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Commentary: Once again—the heart and the brain

Justus Reitz^a and Can Yerebakan, MD^b

Nowadays the vast majority of children born with congenital heart disease (CHD) will reach adulthood,¹ but children with CHD are still at increased risk of developmental disorders, disabilities, or development delay.² Although life expectancy is steadily rising even in cases of complex CHD, efforts to ensure a good long-term neurologic outcome of patients with CHD are warranted. Because it has been shown that brain injury may already be present in patients with CHD preoperatively, and that prenatal brain immaturity increases the risk of postoperative brain injury,³ it is highly relevant to investigate the connection and potential prenatal risk factors of brain immaturity and injury in this group.

In this issue of the *Journal*, Peyvandi and colleagues⁴ report their longitudinal multicenter study demonstrating the association between lower total brain volume (TBV) and elevated risk of acquired neonatal preoperative white matter injury (WMI) in patients with dextro-transposition of the great arteries (d-TGA). For this purpose, the cohort comprised 63 patients, including 37 with d-TGA and 26 with hypoplastic left heart syndrome (HLHS) with fetal (third trimester) as well as postnatal preoperative brain magnetic resonance imaging (MRI). TBV and WMI were scored on prenatal and neonatal MRI. Repeated-measures analysis for the d-TGA group, adjusted for both postmenstrual age at MRI and site, revealed that overall TBV was lower in patients with acquired moderate to severe WMI each week from fetal to neonatal life compared with those with none/mild WMI. The increase in TBV did not differ by injury group. Interestingly, in patients with HLHS, no association was found between TBV and increases in TBV or postnatal brain injury.

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CENTRAL MESSAGE

Low total brain volume is a predictor for preoperative white matter injury in dextro-transposition of the great arteries but not in hypoplastic left heart syndrome.

The authors point out the pathophysiological background of these findings and possible underlying causes of prenatal and postnatal brain injury in patients with CHD. Starting at midgestation, oligodendrocytes originate from the subventricular zone, migrate, expand, and speed myelination, resulting in new connections of neurons.⁵ In this period, the fetal brain develops from a smooth mass toward its fully grown form with gyri and sulci. This differentiated process is highly susceptible to negative influences, such as malnutrition and hypoxemia, often prevalent in fetuses with CHD. As a result, it could be shown that in fetuses with CHD, cortical gyrification is reduced, and 25% of children with complex CHD are microcephalic at birth.^{6,7} This has been strongly associated with brain injuries⁸ and neurodevelopmental abnormalities, and the authors' findings strengthen this hypothesis.

Nonetheless, these findings do not explain why lower TBV is predictive for higher postnatal WMI in the d-TGA group but not in the HLHS group. The authors speculate that even though nutrient and oxygen delivery to the brain is believed to be similar in HLHS and d-TGA, the physiology during the transition from fetal to neonatal circulation could have a major impact on the brain and result in an increased risk for cerebral hypoxia in the perinatal period. This thesis is supported by an increasing number of studies pointing out that earlier repair of d-TGA is associated with better brain health. Lim and colleagues⁹ recently contributed to this topic by showing that surgery in patients with d-TGA beyond age 2 weeks is associated with impaired brain growth and slower language development. This highlights once more that among the many preoperative risk factors for brain injury, establishing normal oxygen and

nutrient delivery to the rapidly developing neonatal brain earlier, by preponed surgery in d-TGA, might be an effective strategy to reduce brain injury. Considering the findings of Peyvandi and colleagues, patients with d-TGA and low TBV could especially benefit from this strategy. Further studies are needed to investigate the origin and predictors of preoperative brain injuries and strategies to prevent them.

These findings add an important piece to the puzzle of myriad risk factors for neurodevelopmental delays in children with CHD.¹⁰⁻¹² As a result, TBV analysis in prenatal brain MRI can be used for a fetus with d-TGA as a predictor for increased risk of postnatal brain injury, and accordingly, adapted perinatal management in this high-risk group can be planned in advance. We congratulate Peyvandi and colleagues for their excellent work.

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Check for updates

Commentary: Will fetal brain magnetic resonance imaging guide our timing of surgery for hypoplastic left heart syndrome and transposition of the great arteries?

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CENTRAL MESSAGE

Elucidating the mechanism of white matter injury in critical congenital heart disease could help us predict neurodevelopmental outcomes.

With the decreasing mortality after congenital heart surgery, neurodevelopmental outcomes have become an area