Effect of congenital heart disease on neurodevelopmental outcomes within multiple-gestation births

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Objectives: We sought to assess the effect of congenital heart disease requiring surgical intervention with cardiopulmonary bypass at 6 months of age or less on developmental outcomes and growth at 1 year of age while controlling for socioeconomic status, prematurity, home environment, and parental intelligence.

Methods: We performed within-family comparison of 11 multiple-gestation births in which one child had congenital heart disease. At 1 year of age, the Bayley Scales of Infant Development II were administered, and growth parameters were assessed. Paired comparisons were made by using fixed effects regression conditioned on family.

Results: The multiple-gestation subjects were mildly premature on average (mean gestational age, 35.4 ± 3.0 weeks). At 1 year of age, children with congenital heart disease scored lower on the Mental Development Index (85.0 ± 19.3 vs 93.9 ± 16.0, $P = .037$) and the Psychomotor Development Index (76.6 ± 16.9 vs 91.3 ± 14.9, $P = .015$) on the Bayley Scales of Infant Development II than did their siblings without congenital heart disease. There were no differences between siblings in weight, height, or head circumference.

Conclusions: The presence of congenital heart disease requiring surgical intervention with cardiopulmonary bypass at 6 months of age or less is associated with a deficit in developmental achievement at 1 year of age, as measured by using the Bayley Scales of Infant Development II.

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Neurocognitive outcomes after surgical intervention for congenital heart disease (CHD) in infancy are the focus of great clinical interest and much research. As mortality among children with CHD has decreased, neurodevelopmental impairment has been identified as one of the most significant morbidities among survivors of CHD operations. Multiple studies have shown that in comparison with general population norms, survivors of surgical intervention for complex CHD typically have lower scores on neuropsychological testing, with performance scores often more impaired than verbal scores.[1-4] However, comparison of children with CHD with published norms for the general population is complicated by the potential confounding effects of socioeconomic status (SES), parental intelligence, home environment, and prematurity, all of which highly influence developmental outcome.[1,5-9] To isolate the effect of CHD and its management on neurodevelopmental outcomes at 1 year of age, we evaluated multiple-gestation births in which one child had CHD. This study design affords a unique opportunity to match study subjects and sibling control subjects for familial factors, including SES, parental intelligence, home environment, and gestational age.

Methods

Patient Population

Between September 1998 and April 2003, 550 infants with CHD undergoing surgical intervention with cardiopulmonary bypass (CPB) at 188 days (6 months) of age or less were

Abbreviations and Acronyms
CHD = congenital heart disease
CPB = cardiopulmonary bypass
DHCA = deep hypothermic circulatory arrest
HLHS = hypoplastic left heart syndrome
MDI = Mental Development Index
PDI = Psychomotor Development Index
SES = socioeconomic status

enrolled in a single-institution study of the association between apolipoprotein E genotype and postoperative neurodevelopmental dysfunction.[4] 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, subjects who were the product of a multiple gestation were identified; this group forms the study population for this report. Subjects with microdeletion of chromosome 22q11 were excluded from this study. Siblings of the same gestation were recruited to participate in the follow-up evaluation. Neonatal records of both the subjects with CHD and their siblings were reviewed for information about the pregnancy and perinatal course. Gestational age was recorded in completed weeks by best obstetric estimate.

The Institutional Review Board at The Children's Hospital of Philadelphia approved the study. Written informed consent was obtained from the parent or guardian. The funding agencies had no role in data collection, interpretation, or analysis or in the preparation of the manuscript.

Intraoperative Management

Operations were performed by 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 a combination of core cooling on CPB and topical hypothermia. Modified ultrafiltration was performed in all patients.

One-Year Follow-up Evaluation

A study follow-up visit was conducted at 12 months of age, corrected for prematurity, plus or minus 2 weeks. Siblings were assessed on the same day. Personnel involved in the evaluation were not blinded to CHD status. One of 3 specialists in developmental pediatrics measured growth parameters and performed a neurologic examination. The same investigator evaluated all children in a family. Length was determined by using a supine board. Neurologic findings were classified as normal, suspect, or abnormal. A single psychologist administered the Bayley Scales of Infant Development II. Each child with CHD was evaluated by a genetic dysmorphologist to identify children with genetic syndromes that might not have been apparent earlier in infancy. Children were eliminated if the geneticist believed there were marked dysmorphisms, even if no named syndrome was diagnosed. SES, as measured by the Hollingshead Index,[10] and ethnicity were determined by means of parental questionnaire.

The Bayley Scales of Infant Development II yields 2 scores: the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). Each of these scores has a mean of 100 and a standard deviation of 15 in the general population. The MDI assesses memory, problem solving, early number concepts, generalization, expressive and receptive language, and social skills. The PDI evaluates control of gross motor functioning, including crawling and walking, as well as fine motor skills necessary for prehension, use of writing instruments, and imitation of hand movements.

Data Analysis and Statistical Methods

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.[11] Class I includes patients whose repair achieves a biventricular circulation and in whom there is no preoperative arch obstruction, class II includes patients whose repair achieves a biventricular circulation with arch obstruction, class III includes patients whose repair achieves a single-ventricle circulation without arch obstruction, and class IV includes patients whose repair achieves a single-ventricle circulation with arch obstruction.

Descriptive statistics were used to characterize the study population and other subsets of the larger cohort. Comparisons were made across groups by using t tests, contingency tables, or Wilcoxon rank sum tests. Exact methods were used for contingency tables when any expected value was less than 5. Within the multiple-gestation subjects, the distribution of MDI and PDI scores and growth parameters were inspected, and adequate symmetry was believed to be present to allow the use of parametric tests. Fixed effects regression conditioned on family group was used to make paired comparisons between subjects with CHD and their siblings. This strategy allowed incorporation of the data from both siblings in the sets of triplets. Statistical analyses were performed using STATA 7.0 (College Station, Tex).

The relationship between apolipoprotein E genotype and neurodevelopmental outcome was not explored in the multiple-gestation cohort. The allele associated with increased risk of neurodevelopmental delay, $\epsilon 2$, had an allele frequency of approximately 8% in the larger cohort. Thus only 1 or 2 multiple-gestation subjects with CHD and the $\epsilon 2$ allele could be expected in this study cohort, a number too small for any meaningful relationships to be identified.

Results

Study Population

Among 550 subjects enrolled in the larger cohort, 30 subjects (29 families) were the product of a multiple gestation. In 10 families one or more children died before 1 year of age (in 8 families the child with CHD died, in 1 the sibling without CHD died, and in 1 both members of a twin pair are known to have died). Three families were excluded because of microdeletion of chromosome 22q11 or diagnosis of a genetic syndrome in the child with CHD at the follow-up visit. One family was excluded because of the presence of CHD in both members of the twin pair. In 11 (73%) of 15 remaining families (9 twin sets and 2 triplet sets), both the

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