Effect of congenital heart disease on 4-year neurodevelopment within multiple-gestation births

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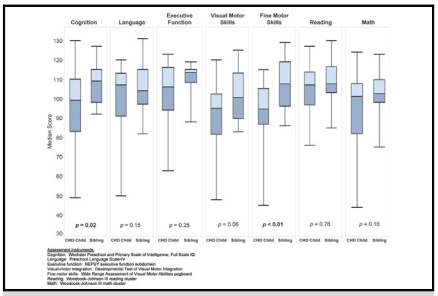
ABSTRACT

Objectives: We sought to assess the effect of congenital heart disease requiring infant surgery with cardiopulmonary bypass on neurodevelopmental outcomes and growth at 4 years of age, while matching for gestational age, socioeconomic status, maternal gestational conditions, home environment, and parental intelligence by studying multiple-gestation births.

Methods: We performed within-family comparison of 14 multiple-gestation births in which 1 child had congenital heart disease requiring surgery with cardiopulmonary bypass at ≤6 months of age. Between 4 and 5 years of age, a comprehensive neurodevelopmental assessment was performed. Paired comparisons were conducted between siblings with and without heart defects using a series of nonparametric tests.

Results: On average, the children qualified as late preterm (mean gestational age 35.4 ± 2.6 weeks). At an average age of 4.8 ± 0.1 years, children with congenital heart disease weighed less than their siblings (median weight for age *z* score −0.4 vs 0.1, $P = .02$) and had worse performance for cognition (median full-scale IQ 99 vs 109, $P = .02$) and fine motor skills (median Wide Range Assessment of Visual Motor Ability, Fine Motor score 94.5 vs 107.5, $P < .01$).

Conclusions: After controlling for socioeconomic status, home environment, parental intelligence, and gestational factors by using multiple-gestation births, congenital heart disease requiring surgery with cardiopulmonary bypass at ≤6 months of age is associated with lower weight, cognitive abilities and fine motor skills at 4 years of age. (J Thorac Cardiovasc Surg 2017;154:273-81)



Developmental outcomes: children with congenital heart disease versus same-gestation siblings.

Central Message

Controlling for family- and pregnancy-related factors, congenital heart disease requiring infant surgery is associated with developmental deficits at 4 years.

Perspective

Many studies find developmental deficits in children with congenital heart disease (CHD) compared with norms, but cannot adjust for gestational factors, home environment, or parental intelligence. Our unique cohort compares children with CHD requiring infant surgery to same-gestation siblings. Developmental deficits at 4 years were associated with CHD, controlling for important confounders.

See Editorial Commentary page 282.

Neurodevelopmental (ND) deficits are common and significantly disabling complications of congenital heart disease (CHD) and its treatment.[1,2] Previous studies have identified an increased incidence of mild cognitive impairment, impaired social interactions, deficits in fine motor skills and executive function, inattention, and impulsivity compared with the general population. In studies of ND outcomes, it is difficult to control for

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Abbreviations and Acronyms

APOE = Apolipoprotein E
AS = aortic stenosis
CHD = congenital heart disease
CPB = cardiopulmonary bypass
DHCA = deep hypothermic circulatory arrest
D-TGA = D-transposition of the great arteries
FSIQ = Full-Scale IQ
HLHS = hypoplastic left heart syndrome
IVS = intact ventricular septum
ND = neurodevelopmental
NEPSY = A Developmental NEuroPSYchological Assessment
PA = pulmonary atresia
SES = socioeconomic status
TAPVC = total anomalous pulmonary venous connection
TOF = tetralogy of Fallot
VSD = ventricular septal defect
WHO = World Health Organization

Scanning this QR code will take you to the online appendix for this article.

potential confounders, such as gestational age, maternal conditions during pregnancy, home environment, socioeconomic status (SES), and parental intelligence, all of which are likely to highly influence ND outcome.[3-8] Multiple-gestation births, in which one child has CHD, provide a unique opportunity to match for these factors. We have previously shown in such a cohort that at 1 year of age, the children with CHD had lower scores on the Bayley Scales of Infant Development than their siblings.[9] However, ND measures assessed at 1 year of age may not predict long-term outcomes.[10,11] Therefore, the cohort was reevaluated at 4 years of age.

PATIENTS AND METHODS

Patient Population

Between September 1998 and April 2003, 550 infants with CHD undergoing surgery with cardiopulmonary bypass (CPB) at ≤188 days (6 months) of age were enrolled in a single-institution study of the association between apolipoprotein E (*APOE*) genotype and postoperative neurodevelopmental dysfunction.[12] Exclusion criteria included (1) multiple congenital anomalies, (2) recognizable genetic or phenotypic syndrome other than chromosome 22q11 microdeletion, and (3) language other than English spoken in the home.

Among this cohort, children who were the product of a multiple gestation were identified; this group formed the study population that was the focus of this report. Sibling(s) of the same gestation were recruited to participate in the follow-up evaluation with the intent to perform a matched pairs evaluation. Children with identified genetic abnormalities (including microdeletion of chromosome 22q11) or marked dysmorphisms as determined by a geneticist (see the section "Four-Year Follow-up Evaluation" later in this article for details) were excluded from this study. In addition, children were excluded from the study if the sibling was not available for evaluation or if the sibling also had CHD. Gestational age was recorded in completed weeks by best obstetric estimate.

As a measure of complexity of CHD, patients were categorized according to a previously described classification that has been shown to be predictive of postoperative mortality.[13] Class I includes patients whose repair achieves a biventricular circulation and in whom there is no preoperative arch obstruction; class II, biventricular circulation with arch obstruction; class III, single-ventricle circulation without arch obstruction; and class IV, single-ventricle circulation with arch obstruction. In general, patients with class I or II CHD achieve normal physiology after a single operation, whereas those in class III or IV require multiple palliative operations and may experience ongoing cyanosis and/or congestive heart failure.

The institutional review board at the Children's Hospital of Philadelphia approved the study. Written informed consent was obtained from the parent or guardian.

Intraoperative Management

Operations were performed by 1 of 3 cardiac surgeons with a dedicated team of cardiac anesthesiologists. Alpha-stat blood gas management was used. Deep hypothermic circulatory arrest (DHCA) was used at the surgeon's discretion. Before DHCA, patients were cooled to a nasopharyngeal temperature of 18°C by using a combination of core cooling on CPB and topical hypothermia. Modified ultrafiltration was performed in all patients.

Four-Year Follow-up Evaluation

A study follow-up visit was conducted between the fourth and fifth birthdays. Siblings were assessed on the same day. Growth parameters (weight, height, and head circumference) were measured. A comprehensive ND assessment was performed. This included investigator-administrated instruments to assess cognition (Wechsler Preschool and Primary Scale of Intelligence, Full-Scale IQ [FSIQ]),[14] language (Preschool Language Scale-IV),[15] executive function (A Developmental NEuroPSYchological Assessment [NEPSY] executive function subdomain),[16] visual motor integration (Developmental Test of Visual Motor Integration),[17] fine motor skills (Wide Range Assessment of Visual Motor Abilities pegboard),[18] and academic skills (Woodcock-Johnson III reading and math clusters).[19] All of these instruments are designed to have a mean score of 100 in the normal population with a standard deviation of 15. Throughout the project, study personnel were trained to use standardized assessment practices. Each protocol was reviewed for accuracy, with attention to all subsets, including those requiring interpretation of verbal responses. Interrater reliability and administration standards for every test were established and maintained. The assessors were not fully masked to the child's CHD status; however, no information was directly provided to the assessor about the child's history. Language testing was conducted by 1 of 2 speech language pathologists experienced in test administration and scoring. Audiologic evaluations were conducted using standard pediatric assessment methods based on developmental ability. For the fine motor assessment, hand dominance was established first, and testing was then performed only for the dominant hand. Parents completed questionnaires to report social competence,[20] hyperactivity/impulsivity and attention,[21] SES (Hollingshead index),[22] interim medical history, and race/ethnicity. For details of the instruments used, see Appendix E1. Each child with CHD was evaluated by a genetic dysmorphologist (DMM, EZ) at either the 1-year or 4-year visit. Based on this evaluation, further genetic