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EDITORIAL

Challenges for Adult Survivors of Simple Congenital Heart Disease

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The article by Asschenfeldt et al entitled "Neuropsychological status and structural brain imaging in adults with simple congenital heart defects closed in childhood" that appears in this issue of the *Journal of the American Heart Association* (*JAHA*) describes a comprehensive study of 66 adult patients with simple congenital heart defects, either an atrial–septal defect (ASD) or ventricular–septal defect (VSD), which were repaired in childhood.[1] Patients underwent comprehensive neuropsychological testing and magnetic resonance imaging studies of the brain at a mean age of 26 years and were controlled with 40 matched peers. The patients with repaired congenital heart disease were found to have significantly lower scores on many of the neuropsychological tests including full-scale IQ, verbal comprehension, memory, and visual–spatial abilities. Attention deficit disorder and psychiatric disease were more common in the congenital heart group. The authors speculate that these patients, all of whom had an uncomplicated perioperative course, may have had worse outcomes than the control group as a consequence of a genetic link between even simple congenital heart disease and brain development.

See Article by Asschenfeldt et al.

This is an important and disturbing article. The general consensus among cardiac teams including their neurodevelopmental colleagues has been that the outcomes described in this study are not uncommonly seen in the setting of complex congenital heart disease, particularly in patients with long and complex hospitalizations at the time of surgery. In general it has been thought that straightforward cardiac problems such as ASDs and VSDs are relatively rarely impacted by the disabilities described.[2] However, many of the earlier studies from which these inferences were drawn were conducted in children rather than in adults.

The current study describes findings similar to previous studies of cohorts followed through teenage and adult years, though there are also differences. For example, the prospective, randomized clinical trial known as the Boston Circulatory Arrest study, which looked at 171 patients with transposition of the great arteries, initially demonstrated impairments in motor skills in infancy and early childhood.[3] Cognitive skills were minimally affected at any time point in contrast to the current study. As infants reached school age, their motor impairments became less noticeable. However, as they were followed into their teenage years, what became increasingly prominent were behavioral problems and subsequently psychiatric problems. All of the problems seen in the prospective Boston Circulatory Arrest study are consistent with impaired frontal lobe development, particularly white matter development. The frontal lobe contains the primary motor cortex responsible for skeletal movement, the premotor cortex responsible for

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spatial control of movement, and the prefrontal cortex that is important in shaping response to emotion and inhibition of socially unacceptable behavior.

The good news for patients with congenital cardiac disease is that whatever the manifestations of neurobehavioral abnormalities may be, currently there is intense research focused on understanding the mechanisms that lead to such consequences.[4] In addition to now anticipating behavioral and psychiatric problems, there is an aggressive effort in most congenital cardiac programs to minimize these abnormalities through aggressive early intervention programs and behavioral treatments. The Cardiac Neurodevelopmental Outcomes Consortium is a multidisciplinary group of individuals who focus their attention on exactly such issues.[5]

Before becoming too concerned about the findings of the present study, it is important to recognize that there are a number of limitations of the study that might weaken some of its conclusions.

EVOLUTION OF CONGENITAL CARDIAC SURGERY AND AGE AT REPAIR

The cohort of adults studied underwent surgical repair in the 1990s. Although Denmark was a pioneering country in the field of congenital heart repair, nevertheless the hardware and methods of cardiopulmonary bypass anywhere in the 1990s were not designed for neonatal and infant repair. Patients were exposed to large volumes of transfused blood because of the large priming volumes of heart/lung circuits. Arterial line filters were still in their infancy. Methods of monitoring such as near infrared spectroscopy were also in an early stage of development. As a consequence, the age at surgical repair for the cohort studied is substantially older than would be the case for a similar cohort of patients undergoing surgery currently. Although noncyanotic conditions with a left-to-right shunt such as ASD and VSD are not associated with reduced atrial oxygen saturation (ie, cyanosis), they are associated with significant congestive heart failure and particularly failure to thrive. Brain development and most importantly frontal lobe white matter undergo critically important growth and maturation during the first year of life. For patients who are falling off the growth curve during this critical period, it is highly probable that brain development is impacted in the same way that whole body development is impacted. Hopefully going forward, current-day patients who undergo repair at a much younger age (eg, early infancy) for a VSD rather than at 1.7 years as in the current study, no older than 1 or 2 years of age for an ASD versus 7.8 years of age for the study cohort will mean that current-day patients are less impacted by failure to thrive and consequent brain growth impairment relative to the study patients.[6] This is not to say that identifying the risk of behavioral and psychiatric problems for patients who underwent surgery in the 1970s, 1980s, and 1990s is not an important finding in itself. But perhaps it is a reason for optimism going forward.

NO STRUCTURAL BRAIN ANOMALIES IDENTIFIED IN THE STUDY COHORT

The authors undertook magnetic resonance imaging scans of the brains of their study and control patients. They found no significant differences in global or regional brain volumes between the 2 groups. This is an encouraging finding because it contrasts with clear differences seen in fetuses with congenital heart disease relative to control fetuses in studies conducted by Limperopoulos et al.[7] Going forward it will be important to undertake more sophisticated magnetic resonance imaging studies including studies of white matter connectivity using techniques such as diffusion tensor imaging.

LACK OF GENETIC TESTING

Although the authors have speculated that genetic anomalies may underlie the findings of their study, they did not undertake comprehensive genetic screens of their patients. ASDs have been identified as hereditary in some cases secondary to an autosomal dominant gene. Furthermore, VSDs can be associated with microdeletion of chromosome 22, though much less commonly than conditions such as tetralogy of Fallot, truncus arteriosus, and interrupted aortic arch. The association of chromosome 22 microdeletion and a number of conotruncal abnormalities appears to be a consequence of impaired migration of neural crest cells. The fact that these cells that play a key role in conotruncal development develop from the neural tube that will itself ultimately form the central nervous system is an obvious genetic link between heart and brain development. Important developmental delay is frequently a consequence of microdeletion of chromosome 22 (DeGeorge syndrome).[8] It has also been associated with behavioral and later psychiatric problems. So perhaps the authors are indeed correct that many of their findings can be attributed to an underlying genetic anomaly.

CONCLUSIONS

Over the past 40 years there has been continuous evolution in our understanding of the causes of neurodevelopmental and behavioral problems after cardiac surgery. Early investigators attributed any impairment as almost certainly a direct consequence of surgical repair and particularly exposure to cardiopulmonary bypass

or circulatory arrest, despite the fact that family socioeconomic status and parental education consistently emerged as the most important factors in shaping developmental scores. As cardiopulmonary bypass has become more refined and with improving research tools to study the genetic basis of disease as well as study of the fetal environment, including oxygen supply to the fetal brain and observation of fetal brain development, attention has shifted toward the genetic basis for neurodevelopmental and behavioral problems as well as consequences of the altered fetal environment. Hopefully these more sophisticated studies will point us towards effective treatment options. Already single-gene genetic anomalies such as cystic fibrosis and sickle cell disease are close to having effective treatments. Treatment of congenital heart disease, which almost certainly involves multiple gene anomalies, will remain a more distant goal. Fetal intervention and early primary repair of congenital heart anomalies to avoid the secondary consequences of an abnormal circulation are additional strategies that should improve the outlook for individuals with congenital heart disease. The establishment of multidisciplinary longitudinal monitoring groups such as the Cardiac Neurodevelopmental Outcomes Consortium will be an essential factor in determining progress in this vital area.

ARTICLE INFORMATION

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Disclosures

None.

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