Neurodevelopmental outcomes in preschool survivors of the Fontan procedure

J. William Gaynor, MD,[a] Richard F. Ittenbach, PhD,[b] Marsha Gerdes, PhD,[c] Judy Bernbaum, MD,[d] Robert R. Clancy, MD,[e] Donna M. McDonald-McGinn, MS,[f] Elaine H. Zackai, MD,[f] Gil Wernovsky, MD,[g] Susan C. Nicolson, MD,[h] and Thomas L. Spray, MD[a]

Objectives: The study objectives were to compare the neurodevelopmental outcomes of preschool survivors of the Fontan procedure with those of children with congenital heart disease undergoing biventricular repair and to investigate predictors of neurodevelopmental outcome for those with single ventricle congenital heart disease, including hypoplastic left heart syndrome.

Methods: Neurodevelopmental outcomes were assessed at 4 years of age, including cognition, visual–motor integration, behavior, social skills, and academic achievement. Unadjusted outcomes were compared between patients with biventricular circulation and patients with single ventricles. Predictors of neurodevelopmental outcome were assessed in the patients with single ventricles. Multiple covariate models were evaluated using patient-related, operative, and postoperative covariates.

Results: Neurodevelopmental evaluation was performed in 365 children, 112 after the Fontan procedure (hypoplastic left heart syndrome, n = 91; other single ventricle, n = 21) and 253 after biventricular repair. Compared with patients with biventricular circulation, patients with single ventricles performed worse in terms of processing speed, inattention, and impulsivity. Otherwise, there were no significant differences between the groups for any domain. There was a trend toward lower performance for patients with single ventricles on visual motor integration. Outcomes for patients with hypoplastic left heart syndrome were not worse than for other forms of functional single ventricle. Patient factors were more important predictors of neurodevelopmental outcomes than were operative management variables.

Conclusions: In this cohort, unadjusted neurodevelopmental outcomes for preschool survivors of the Fontan procedure are similar to those for children with congenital heart disease undergoing biventricular repair for most domains. Among the patients undergoing the Fontan procedure, hypoplastic left heart syndrome was not associated with worse outcomes compared with other forms of single ventricle. (J Thorac Cardiovasc Surg 2014;147:1276-83)

CHD

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From the Division of Cardiac Surgery,[a] The Children's Hospital of Philadelphia, Philadelphia, Pa; Division of Biostatistics,[b] Cincinnati Children's Hospital, Cincinnati, Ohio; Divisions of Psychology,[c] Pediatrics,[d] Neurology,[e] Genetics,[f] and Cardiology,[g] The Children's Hospital of Philadelphia, Philadelphia, Pa; and Division of Cardiac Anesthesiology,[h] The Cardiac Center, The Children's Hospital of Philadelphia, Philadelphia, Pa.

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Address for reprints: J. William Gaynor, MD, Division of Cardiothoracic Surgery, The Children's Hospital of Philadelphia, 34th and Civic Center Blvd, Philadelphia, PA 19104 (E-mail: gaynor@email.chop.edu).

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Over the past 15 years, innovations in surgical techniques and perioperative care have resulted in improving survival for patients with the most complex forms of congenital heart disease (CHD), especially those born with a functional single ventricle (SV), including hypoplastic left heart syndrome (HLHS).[1] With improved survival has come the realization of neurobehavioral disabilities and impaired functional outcomes in a significant portion of the survivors. Indeed, for all children with CHD, neurodevelopmental (ND) dysfunction has become the most common and potentially the most disabling outcome for CHD and their treatment.

Patients with SVs who ultimately undergo the Fontan operation are at the greatest risk for ND disability. These patients usually undergo multiple surgical procedures with cardiopulmonary bypass (CPB) and often deep hypothermic circulatory arrest (DHCA). Hospitalizations are multiple and typically longer than for those with a biventricular (BV) circulation. In addition, before the completion of the Fontan operation all patients with SVs have chronic hypoxemia, which may be a significant risk factor for later cognitive dysfunction and ND abilities. Previous studies have suggested that as a group, patients

Abbreviations and Acronyms

APOE = apolipoprotein E
BV = biventricular
CHD = congenital heart disease
CPB = cardiopulmonary bypass
DHCA = deep hypothermic circulatory arrest
HLHS = hypoplastic left heart syndrome
IQ = intelligence quotient
ND = neurodevelopmental
SD = standard deviation
SV = single ventricle

with SVs function within the low normal range for cognitive performance and many other developmental domains.[2-4]

The current study was undertaken to access ND performance in multiple domains for children with various forms of SV physiology undergoing staged reconstruction surgery and ultimately the Fontan procedure, and to (1) compare the ND outcomes with children with other forms of CHD who underwent a BV repair and (2) evaluate potential risk factors for adverse ND outcomes in the cohort of children with SV physiology.

MATERIALS AND METHODS

The current study is a secondary analysis of data from a prospective longitudinal study evaluating the association between ND dysfunction and polymorphisms of the apolipoprotein E (*APOE*) gene in preschool patients (aged 4-5 years) after cardiac surgery.[5] Patients aged 6 months or less undergoing surgery for CHD using CPB with or without DHCA were eligible. Exclusion criteria included multiple congenital anomalies, a recognizable genetic syndrome other than chromosome 22q11 microdeletion syndrome, and language other than English spoken in the home. The institutional review board at The Children's Hospital of Philadelphia approved the study, and the parent or guardian provided informed consent.

The population for the current study consisted of all patients who had returned for ND evaluation at 4 to 5 years of age and who had achieved an end state of a BV repair or Fontan procedure. Children who had not achieved one of these end states or who had undergone cardiac transplantation were not included in the analysis.

Operative Management

Operations were performed by 5 cardiac surgeons with a dedicated team of cardiac anesthesiologists. Alpha-stat blood gas management was used. Pump flow rates were not standardized for this study. DHCA was used at the surgeon's discretion. Before DHCA, patients underwent core cooling and topical hypothermia of the head to a nasopharyngeal temperature of 18°C. Modified ultrafiltration was performed in all patients. Patients recovered in a cardiac intensive care unit with a dedicated group of cardiac intensivists.

Data Collection

Preoperative factors, including gestational age, birth head circumference, birth weight, and preoperative intubation, were obtained from birth and hospital records. Weight, age at operation, and type of operation were recorded along with perfusion data, including CPB time, aortic crossclamp time, and duration of DHCA. Total support time was calculated as CPB time plus DHCA time. Total DHCA time was calculated as the sum of the duration of each episode of DHCA.

Four-Year Neurodevelopmental Examination

The ND examination was performed between the fourth and fifth birthdays. Maternal education, socioeconomic status, and ethnicity were determined by parental report. A medical history was obtained focusing on illness, rehospitalizations, neurologic events or interim evaluations, current medications, and parent concerns over health.

Patients were evaluated by a genetic dysmorphologist at 1- or 4-year evaluations. Additional genetic analyses were performed if indicated. Neonatal recognition of dysmorphic features can be difficult; therefore, some patients were enrolled for whom the diagnosis of a genetic syndrome was not made until a later evaluation. Patients were classified as having no definite syndromic/chromosomal abnormality (normal), a suspected genetic syndrome (suspect), or a definite syndromic/chromosomal abnormality (abnormal). *APOE* genotype determination, whole blood, or a buckle swab was obtained before the operation and stored at 4°C. Genomic DNA was prepared to determine the *APOE* genotype using a previously published method.[5]

Cognitive outcomes were assessed using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition,[6] which provides 4 scales: Verbal intelligence quotient (IQ) estimates verbal reasoning and comprehension and attention to verbal stimuli. Performance IQ estimates nonverbal reasoning, including fluid reasoning, spatial processing, and perceptual organization. Full Scale IQ is a summary of both types of reasoning. Processing Speed estimates the ability to process information without making errors. Visual-motor integration was assessed with the Developmental Test of Visual Motor Integration, a simple copying task that assesses the child's fine-motor and visual-motor coordination skills.[7] Academic achievement (school readiness for reading and math) was tested using the reading and math clusters of the Woodcock-Johnson III, a standardized achievement test for children from 2 years to adulthood.[8] If a child was judged to be too developmentally impaired to complete the tasks, he/she was assigned the lowest possible score for the specific test; if a child was unable to complete the task for other reasons, the child was excluded from the analysis for that domain.

Inattention, impulsivity, and social skills were assessed by parental report. Inattention and impulsivity were also assessed by the Impulsivity and Inattention Scales of the Attention Deficit/Hyperactivity Disorder Rating Scale-IV Preschool Version.[9] Social Competence was assessed by the Preschool and Kindergarten Behavior Rating Scales Social Skills Total Score, which details social cooperation, social interaction, and social independence as reported by parents.[10] Social interaction skills were also assessed using the Child Behavior Checklist for ages 1.5 to 5 years,[11] which is a questionnaire used to obtain parental reports of behavior problems and prosocial adaptive skills demonstrated within the previous 6 months. Specifically, the Pervasive Developmental Problem scale was used to assess the prevalence of problems in the area of reciprocal social interactions and restricted behaviors (eg, repetitive behavior or disturbed by change). This scale was developed to incorporate some of the behavioral symptoms that the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, lists as criteria for the diagnosis of an autism spectrum disorder (autism, Asperger syndrome, or pervasive developmental disorder not otherwise specified). High scores on the Pervasive Developmental Problem scale do not confirm the diagnosis of an autism spectrum disorder but suggest that further evaluation is warranted.

Data Analysis

Data analysis proceeded in 3 distinct phases: a descriptive phase in which we computed and evaluated the descriptive information for the group