Risk Factors for Abnormal Developmental Trajectories in Young Children With Congenital Heart Disease

Kathleen A. Mussatto, PhD, RN; Raymond Hoffmann, PhD; George Hoffman, MD; James S. Tweddell, MD; Laurel Bear, MD; Yumei Cao, PhD; Jena Tanem, MSN, APNP; Cheryl Brosig, PhD

Background—Children with congenital heart disease are at risk for developmental delay. This study sought to identify early risk factors for abnormal developmental trajectories in children with congenital heart disease.

Methods and Results—Children with congenital heart disease at high risk for developmental delay, without known genetic abnormality, and with ≥3 assessments by the use of the Bayley Scales of Infant and Toddler Development, Third Edition, were studied. Logistic regression was used to assess the impact of patient and clinical factors on cognitive, language, and motor score trajectories; classified as: average or improved if all scores were ≥85 (<1 standard deviation below the mean) or increased to ≥85 and never decreased; or abnormal if all scores were <85, fell to <85 and never improved, or fluctuated above and below 85. Data on 131 children with 527 Bayley Scales of Infant and Toddler Development, Third Edition assessments were analyzed. Subject age was 5.5 to 37.4 months. Overall, 56% had cognitive, language, and motor development in the average range. Delays occurred in single domains in 23%. Multiple domains were delayed in 21%. More cardiac surgeries, longer hospital stay, poorer linear growth, and tube feeding were associated with worse outcomes in all domains (P<0.05). In the multivariable model, the need for tube feeding was a risk factor for having an abnormal developmental trajectory (odds ratio, 5.1–7.9). Minority race and lack of private insurance had significant relationships with individual domains.

Conclusions—Longitudinal developmental surveillance identified early factors that can help quantify the risk of developmental delay over time. Strategies to improve modifiable factors and early therapeutic intervention can be targeted to children at highest risk. (Circulation. 2015;132:755-761. DOI: 10.1161/CIRCULATIONAHA.114.014521.)

Key Words: growth & development ▪ heart defects, congenital ▪ heart diseases ▪ outcome assessment (health care) ▪ pediatrics ▪ thoracic surgery

It is well established that children with congenital heart disease (CHD) experience a higher prevalence of developmental delays and disabilities in early childhood than typically developing healthy children. This has been demonstrated in children with isolated lesions that have been anatomically corrected, such as transposition of the great arteries, children developing healthy children.

Children with CHD experience multiple sources of developmental risk including genetic abnormalities, prenatal alterations in cerebral blood flow and brain maturation, the impact of early diagnosis and surgery, perioperative risk related to low cardiac output, and long-term issues that are associated with physiology, socioeconomic status, and parenting practices. The American Heart Association and the American Academy of Pediatrics have recommended systematic surveillance, evaluation, and management of developmental outcomes in children with CHD throughout childhood to promote the early detection of delays and to optimize long-term outcomes.

It is not known how specific patient and clinical factors impact the patterns of development in early childhood. Individual children with CHD may display different patterns of developmental competencies over time. The aim of this
study was to examine factors that contribute to developmental trajectories in cognitive, language, and motor skills over the first 3 years of life in a cohort of children with CHD who were being systematically evaluated and referred for early intervention services.

Methods

Patient Population

Children with CHD believed to be at high risk for developmental delay, as defined by the American Heart Association/American Academy of Pediatrics guideline,1 were recruited from the Herma Heart Center Developmental Follow-up Clinic (HHCDC) at Children’s Hospital of Wisconsin. Eligibility criteria and operation of the HHCDC have been previously described.12,23 Families were invited to participate in systematic developmental follow-up as part of routine clinical care. HHCDC visits were scheduled to occur approximately every 6 months during the first 3 years of life. Referrals for early intervention services (Birth to 3 in the state of Wisconsin) were made for all children who required cardiac surgery at <1 year of age and for those who scored >1 standard deviation below the mean (composite score <85) on cognitive, language, or motor assessment. To be eligible for this study, children had undergone formal developmental evaluation of cognitive, language, and motor skills with the use of the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)24 a minimum of 3 and ≤5 times during the first 3 years of life. Parents provided informed consent to have their child’s data included in a databank approved by the institutional review board at Children’s Hospital of Wisconsin. No subjects were excluded based on race, language, or other coexisting medical condition. To focus specifically on structural heart disease, subjects were excluded from this analysis if they had a clinically diagnosed genetic abnormality or if their primary diagnosis was cardiomyopathy (Figure 1).

Statistical Analysis

Sample characteristics and clinical variables are presented as medians with interquartile range for continuous data and frequencies (%) for categorical data. Cognitive, language, and motor composite scores on the BSID-III were compared with the population mean of 100 (standard deviation, 15). Univariate and multivariable logistic regression analyses were used to assess the impact of patient and clinical factors on the cognitive, language, and motor composite score trajectories for each patient. Trajectories in each domain were classified as average or improved if all scores were ≥85 (<1 standard deviation below the population mean), or scores increased to ≥85 and never decreased. Trajectories were classified as abnormal if all scores were <85, if scores fell to <85 and never improved, or if scores fluctuated above and below 85 over time. P<0.05 was considered significant. All statistical analyses were performed by using SAS version 9.4 (SAS Institute, Cary, NC) software.

Results

From January 2007 through March 2014, 131 subjects with CHD completed a total of 527 BSID-III assessments, which are included in this analysis (Figure 1). Median age at first BSID-III assessment was 7.5 months, interquartile range interquartile range 6.6 to 8.6. Age at evaluation ranged from 5.5 to 37.4 months. The median time interval between BSID-III assessments was 6.0 months (interquartile range, 6.0–6.4). The subjects represented a wide spectrum of CHD, but all were considered to be at risk of developmental delay as defined by the American Heart Association/American Academy of Pediatrics guideline.1 Anatomy was classified according to the child’s fundamental diagnosis at birth. The sample was further classified as to whether the child’s anatomy resulted in achievement of a 2-ventricle repair or a single functional ventricle and whether or not aortic arch obstruction was present. These categories have been previously established as representing increasing complexity.25 Aortic arch obstruction is associated with altered fetal cerebral blood flow and may therefore have an impact on neurodevelopmental outcomes.26 Thirty-eight percent of the subjects had anatomy that required surgical palliation resulting in a single functional ventricle. Of these, 2 subjects with hypoplastic left heart syndrome underwent orthotopic heart transplantation during the study period. No subjects with 2-ventricle anatomy underwent transplantation. Thirty-two percent (n=42) of the subjects had a known medical comorbidity in addition to their CHD involving the following systems: airway issues (n=14), chronic lung disease (n=5), neurologic or neuromuscular (n=6), orthopedic (n=5), gastrointestinal (n=3), hearing loss (n=3), and multisystem (n=6). Characteristics of the sample are presented in Table 1. Table 2 presents detailed anatomic diagnostic information for the subjects by the use of the fundamental diagnosis assigned in the Society of Thoracic Surgeons Congenital Heart Surgery Database.

Subject and treatment characteristics at the time of first BSID-III assessment are presented in Table 3. For variables

![Figure 1. Herma Heart Center Developmental Follow-up Clinic (HHCDC) patients. Shaded boxes identify current study cohort. BSID-III indicates Bayley Scales of Infant and Toddler Development, Third Edition; and CHD, congenital heart disease.](image-url)
The majority of subjects had average or improving developmental trajectories: cognitive, 104 of 131 (79%); language, 89 of 131 (68%); and motor, 102 of 131 (78%). A smaller portion had developmental trajectories that were significantly below average or declined over time: cognitive, 16 of 131 (12%); language, 28 of 131 (21%); and motor, 15 of 131 (11%). Scores fluctuated above and below –1 standard deviation below the mean in others: cognitive, 11 of 131 (8%); language, 14 of 131 (11%); and motor, 14 of 131 (11%). Overall, 56% of subjects had all trajectories for cognitive, language, and motor development in the average range (Figure 2). Trajectories were abnormal in single domains in 23%, in cognitive domains in 4%, in language domains in 13%, and in motor domains in 6%. Twenty-one percent of the subjects had multiple domains delayed. Two example subject trajectories are shown in Figure 3. Both children were born with hypoplastic left heart syndrome, were non-Hispanic white, had undergone 2 cardiac surgeries before their first BSID-III assessment, and had prolonged hospitalizations. They differed on feeding status, insurance, and the occurrence of postoperative seizures. As the graphs demonstrate, their developmental trajectories were profoundly different.

Univariate logistic regression identified multiple patient and clinical factors associated with cognitive, language, and motor development (Table 4). An odds ratio >1 represented an increased likelihood of having an abnormal developmental trajectory. A greater number of cardiac surgical procedures, longer hospital stay, poorer linear growth, and the need for supplemental tube feeding were associated with worse outcomes in all areas of development. The presence of single-ventricle anatomy was associated with higher odds of having an abnormal cognitive trajectory (odds ratio, 2.5; 95% confidence interval, 1.04–5.83; \( P < 0.05 \)), but was not associated with language (odds ratio, 1.4; 95% confidence interval, 0.63–2.83; \( P > 0.05 \)) or motor (odds ratio, 1.4; 95% confidence interval, 0.62–3.29; \( P > 0.05 \)) development. The 34 patients with single-ventricle anatomy and aortic arch obstruction (AAO) were compared with those without AAO, and there were no differences in cognitive, language, or motor outcomes. All the patients with single-ventricle anatomy and AAO had undergone either a Norwood procedure (n=31) or a coarctation repair in the neonatal period followed by a Damus-Kaye-Stansel procedure (n=3). There were also no differences in outcomes detected for patients with 2-ventricle anatomy with AAO in comparison with those without AAO. It is noteworthy that sex, prematurity (<37 weeks gestational age), prenatal diagnosis, birth weight or height percentile, age at first open heart operation, highest Society of Thoracic Surgeons risk category of operation,27 weight, oxygen saturation, and minutes of deep hypothermic circulatory arrest at the time of first BSID-III assessment were not significantly associated with any developmental domains.

Predictors identified from the univariate analysis were used in a multivariable logistic regression model. Potential predictors (as noted at time of first BSID-III assessment) included race, anatomy (single-ventricle versus 2-ventricle), total number of open and closed cardiac surgeries, height percentile, head circumference percentile, the presence of other medical conditions, feeding status, length of hospital stay, cardiopulmonary bypass (CPB) time, maternal education, and insurance status. A forward stepwise selection method was used and the final model included predictors that were significant or had \( P < 0.1 \). The need for supplemental tube feeding was highly correlated with length of hospital stay, CPB time, and the total number of surgeries (\( P < 0.01 \)). Because it was difficult to determine whether feeding status was an outcome or a predictor of developmental progress over time, models were created with and without feeding status at first BSID-III assessment. Results are presented in Table 5. When feeding status was included, the
Cardiac surgery and neuroprotective strategies, our research has identified that developmental delays are both common and dynamic in this population.2,4,6,7,9–11 This study provides a unique characterization of changes in developmental trajectories in multiple domains over time in a large sample treated with a consistent approach to developmental evaluation and support. This is a novel approach to longitudinal data using a person-centered method addressing patterns of development over time in individual children29 as opposed to a single time point or a change from 1 time point to another. Despite the known risk owing to the severity of their CHD, developmental outcomes for individual subjects varied widely. Over half of the sample demonstrated normal development in all domains, but >1 in 5 children had delays in multiple domains. It was shown that children with similar clinical backgrounds can have very different developmental outcomes.

Several factors have consistently emerged as predictors of poorer developmental outcomes including longer duration of hospital stay, poorer linear growth, problems with feeding, and socioeconomic risks.1,4,6,8–12 The presence of any of these factors should alert clinicians to the need for systematic surveillance of development and the need for early intervention to minimize delays. However, despite intense scrutiny, there has been no clear composite of patient and clinical factors that can be identified early in life that consistently predict development over time. This highlights the importance of incorporating the evaluation and management of developmental outcomes into our pediatric cardiology and cardiovascular surgery programs. It should also guide our prenatal and postnatal counseling of families.

Parents should be educated that it cannot be assumed that if a child is doing well at 1 time point that they will continue to do well, as evidenced by the fact that 11% to 21% of patients in the present cohort had scores that declined over time. This supports the need for serial developmental assessments, because some children may not show any deficits until later in life, and early results on the BSID-III are not highly predictive of school age performance.29 Formal evaluation of development can provide parents and clinicians with information and unique insight into each individual child’s strengths and weaknesses. The examination of patterns of development over time in individual children28 as opposed to a single time point or a change from 1 time point to another. Despite the known risk owing to the severity of their CHD, developmental outcomes for individual subjects varied widely. Over half of the sample demonstrated normal development in all domains, but >1 in 5 children had delays in multiple domains. It was shown that children with similar clinical backgrounds can have very different developmental outcomes.

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The need for supplemental tube feeding was once again found to be an important risk factor for abnormal development in the cognitive, language, and motor domains. The inability to achieve full oral feeding was multifactorial and was correlated with a more complex clinical course involving longer hospitalization, more CPB time, and a greater number of cardiac surgeries. Some infants did not feed owing to the inability to protect their airway and the risk of aspiration. Other infants did not have the stamina to consume the number of calories needed to sustain adequate growth. Further research is ongoing to improve our understanding of why feeding problems occur and what approach to feeding management over time can reduce long-term feeding problems. Similar to previous work, we found that height percentile at the time of BSID-III assessment was related to development but not weight percentile.8 Neither birth weight nor height percentile was significantly associated with developmental outcomes.

**Discussion**

Consistent with previous research on developmental outcomes for children with CHD in the modern era of pediatric cardiology and cardiovascular surgery programs. It should also guide our prenatal and postnatal counseling of families.

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The effects of socioeconomic disadvantage have long been known to put child development at risk. In this cohort, the presence of social risk factors including minority race, lack of private insurance, and lower maternal education emerged as significant risk factors for poorer outcomes in specific domains. These factors are typically not modifiable and tend to exert their influence more in the second and third years of life. The use of the patterns of development over time as the primary outcome allowed detection of these risk factors. The presence of social risk factors should alert clinicians to the need for ongoing monitoring and support. Luby and colleagues found that more supportive parenting practices mediated the effect of poverty on child brain development. Interventions designed to provide guidance to parents and help them manage the stress of having a child with a chronic health condition may be beneficial. One study that targeted promotion of maternal coping and adjustment after the birth of an infant with CHD was able to demonstrate significantly lower maternal worry at 6 months and a statistically significant improvement in the mental development index on the BSID-II in the infants of mothers who participated in the intervention.

There are some important limitations to the current study. The cohort studied represents a single-center experience and the findings may not be generalizable to the population of young children with CHD as a whole. Not all children who were eligible attended the developmental follow-up program, and it is likely that parents of children with more obvious developmental delays were more motivated to participate. The most common reason parents cited for not participating was that they perceived that their child was doing well. Nonattendees lived farther away from the treatment center and had less complex cardiac surgery; however, in most cases, we do not know why families chose not to attend the program.

We excluded children with any clinically diagnosed genetic abnormality despite the fact that they make up ≈20% of the CHD population. Further research is needed to understand the combined impact of CHD and genetic abnormalities on child development. We also excluded 5 children with

### Table 4. Univariate Predictors of Abnormal Developmental Trajectories

<table>
<thead>
<tr>
<th></th>
<th>Cognitive</th>
<th>Language</th>
<th>Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic white vs others</td>
<td>0.23† (0.09–0.55)</td>
<td>0.39‡ (0.18–0.84)</td>
<td>0.49 (0.21–1.13)</td>
</tr>
<tr>
<td>Single-ventricle anatomy</td>
<td>2.57‡ (1.09–6.10)</td>
<td>1.40 (0.66–2.97)</td>
<td>1.24 (0.53–2.88)</td>
</tr>
<tr>
<td>Maternal education: ≤HS vs &gt;HS</td>
<td>3.06‡ (1.17–7.98)</td>
<td>2.96‡ (1.23–7.12)</td>
<td>0.56 (0.17–1.78)</td>
</tr>
<tr>
<td>Public or no insurance vs private</td>
<td>5.17§ (2.00–13.37)</td>
<td>1.47 (0.70–3.08)</td>
<td>1.53 (0.67–3.50)</td>
</tr>
<tr>
<td>Total # open and closed* operations</td>
<td>1.79† (1.07–3.01)</td>
<td>1.94‡ (1.16–3.24)</td>
<td>2.04‡ (1.18–3.53)</td>
</tr>
<tr>
<td>Height, %ile*</td>
<td>0.98‡ (0.97–1.00)</td>
<td>0.98‡ (0.97–1.00)</td>
<td>0.98‡ (0.97–1.00)</td>
</tr>
<tr>
<td>Head circumference, %ile*</td>
<td>0.98‡ (0.97–1.00)</td>
<td>0.99 (0.98–1.00)</td>
<td>0.99 (0.97–1.00)</td>
</tr>
<tr>
<td>Other medical condition* vs none</td>
<td>2.92‡ (1.22–6.98)</td>
<td>1.49 (0.69–3.23)</td>
<td>1.15 (0.48–2.76)</td>
</tr>
<tr>
<td>Supplemental tube feeding* vs none</td>
<td>15.27§ (5.62–41.49)</td>
<td>5.32§ (2.29–12.36)</td>
<td>6.15§ (2.51–15.11)</td>
</tr>
<tr>
<td>Length of hospital stay (per 10 days)*</td>
<td>1.32§ (1.16–1.49)</td>
<td>1.21§ (1.08–1.34)</td>
<td>1.18§ (1.07–1.31)</td>
</tr>
<tr>
<td>CPB time (per 60 min)*</td>
<td>1.27† (1.06–1.52)</td>
<td>1.20† (1.06–1.43)</td>
<td>1.20 (1.00–1.35)</td>
</tr>
</tbody>
</table>

The values presented are odds ratio (95% confidence interval). BSID-III indicates Bayley Scales of Infant and Toddler Development; CPB, cardiopulmonary bypass; and HS, high school.

†P<0.01.‡P<0.05. §P<0.001.
cardiomyopathy, because their clinical course was quite different than the clinical course of children with structural heart disease.

We relied on parent report of use of early intervention services, but we know very little about the quality or quantity of the services the children were receiving. This makes it challenging to measure the impact of early developmental surveillance and intervention on later outcomes. Although some children demonstrated notable improvements over time (cognitive, 3%; language, 7.6%; and motor, 24%), it is impossible to know if these improvements would have occurred without regular surveillance. It has been repeatedly shown that children at known developmental risk do not necessarily receive the school-based support services mandated by the Individuals with Disabilities Education Act.32,33 Future studies should attempt to recruit age-matched subjects who did not participate in developmental follow-up to determine whether differences can be detected between those who did and did not receive longitudinal assessments.

Although it is too soon to speculate on the cost-effectiveness and impact of developmental follow-up programs within our cardiac centers, the societal costs of early childhood developmental delay are enormous and have an impact across the lifespan. One recent study found that for every child with mental development >1.5 standard deviations below the mean at <3 years of age, there was a cost of $34,532 attributable to increased preschool special education services.34 This cost will increase exponentially if the needs for special education persist and if developmental delays have a negative impact on the potential for lifetime employment and earnings.

Few studies have characterized factors that contribute to the patterns of development over time. In this study, longitudinal developmental surveillance identified early factors that can help quantify the risk of developmental delay over time. Strategies to improve modifiable factors and early therapeutic intervention can be targeted to children at highest risk. Research to understand and improve these outcomes is our ongoing obligation.

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**Disclosures**

None.

**References**


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