Neurodevelopmental Outcome in Children after Fetal Cardiac Intervention for Aortic Stenosis with Evolving Hypoplastic Left Heart Syndrome

Kristin Laraja, MD[1,2], Anjali Sadhwani, PhD[3,4], Wayne Tworetzky, MD[1,2], Audrey C. Marshall, MD[1,2], Kimberlee Gauvreau, ScD[1,2], Lindsay Freud, MD[1,2], Cara Hass, BA[1], Carolyn Dunbar-Masterson, BSN, RN[1], Janice Ware, PhD[4,5], Terra Lafranchi, NP-C[1], Louise Wilkins-Haug, MD[6,7], and Jane W. Newburger, MD, MPH[1,2]

Objective To characterize neurodevelopmental outcomes after fetal aortic valvuloplasty for evolving hypoplastic left heart syndrome and determine the risk factors for adverse neurodevelopment.

Study design Questionnaires were mailed to families of children who underwent fetal aortic valvuloplasty from 2000 to 2012, and medical records were reviewed retrospectively. The primary outcome was the General Adaptive Composite score of the Adaptive Behavior Assessment System Questionnaire-Second Edition. Other questionnaires included the Behavior Assessment System for Children, Behavior Rating Inventory of Executive Function, Ages and Stages, and Pediatric Quality of Life Inventory.

Results Among 69 eligible subjects, 52 (75%) completed questionnaires at median age of 5.5 (range 1.3-12) years; 30 (58%) had biventricular status circulation. The General Adaptive Composite mean score (92 ± 17) was lower than population norms ($P < .001$) and similar to published reports in patients with hypoplastic left heart syndrome without fetal intervention; scores in the single ventricular versus biventricular group were 97 ± 19 vs 89 ± 14, respectively ($P = .10$). On multivariable analysis, independent predictors of a lower General Adaptive Composite score were total hospital duration of stay in the first year of life ($P = .001$) and, when forced into the model, biventricular status ($P = .02$). For all other neurodevelopmental questionnaires (Behavior Assessment System for Children, Behavior Rating Inventory of Executive Function, Ages and Stages, Pediatric Quality of Life Inventory), most subscale scores for patients with biventricular and single ventricular status were similar.

Conclusion Children who underwent fetal aortic valvuloplasty have neurodevelopmental delay, similar to patients with hypoplastic left heart syndrome without fetal intervention. Achievement of biventricular circulation was not associated with better outcomes. We infer that innate patient factors and morbidity during infancy have the greatest effect on neurodevelopmental outcomes. *(J Pediatr 2017;184:130-6).*

Over the past 12 years, in utero aortic valvuloplasty has been offered in the Cardiovascular Program at Boston Children's Hospital for fetuses who have aortic stenosis with evolving hypoplastic left heart syndrome (HLHS). This procedure can interrupt the evolution to HLHS, resulting in a biventricular circulation at birth in 30% of patients; an additional 8% of patients are converted to a biventricular circulation after initial univentricular palliation. We have reported previously on the technical success, adverse events, effects on fetal left heart physiology and cerebral blood flow characteristics, and postnatal cardiac outcomes.[1-6] Fetal cardiac intervention (FCI) could improve neurodevelopmental outcomes theoretically by increasing cerebral oxygen delivery and consumption during fetal life,[7] as well as by improving postnatal hemodynamics through achievement of a biventricular circulation. However, neurodevelopmental outcomes of this high-risk group have not been reported previously.

The purpose of this study was to characterize the neurodevelopmental and behavioral outcomes of this growing population of children after fetal aortic valvuloplasty for aortic stenosis with evolving HLHS, including patients who achieved a biventricular circulation and those who

ABAS-II	Adaptive Behavior Assessment System Questionnaire, Second Edition
ASQ-3	Ages and Stages Questionnaire, Third Edition
BASC-II	Behavior Assessment System for Children—Second Edition
BRIEF	Behavior Rating Inventory of Executive Function
BSID-III	Bayley Scales of Infant and Toddler Development—Third Edition
DAS-II	Differential Abilities Scales—Second Edition
FCI	Fetal cardiac intervention
GAC	General Adaptive Composite
HLHS	Hypoplastic left heart syndrome
PedsQL	Pediatric Quality of Life Inventory

From the [1]Department of Cardiology, Boston Children's Hospital; [2]Department of Pediatrics, Harvard Medical School; [3]Department of Psychiatry, Boston Children's Hospital; [4]Department of Psychiatry, Harvard Medical School; [5]Developmental Medicine Center, Boston Children's Hospital; [6]Department of Obstetrics and Gynecology, Brigham and Women's Hospital; and [7]Department of Obstetrics and Gynecology, Harvard Medical School, Boston, MA

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underwent staged single ventricle palliation. In addition, we identified risk factors for adverse neurodevelopment outcomes unique to this population and compared their development with published data in the HLHS group who did not undergo FCI and were treated with single ventricle staged palliation.

Methods

This cohort study involved cross-sectional measurement of neurodevelopment and behavior, together with retrospective review of medical records.

Eligible subjects were those who had undergone fetal aortic valvuloplasty for aortic stenosis with evolving HLHS in our Fetal Cardiac Intervention Program between March 2000 and November 2012, and thus were >12 months of age by December 1, 2013. Exclusion criteria included aortic valve dilation as part of a salvage procedure for hydrops and cardiac transplantation. This study was conducted with the approval from the Boston Children's Hospital Institutional Review Board and conducted in accordance with institutional guidelines. Written informed consent from parents or guardians was obtained for all subjects, and assent was obtained according to institutional guidelines.

We performed a retrospective maternal and fetal chart review. The year of fetal intervention, gestational age at intervention, and type of maternal anesthesia were recorded. Technical success of the aortic valvuloplasty was defined as one in which the aortic valve was crossed and a balloon inflated, with clear evidence of increased flow across the valve and/or of new aortic regurgitation by color Doppler as assessed by 2 echocardiographers. Fetal resuscitation was defined as bradycardia or dysfunction requiring nonprophylactic epinephrine or drainage of a pericardial effusion.[6] The degree of aortic regurgitation was recorded from the echocardiogram performed 24 hours after fetal intervention.

We defined a biventricular circulation at time of neurodevelopment testing as one in which the left ventricle was the sole source of systemic output, with no intracardiac or great arterial shunts except an atrial septal defect or patent foramen ovale. Patients with biventricular circulation included those whose circulation was biventricular from birth (ie, with no univentricular staging procedures), as well as patients who underwent initial univentricular palliation that was later converted to a biventricular circulation. We defined single ventricle circulation as a definitive or intermediate univentricular circulation at the time of neurodevelopment testing. We recorded characteristics at birth, including gestational age, sex, ascending aorta diameter, genetic syndrome, and perinatal interventricular hemorrhage. We recorded growth measures at birth, before a bidirectional Glenn procedure or at approximately 6 months of age, and at the time of neurodevelopment testing. Growth measures were converted to age-adjusted z scores based on World Health Organization standards. We also recorded initial and current feeding modality; hospital duration of stay after the initial intervention and throughout the first year of life; surgical and catheterization interventions; intraoperative perfusion times; complications, including cardiopulmonary resuscitation, extracorporeal membrane oxygenation, necrotizing enterocolitis, arrhythmias, and seizures; current cardiac medications; and maternal education and socioeconomic status (Hollingshead Four-Factor Index of Social Status).[8]

Our primary outcome measure was the General Adaptive Composite (GAC) score of the Adaptive Behavior Assessment System Questionnaire-Second Edition (ABAS-II).[9] This is a parent-completed, standardized questionnaire that assesses adaptive skills in children from birth to 21 years of age. Composite scores for overall adaptive functioning (GAC), conceptual, social and practical domains (mean ± standard deviation, normal range 100 ± 15) as well as the 9 subscales (mean ± standard deviation, normal range 10 ± 3) were reported.

Parents also completed the Ages and Stages Questionnaire, Third Edition (ASQ-3), a developmental screener for children ages 1 month to 5 years of age.[10] The ASQ-3 assesses concern or risk of development delay in the domains of communication, gross and fine motor development, problem solving, and personal-social skills using pre-established threshold cutoffs.

The Behavior Rating Inventory of Executive Function (BRIEF) is a parent-completed standardized measure that assesses executive function at home.[11,12] We report T scores for 3 domain scores (global executive composite, metacognition index and behavior regulation index) and 8 subscales (normal mean [SD] of 50 ± 10). Parents of children 2-5 years of age completed the BRIEF—Preschool Version Questionnaire, and parents of children 6-13 years of age completed the BRIEF.[11,12]

The Behavior Assessment System for Children-Second Edition (BASC-II) is a measure of social-emotional functioning completed by parents of children aged 2-21 years.[13] We report T scores of the 4 domains (externalizing problems, internalizing problems, behavioral symptoms index, and adaptive skills) and 12-15 subscales (normal 50 ± 10). In addition, pre-established threshold cutoffs were used to determine whether a child's score represents an area of 'risk' or 'concern' outside the normal range.

Health-related quality of life was assessed by the Pediatric Quality of Life Inventory (PedsQL) completed by parents of children ≥2 years of age and by children if they were older than 5 years of age.[14] It assesses the domains of physical, emotional, social, and school functioning of children with cardiac disease. For each of the 4 domains, higher scores represent better health-related quality of life.

Children whose families agreed to return to our institution for evaluation underwent in-person neurodevelopmental testing administered by a psychologist. Children younger than 3 years of age were administered the Bayley Scales of Infant and Toddler Development-Third Edition (BSID-III).[15] Composite scores (normal 100 ± 15) and subscale scores (normal 10 ± 3) were reported for the cognitive, language, and motor domains. Children ages 3 years of age and older were administered the Differential Abilities Scales-Second Edition (DAS-II).[16] The DAS is a standardized assessment of a child's