Hypoxia due to CHD linked to abnormal neurogenesis and impaired cortical growth

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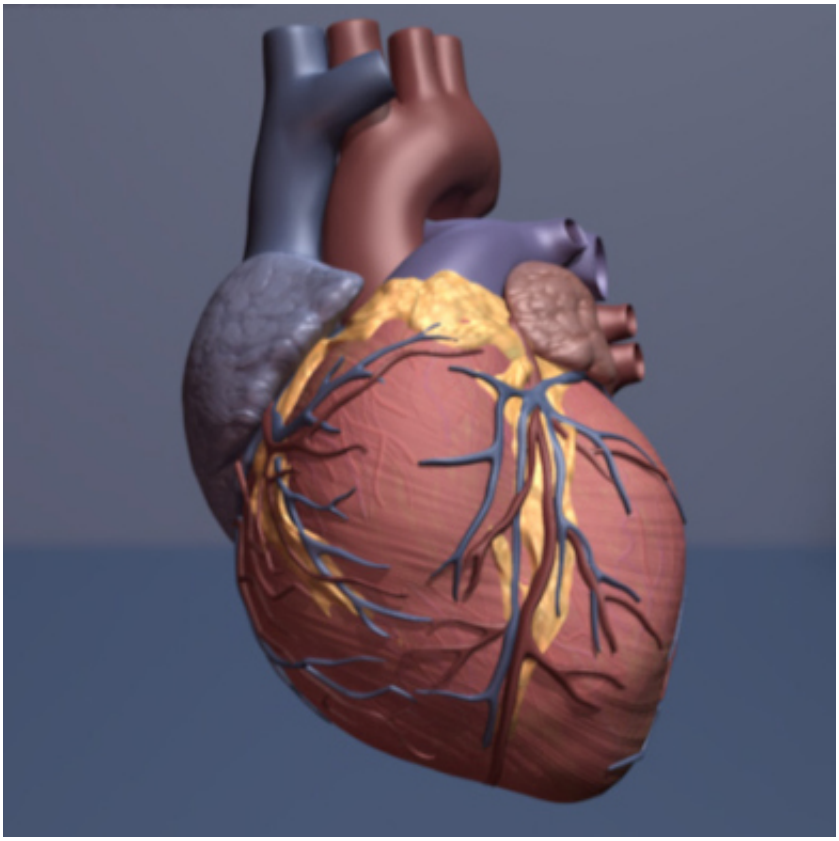

Human heart. Credit: copyright American Heart Association

The subventricular zone (SVZ) in normal newborns' brains is home to the largest stockpile of neural stem/progenitor cells, with newly generated neurons migrating from this zone to specific regions of the frontal cortex and differentiating into interneurons. When newborns

experience disruptions in cerebral oxygen supply due to congenital heart disease, essential cellular processes go awry and this contributes to reduced cortical growth. The preliminary findings derived from a preclinical model by a research team led by Children's National Health System point to the importance of restoring these cells' neurogenic potential, possibly through therapeutics, to lessen children's long-term neurological deficits.

Published online Jan. 25 by *Science Translational Medicine*, the findings were discovered by a multidisciplinary team of seven Children's National co-authors and collaborators from the National Institutes of Health, Children's Hospital Boston and Johns Hopkins School of Medicine. The article was featured on the journal's cover.

"We know that congenital heart disease (CHD) reduces cerebral oxygen at a time when the developing fetal brain most needs oxygen. Now, we are beginning to understand the mechanisms of CHD-induced brain injuries at a cellular level, and we have identified a robust supply of cells that have the ability to travel directly to the site of injury and potentially provide help by replacing lost or damaged neurons," says Nobuyuki Ishibashi, M.D., Director of the Cardiac Surgery Research Laboratory at Children's National, and co-senior study author.

The third trimester of pregnancy is a time of dramatic growth for the fetal brain, which expands in volume and develops complex structures and network connections that growing children rely on throughout adulthood. According to the National Heart, Lung, and Blood Institute, congenital heart defects are the most common major birth defect, affecting 8 in 1,000 newborns. Infants born with CHD can experience myriad neurological deficits, including behavioral, cognitive, social, motor and attention disorders, the research team adds.

Cardiologists have tapped non-invasive imaging to monitor fetal hearts

during gestation in high-risk pregnancies and can then perform corrective surgery in the first weeks of life to fix damaged hearts. Long-term neurological deficits due to immature cortical development also have emerged as major challenges in pregnancies complicated by CHD.

"I think this is an enormously important paper for surgeons and for children and families who are affected by CHD. Surgeons have been worried for years that the things we do during corrective heart surgery have the potential to affect the development of the brain. And we've learned to improve how we do heart surgery so that the procedure causes minimal damage to the brain. But we still see some kids who have behavioral problems and learning delays," says Richard A. Jonas, M.D., Chief of the Division of Cardiac Surgery at Children's National, and co-senior study author. "We're beginning to understand that there are things about CHD that affect the development of the brain before a baby is even born. What this paper shows is that the low oxygen level that sometimes results from a congenital heart problem might contribute to that and can slow down the growth of the brain. The good news is that it should be possible to reverse that problem using the cells that continue to develop in the neonate's brain after birth."

Among preclinical models, the spatiotemporal progression of brain growth in this particular model most closely parallels that of humans. Likewise, the SVZ cytoarchitecture of the neonatal preclinical model exposed to hypoxia mimics that of humans in utero and shortly after birth. The research team leveraged CellTracker Green to follow the path traveled by SVZ-derived cells and to illuminate their fate, with postnatal SVZ supplying the developing cortex with newly generated neurons. SVZ-derived cells were primarily neuroblasts. Superparamagnetic iron oxide nanoparticles supplied answers about long-term SVZ migration, with SVZ-derived cells making their way to the prefrontal cortex and the somatosensory cortex of the brain.

"We demonstrated that in the postnatal period, newly generated neurons migrate from the SVZ to specific cortices, with the majority migrating to the prefrontal cortex," says Vittorio Gallo, Ph.D., Director of the Center for Neuroscience Research at Children's National, and co-senior study author. "Of note, we revealed that the anterior SVZ is a critical source of newborn neurons destined to populate the upper layers of the cortex. We challenged this process through chronic hypoxia exposure, which severely impaired neurogenesis within the SVZ, depleting this critical source of interneurons."

In the preclinical model of hypoxia as well as in humans, brains were smaller, weighed significantly less and had a significant reduction in cortical gray matter volume. In the prefrontal cortex, there was a significant reduction in white matter neuroblasts. Taken as a whole, according to the study authors, the findings suggest that impaired neurogenesis within the SVZ represents a cellular mechanism underlying hypoxia-induced, region-specific reduction in immature neurons in the cortex. The prefrontal cortex, the region of the brain that enables such functions as judgment, decision-making and problem-solving, is most impacted. Impairments in higher-order cognitive functions involving the prefrontal cortex are common in patients with CHD.

More information: "Abnormal neurogenesis and cortical growth in congenital heart disease," *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/ … scitranslmed.aah7029

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