioral functioning (mean T scores, 50 ± 10).

There was some variability in the number of subjects who completed several of the tasks. Finger tapping is valid only for children 5 years of age or older ($n = 18$). Teacher report measures were available only for children attending school ($n = 18$) or daycare ($n = 2$).

Statistical Analysis

Means and standard deviations are reported when data were normally distributed. Median and interquartile ranges are used for skewed variables. Percentages are used for categorical variables. All ND test scores were first normalized by conversion to z -scores and then compared with test norms using one-sample t tests.

Scores were categorized as falling within the normal (within one SD from the test mean), at-risk (one to two SDs below the test mean), or impaired (>2 SDs below the test mean) range. A one-sample test for proportions was used to test whether the percentage of scores in each category was significantly different from what was expected based on a normal distribution. Data that were skewed, such as LOS or CPB time, were compared using Mann–Whitney or Kruskal–Wallis nonparametric tests.

Star plots were created as a graphic method of displaying multivariate data. Each star represents a single group observation and summarizes the group's performance, highlighting which ND domains are areas of strength or weakness. By presenting each variable as a standardized z -value, comparisons of many variables can be made simultaneously, even if the scale is different.

Linear regression analysis was used to examine univariate relationships with the ND outcome scores. Forward stepwise multivariable linear regression analyses were used to assess whether the contribution was independent or associated with some other covariate. Based on a review of the literature, the following variables were considered as possible predictors in logistic regression models for “at-risk or impaired” patients: age at Norwood, SES, history of growth failure, weight percentile at birth, cumulative CPB time, cumulative DHCA time, cumulative hospital LOS, presence of other medical conditions, and parental IQ score.

Unfortunately, there is no equivalent to the R^2 measure of how much variation is explained (from linear regression) for logistic regression. However, the Hosmer–Lemeshow goodness-of-fit test for the logistic model is presented. A nonsignificant value indicates that the model fits the observed data. The closer the p value is to 0.99, the better the fit. A Bonferroni multiple testing adjustment (threshold for a significant result = $0.05/\text{number of outcomes}$) was used to correct for the number of ND measures. For example, the threshold for statistical significance at the 0.05 overall level for the six ND domains would be $0.05/6 = 0.008$.

Results

Demographic and Treatment Characteristics

Of the eligible cohort contacted to participate ($n = 72$), 37 were scheduled for ND testing before close of the study. Three subjects could not complete the full ND testing battery due to late stroke and were excluded from analyses. The remaining 34 subjects completed ND testing and were included in the analysis. These 34 subjects were compared with the 35 nonparticipants including those who declined to participate ($n = 1$), those who did not respond to our invitation to participate ($n = 27$), and those who agreed to participate but could not be scheduled before the close of the study ($n = 7$).

No significant differences existed between the study subjects and the nonparticipants in terms of hospital LOS after the Norwood operation, CPB time, DHCA time, modified Blalock–Taussig (BT) shunt at Norwood, high-risk status at Norwood, feeding method at Norwood discharge, or incidence of stroke. The subjects did have a higher mean family income (estimated based on the zip code where they resided) than the nonparticipants (\$53,088 vs. \$47,542; $p < 0.05$). Of those who did not participate in the study, 40 % ($n = 14$) lived farther than 100 miles from the hospital.

The demographic and treatment characteristics of the 34 subjects are presented in Table 1. As shown, 97 % of the sample was white, the mean SES was middle class, and 88 % of the parents were married. The mean age at ND testing was 5 ± 0.6 years.

In addition to their univentricular heart disease, 35.3 % of the subjects had other chronic medical conditions involving the following systems: respiratory ($n = 6$), neurologic ($n = 2$), immunologic ($n = 2$), and urologic ($n = 2$). At Norwood, 12 % of the sample ($n = 4$) was classified as high risk. The study subjects were receiving a variety of intervention services at ND testing including physical therapy (17.6 %, $n = 6$), occupational therapy (20.6 %, $n = 7$), speech therapy (26.5 %, $n = 9$), early childhood (14.7 %, $n = 5$), and mental health (2.9 %, $n = 1$).

Neurodevelopmental Outcomes

The IQ of the parents fell within the average range (mean, 107.1 ± 13.1 ; range, 79–132). The mean child ND test scores and z -scores are summarized in Table 2. The average performance in the tested domains was normal, with overall ND testing at a z score of -0.23 , corresponding to a score of 96 on a 100 ± 15 scale. However, the cohort had significantly lower mean scores on the VMI, NEPSY Imitating Hand Positions, DAS Recall of Objects, and CELF Word Structure subtests than the test norms (all $p < 0.005$). The study cohort scored higher than test norms on NEPSY Visual Attention ($p = 0.0003$). The z -score differences between the study subjects and the test norms on the ND tests are depicted in the star plot in Fig. 1a.

The percentages of the subjects that fell within the normal (within 1 SD of the test norm), at-risk (1–2 SD below the test norm), and impaired (>2 SD below the test norm) ranges are

depicted in Fig. 1b. In a normal distribution, 84 % of a given sample should fall within the normal range, 14 % within the at-risk range, and approximately 2.5 % within the impaired range. Using these expected values, the study cohort fell within the impaired range on the VMI (8.8 vs. 2.5 %; $p = 0.004$) and Gordon commissions (9.1 vs. 2.5 %; $p = 0.004$) more often than expected. The cohort also fell within the at-risk range on the NEPSY Imitating Hand Positions (32.4 vs. 14 %; $p = 0.002$), the DAS Recall of Objects (38.7 vs. 14 %; $p = 0.0001$), and the CELF Sentence Structure (26.5 vs. 14 %; $p = 0.04$) more often than expected.

The mean scores for the parent and teacher rating scales are summarized in Table 2. The subjects scored within one SD from the test norms on all the parent and teacher rating scale scores. The overall behavioral rating score was normal, at a z -score of ± 0.11 , corresponding to a score of 51 on a 50 ± 10 scale. The cohort scored higher than the population norms on the Attention Problems subscale of the CBCL (parent report, $p = 0.0002$) and CTRF (teacher report, $p = 0.0007$). However, the scores were still within the normal range. The z -score differences between the study group and the parent and teacher rating scale norms are depicted in the star plot in Fig. 2a.

The percentages of subjects that fell within the normal (within one SD of the test norm), at-risk (1–2 SD above the test norm), and impaired (>2 SD above the test norm) ranges are depicted in Fig. 2b. Compared with expected values based on a normal distribution, the study group was more likely to fall within the at-risk range on the CTRF Attention Problems subscale (30 vs. 14 %; $p = 0.04$) and in the impaired range on Conners' ADHD Index subscale (parent, 8.8 vs. 2.5 %; $p = 0.004$; teacher, 9.5 vs. 2.5 %; $p = 0.01$).

The subjects were classified by the number of ND domains (cognition, attention, visual motor, fine motor, memory, or language) with scores in the at-risk or impaired range. The findings show that 26 % ($n = 9$) fell within the normal range in all domains and that 74 % ($n = 25$) were in the at-risk or impaired range in at least one area, with 15 % ($n = 5$) having one score in the at-risk range, 50 % ($n = 17$) having two or more scores in the at-risk range, and 9 % ($n = 3$) having one or more scores in the impaired range.

Relationships with Treatment Characteristics

A logistic regression analysis of the estimated odds ratios for the relationship between the ND test score (at-risk or impaired vs. normal) and treatment/demographic characteristics was conducted. A separate model was used for each of the ND domains (cognition, visual motor, fine motor, attention, memory, and language). Using the Bonferroni multiple testing adjusted p value of 0.01, none of the treatment or demographic variables were statistically significant predictors of ND deficits. The multivariable linear regression did not differ from the univariable regressions in terms of odds ratios or significant variables (see online Appendix for more information).

Discussion

The results of the current study indicate that this recent cohort of early school age children who underwent the Norwood operation are scoring within one SD of test norms in all ND domains including cognition, visual motor, fine motor, attention, memory, and language skills. In contrast to previous studies [8, 14, 22], IQ estimate scores for the current cohort did not differ significantly from test norms. Significant impairment in one or more ND domains was found in only 9 % of the cohort, which is encouraging compared with previous studies [1, 28].

It should be noted that comparisons across studies is difficult due to the different ages at which children are assessed and the different ND tests used. In addition, limitations of the study including the sociodemographic characteristics of the sample, the small sample size, and the participation rate may have resulted in bias, potentially limiting the generalizability of our findings.

Our center has changed practice patterns, with the intent of increasing neuroprotection by using strategies such as antegrade cerebral perfusion and goal-directed therapy with near-infrared spectroscopy (NIRS). In addition, we have targeted better nutrition and implemented a home monitoring program. However, the study was not a controlled study designed to identify the impact of these individual strategies on ND outcome. Therefore, whether these changes in practice patterns contributed to ND outcomes is not known. Due to the difficulty conducting this type of research, larger-scale, multicenter studies that use standardized ND testing protocols to assess older children with UVH are needed to make the findings generalizable to this population as a whole.

Although the current cohort scored well as a group, analysis of performance by individual patients indicates that visual motor and attention skills are areas of greater risk, which is consistent with previous research [6, 10, 28, 38]. Although few subjects presented with significant deficits, 50 % scored within the “at-risk” range in two or more ND domains. Thus, when these children have problems, the problems are typically subtle, affecting multiple areas. Such subtle deficits are likely to be missed without careful, routine developmental follow-up assessment by specialists familiar with this particular population. School personnel often are not familiar with the ND issues common among children with univentricular heart disease, so it is important for staff within the cardiac center to build relationships with schools in order to educate school personnel about these issues. In addition, providing assistance to parents so they can advocate for their children within the school system is critical because these children are not likely to meet the typical criteria for special education services.

The need for routine developmental follow-up evaluation for this population has been suggested previously [6, 17, 24, 30, 37], but most pediatric cardiac centers do not routinely assess these patients for developmental delay as part of standard clinical care [20]. More recently, pediatric cardiac programs have developed ND follow-up programs to meet the needs of this group of patients [5]. Recent guidelines from the American Heart Association (AHA) and the American Academy of Pediatrics (AAP) [25] recommend routine developmental screening of these patients. Such screening and follow-up programs are likely to become increasingly important because the availability of services through early intervention programs has declined over the years due to budget cuts [18]. In addition, the need for long-term ND follow-up evaluation is important because some deficits such as learning disabilities or other emotional problems related to self-esteem, body image, and the like may not present until later childhood and adolescence. Additionally, a patient’s risk profile may change over time if he or she undergoes further surgery or experiences poor growth, heart failure, or other morbidity. This highlights the need for continued assessment of ND and psychosocial issues over time, even if early evaluations do not identify any significant delays or problems. Finally, it should be noted that based on the regression modeling, it is difficult to predict long-term ND outcome on the basis of demographic variables or treatment characteristics, which makes routine ND screening and follow-up evaluation even more important.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Neurodevelopmental (ND) testing results. **a** Star plot of mean ND test scores versus test norms. **b** Percentage of patients in the normal, at-risk, and impaired ranges of the ND tests. Test norms are depicted by a z-score of 0. Higher scores indicate better performance. The expected values in a normal distribution are 84 % (normal), 14 % (at-risk), and 2.5 % (impaired)

Fig. 2. Parent/teacher rating scale results. **a** Star plot of mean parent/teacher scores versus test norms. **b** Percentage of patients in the normal, at-risk, and impaired ranges of the parent/teacher scales. Test norms are depicted by a z-score of 0. Higher scores indicate more problems. The expected values in a normal distribution are 84 % (normal), 14 % (at-risk), and 2.5 % [impaired parent (P), teacher (T)]

Table 1Demographics and treatment characteristics ($n = 34$)

Demographics/clinical variables	n (%)		
Gender (male)	22 (64.7)		
Prenatal diagnosis	15 (44.1)		
Other medical conditions	12 (35.3)		
Status post Fontan	32 (94.1)		
History of ECMO	4 (11.8)		
Growth failure (height or weight <5th percentile)	6 (18.7)		
Premature (GA < 37 weeks)	5 (14.7)		
Mean GA (38.2 ± 1.3), SD = 1.3, Range (35–40)			
Treatment variables	Mean	SD	Range
Age at Norwood (days)	6.4	2.9	2–15
Norwood LOS (days)	33.8	17	15–85
Age at BDG (months)	3.9	0.9	2–5.7
Cumulative LOS (days) ^a	56.9	23.6	25–123
Cumulative CPB time (min) ^a	328.5	97.7	170–625
Cumulative DHCA time (min) ^a	13.4	10.5	2–47
Age at ND testing (years)	5.0	0.6	4–6

BDG bidirectional Glenn, *CPB* cardiopulmonary bypass, *DHCA* deep hypothermic circulatory arrest, *ECMO* extracorporeal membrane oxygenation, *GA* gestational age, *LOS* length of stay, *ND* neurodevelopmental

^a Cumulative at time of ND testing

Table 2

Child-completed neurodevelopmental (ND) measures and parent/teacher ratings results

Test	Domain	Raw mean for cases	Standardized mean (z) for cases	p value (cases vs. z = 0)
<i>Child-completed ND measures</i>				
WPPSI IQ estimate	Cognitive	100.2 ± 13.2	0.02	0.92
VMI	Visual motor	92.1 ± 14.0	-0.53	0.002
NEPSY finger tapping	Fine motor	9.8 ± 3.1	-0.06	0.82
NEPSY imitating hand positions	Fine motor	8.4 ± 2.4	-0.54	0.0004
NEPSY visual attention	Attention	11.5 ± 2.1	0.49	0.0003
Gordon commissions	Attention	12.8 ± 21.4	-0.39	0.22
NEPSY narrative memory	Verbal memory	9.2 ± 3.3	-0.28	0.16
DAS recall of objects	Visual memory	44.6 ± 9.3	-0.54	0.003
DAS naming vocabulary	Language	48.9 ± 9.9	-0.11	0.52
CELF sentence structure	Language	9.3 ± 2.8	-0.23	0.17
CELF word structure	Language	8.7 ± 2.2	-0.42	0.002
<i>Parent/teacher ratings</i>				
Total problems				
Parent	Behavior	48.6 ± 11.3	-0.14	0.49
Teacher		50.5 ± 9.4	0.04	0.83
Internalizing problems				
Parent	Behavior	49.4 ± 10.2	-0.06	0.71
Teacher		51.1 ± 9.6	0.11	0.61
Externalizing problems				
Parent	Behavior	47.5 ± 11.9	-0.25	0.23
Teacher		49.6 ± 7.1	-0.04	0.8
Attention problems				
Parent	Attention	54.0 ± 5.6	0.4	0.0002
Teacher		56.2 ± 6.8	0.62	0.0007
Conners' ADHD Index				
Parent	Attention	52.6 ± 12.3	0.26	0.23
Teacher		51.9 ± 10.5	0.19	0.42

Bold values indicate statistically significant

WPPSI Wechsler Preschool and Primary Scale of Intelligence Third Edition, VMI Developmental Test of Visual Motor Integration, NEPSY A Developmental Neuropsychological Assessment, DAS Differential Ability Scales, Second Edition, CELF Comprehensive Evaluation of Language Fundamentals