See Article page 1007.

Commentary: The tip of the iceberg: Physiology of congenital cardiac defects and their influence on brain injury

Christoph Haller, MD

Preoligodendrocytes are the predominant form of the oligodendroglial lineage early during the third trimester and still account for approximately 50% of oligodendroglial cells at term.¹ Preoligodendrocytes are highly vulnerable to cerebral ischemia and inflammation and respond characteristically to injury: Although preoligodendrocytes can survive hypoxic events and even proliferate subsequently, they fail to differentiate further, thereby preventing adequate cerebral myelination.² This process of dysmaturation is the key pathology driving prematurity-associated cerebral white matter lesions. Patients with congenital heart disease are at particularly high risk of acquiring cerebral white matter lesions due to their combination of unfavorable characteristics.³ Neonates with congenital heart disease show a striking impairment of brain maturation, even at term.⁴⁻⁶ Furthermore, the immature brain has underdeveloped distal vascular beds in cerebral white matter.¹ The abnormal physiology of some congenital cardiac lesions results in impaired cerebral blood flow and oxygen delivery,⁷ putting them at risk for cerebral injury.

Peyvandi and colleagues⁸ report a study assessing total fetal and neonatal brain volume as well as the occurrence of cerebral white matter lesions in patients with congenital heart disease. This prospective multicenter study enrolled patients with transposition of the great arteries (TGA) or hypoplastic left heart syndrome (HLHS) for magnetic resonance imaging in the third trimester and postnatally before surgical intervention. White matter lesions were

Christoph Haller, MD

CENTRAL MESSAGE

Congenital cardiac defects, their respective physiology, and the associated immaturity of the brain may lead to a pattern of cerebral injury unique to the respective congenital malformation.

found at similar rates in both patient groups. Total brain volume was significantly lower in patients with TGA and moderate-severe white matter injury compared to patients with TGA and none or only mild white matter lesions. There was no difference in total brain volume in HLHS patients with nonmild white matter injury compared with HLHS patients with more severe injury. Brain growth was maintained in all patients irrespective of diagnosis or brain lesion severity. The authors conclude that the unique physiologic characteristics of TGA in combination with brain immaturity drive the acquisition of significant cerebral white matter lesions.

This study emphasizes once again that care for and therapy of patients with congenital cardiac defects has to begin in utero. It is essential to understand fetal physiology and its perturbations caused by congenital heart disease to develop new therapeutic strategies and intervene at a time of minimal insult and maximal plasticity. However, more granular data on the level of maturity as well as a detailed picture differentiating the respective physiology of TGA from that seen in HLHS is essential to allow meaningful conclusions. Brain volume is a frequently used parameter to assess fetal brain maturation and it is correlated with other parameters indicative for maturity. Readily available characteristics such as gyrification, sulcation, myelination, and presence of germinal matrix could have added another layer of detail to link immaturity to white matter lesions.^{9,10}

From the Department of Cardiovascular Surgery, The Labatt Family Heart Centre, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada. Disclosures: The author reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication Oct 1, 2020; revisions received Oct 1, 2020; accepted for publication Oct 1, 2020; available ahead of print Oct 9, 2020.

Address for reprints: Christoph Haller, MD, Division of Cardiovascular Surgery, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8 (E-mail: christoph.haller@sickkids.ca).

J Thorac Cardiovasc Surg 2021;162:1020-1

0022-5223/\$36.00

Copyright © 2020 by The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2020.10.004>

Metabolic parameters could give further insight into the level of immaturity. Isolated growth restriction relative to total body weight has been reported in patients with TGA but not HLHS, suggesting a physiologic effect on the brain that is unique to TGA physiology.¹¹ Peyvandi and colleagues⁸ neither report if total brain volume differed between TGA and HLHS patients in their cohort, nor assess total brain volume relative to body weight. Although the TGA and HLHS groups appear relatively homogenous at first, they comprise a mix of physiologies that further impairs the interpretation. Ventricular septal defects were present in a substantial number of patients with TGA and moderate-severe white matter injury as opposed to patients with no or mild lesions—statistical significance being blurred by low numbers. That the presence of a ventricular septal defect is important with regard to brain growth and white matter lesions has been shown by the same group recently.¹² Similarly, aortic atresia was more common in HLHS patients with moderate-severe white matter injury as opposed to patients with no or mild lesions. The low numbers, especially in the group with moderate-severe white matter lesions limits the interpretation of the influence of the respective physiology significantly. The addition of flow and saturation measurements could have helped to delineate the specific physiology and objectify the assumptions raised by this analysis.

Preventing brain injury in patients with congenital heart disease is essential to further improve outcomes. The fetal and early postnatal period may offer an attractive therapeutic window. The differences in hemodynamic status, blood flow, and oxygen delivery seen in various types of congenital heart diseases suggest unique cerebral responses and susceptibility to injury. Peyvandi and colleagues⁸ offer a thought-provoking glimpse at the mechanisms of brain injury driven by the physiology of the respective cardiac

defect. However, if brain injury seen in patients with TGA is indeed mainly driven by cerebral immaturity, whereas the injury in HLHS is driven by anatomy and relatively unaffected by immaturity remains yet to be answered.

References

1. Volpe JJ, Kinney HC, Jensen FE, Rosenberg PA. The developing oligodendrocyte: key cellular target in brain injury in the premature infant. *Int J Dev Neurosci.* 2011;29:423-40.
2. Billiards SS, Haynes RL, Folkerth RD, Borenstein NS, Trachtenberg FL, Rowitch DH, et al. Myelin abnormalities without oligodendrocyte loss in periventricular leukomalacia. *Brain Pathol.* 2008;18:153-63.
3. Marelli A, Miller SP, Marino BS, Jefferson AL, Newburger JW. Brain in congenital heart disease across the lifespan: the cumulative burden of injury. *Circulation.* 2016;133:1951-62.
4. Miller SP, McQuillen PS, Hamrick S, Xu D, Glidden DV, Charlton N, et al. Abnormal brain development in newborns with congenital heart disease. *N Engl J Med.* 2007;357:1928-38.
5. Licht DJ, Shera DM, Clancy RR, Wernovsky G, Montenegro LM, Nicolson SC, et al. Brain maturation is delayed in infants with complex congenital heart defects. *J Thorac Cardiovasc Surg.* 2009;137:529-37.
6. Limperopoulos C, Tzoretzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL Jr, et al. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. *Circulation.* 2010;121:26-33.
7. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. *Circulation.* 2015;131:1313-23.
8. Peyvandi S, Lim JM, Marini D, Xu D, Reddy VM, Barkovich AJ, et al. Fetal brain growth and risk of postnatal white matter injury in critical congenital heart disease. *J Thorac Cardiovasc Surg.* 2021;162:1007-14.e1.
9. Vossough A, Limperopoulos C, Putt ME, du Plessis AJ, Schwab PJ, Wu J, et al. Development and validation of a semiquantitative brain maturation score on fetal MR images: initial results. *Radiology.* 2013;268:200-7.
10. Jaimes C, Rofeberg V, Stopp C, Ortinau CM, Gholipour A, Friedman KG, et al. Association of isolated congenital heart disease with fetal brain maturation. *Am J Neuroradiol.* 2020;41:1525-31.
11. Matthiesen NB, Henriksen TB, Gaynor JW, Agergaard P, Bach CC, Hjortdal VE, et al. Congenital heart defects and indices of fetal cerebral growth in a nationwide cohort of 924 422 liveborn infants. *Circulation.* 2016;133:566-75.
12. Lim JM, Porayette P, Marini D, Chau V, Au-Young SH, Saini A, et al. Associations between age at arterial switch operation, brain growth, and development in infants with transposition of the great arteries. *Circulation.* 2019;139:2728-38.