The encephalopathy of congenital heart disease

J. William Gaynor, MD

In the United States, approximately 1 in every 100 neonates has congenital heart disease (CHD) diagnosed, and many (25%-35%) have critical CHD necessitating heart surgery soon after birth. As recently as the 1960s, only 20% of neonates with critical CHD survived to adulthood. Today, thanks to better diagnostic technologies and methods (including prenatal diagnosis), advances in surgery, and improved postoperative care, early survival is greater than 90%. Coincident with improved early outcomes, there has been a sobering recognition of the ongoing risk of late mortality, as well as significant morbidity, for these children. In particular, neurodevelopmental disability is now recognized as the most common long-term complication of critical CHD and has the most negative impact on quality of life, academic performance, and opportunity for independence as an adult.

Most studies of neuroprotection in the CHD population have focused on the intraoperative period and management of cardiopulmonary bypass. There is little evidence, however, that these strategies have yielded significant improvements in neurodevelopmental outcomes. A recent analysis of more than 1700 patients born 1996 to 2009 who underwent cardiac surgery at younger than 9 months old demonstrated improved postoperative care, early survival is greater than 90%. Coincident with improved early outcomes, there has been a sobering recognition of the ongoing risk of late mortality, as well as significant morbidity, for these children. In particular, neurodevelopmental disability is now recognized as the most common long-term complication of critical CHD and has the most negative impact on quality of life, academic performance, and opportunity for independence as an adult.

A systematic review of current practices for neuromonitoring and neuroprotection during cardiac surgery in infants found that the level of evidence is insufficient to support the effectiveness of any of the currently used neuroprotective therapies. These findings suggest that a new approach and new targets for neuroprotection are essential to improve outcomes.

Patient and environmental factors, such as prematurity, genetic syndromes, and socioeconomic status, are likely more important determinants of neurodevelopmental outcomes than are operative management strategies. In addition, there is an increasing body of evidence that altered fetal hemodynamics secondary to CHD lead to decreased blood flow or oxygen delivery to the fetal brain, resulting in impaired brain growth and altered structural and cellular maturation, particularly in the white matter. Magnetic resonance imaging (MRI) studies in CHD fetuses show smaller gestational age- and weight-adjusted total brain volumes and abnormal brain metabolism, as well as delayed cortical development and folding. At birth, brain maturation in neonates with hypoplastic left heart syndrome or transposition of the great arteries is delayed by approximately 1 month relative to a normative sample. Postnatal MRI studies have shown that white matter injury is evident in as many as 20% of infants before cardiac surgery and in 40% to 50% early in the postoperative period. Andropoulos and colleagues showed that a lower brain maturity score at birth by MRI is associated with greater brain injury in both the preoperative and postoperative periods. Beca and colleagues recently reported that severity of brain immaturity at birth predicts the severity of neurodevelopmental impairment at 2 years of age after cardiac surgery in infancy. Thus altered brain development secondary to CHD may increase vulnerability to perioperative hemodynamic instability and hypoxic or ischemic injury. There appear to be long-lasting consequences of this abnormal brain development and white matter injury. For example, showed that brain volumes remain smaller into adolescence and that the magnitude of reduction correlates with neurodevelopmental outcomes. Rollins and coworkers recently evaluated the neurodevelopmental impact of white matter injury and abnormal white matter microstructure in adolescents with transposition of the great arteries enrolled in the Boston Circulatory Arrest Study. They found that regional alternations in white matter microstructure, as assessed by MRI and diffusion tensor imaging, were correlated with performance for mathematics achievement, inattention, executive function, visual and spatial skills, and memory.

Two articles in this issue of the Journal provide important additions to the growing body of data linking CHD, abnormal brain development, white matter injury, and the risk of long-term neurodevelopmental disability. Heinrichs and colleagues from Aachen correlated structural brain abnormalities identified by MRI with neurodevelopmental outcomes in adolescent survivors of the arterial switch operation. Moderate to severe structural abnormalities were found in 32% of subjects. White matter injury, characterized by periventricular leukomalacia, was present in more than 50% of subjects. Greater severity of white matter injury correlated with worse neurodevelopmental impairment.
Importantly, preoperative acidosis and hypoxia were the only independent patient-related risk factors for neurologic dysfunction, reduced intelligence, periventricular leukomalacia, and reduced brain volume. Operative management factors, including duration of deep hypothermic circulatory arrest, were not significant predictors of outcome. Lynch and associates\textsuperscript{19} from our group in Philadelphia provided additional evidence that preoperative factors are important determinants of the risk of perioperative white matter injury. Novel optical imaging strategies were used to assess preoperative and postoperative cerebral hemodynamics in neonates undergoing stage 1 reconstruction for hypoplastic left heart syndrome. Consistent with previous studies, new or worsened white matter injury was identified by MRI in almost 50\% of patients after surgery. Importantly, the risk of acquired post-operative white matter injury was highly correlated with longer time between birth and surgery, whereas perioperative and postoperative variables did not predict injury. These findings, which must be validated, suggest that changes in cerebral hemodynamics and cerebral oxygen metabolism after birth may be important modifiers of the risk of perioperative white matter injury in some neonates with CHD. Further studies are needed before it can be concluded that strategies to modify cerebral blood flow before surgery or altering the time of surgery will lead to decreased brain injury and improved neurodevelopmental outcomes.

In summary, there is growing evidence that abnormal brain development beginning in utero and the resultant brain immaturity at birth are primary major risk factors underlying perioperative hypoxic/ischemic white matter brain injury and subsequent neurodevelopmental disability seen in more than 50\% of neonates after surgery for CHD. These findings support the hypothesis that the presence of CHD leads to a complex combination of developmental abnormalities in the brain and direct brain injury secondary to hypoxia or ischemia, especially to the developing white matter.\textsuperscript{20} Volpe\textsuperscript{20} has noted that this pattern of destructive and developmental disturbances is similar to the brain injury found in infants born prematurely and coined the term “encephalopathy of CHD.” The current body of evidence suggests that neuroprotective strategies initiated at the time of cardiac surgery, although potentially important to prevent further injury, are inadequate to improve the neurodevelopmental outcomes significantly for these patients. To optimize brain development, prevent brain injury, and improve neurodevelopmental outcomes for these vulnerable infants, strategies to provide neuroprotection and enhance neuroplasticity may need to be initiated before birth.

References


