Team gains understanding of white matter in infants receiving heart surgery

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A collaborative team of researchers at Children's National Medical Center are making progress in understanding how to protect infants needing cardiac surgery from white matter injury, which impacts the nervous system. The synergistic team from the Children's National Heart Institute and Center for Neuroscience Research at Children's National Medical Center was led by Nobuyuki Ishibashi, MD, Joseph Scafidi, DO, Richard Jonas, MD, and Vittorio Gallo, PhD. The study, published online in the January edition of *Circulation*, identifies the stages of white matter development, as well as the areas and cells of the brain that are impacted by the amount of oxygen and any inflammation in infants with complex cardiac issues that affect brain oxygenation and cause swelling.

The most common neurological deficits seen in children with CHD requiring cardiac surgery are fine and gross motor deficits, which are consistent with white matter injury. The study, using a porcine cardiopulmonary bypass (CPB) model, monitored how the regions of white matter responded to CPB at 1, 3, and 7 weeks of age. In some groups, observation involved CPB with lack of oxygen (hypoxia) and inflammation. The results found that white matter injury was dependent on the area's stage of maturity. Additionally where there was hypoxia and inflammation, the team saw a halt in the progression of white matter development, or oligodendroctye cell maturation and lineage, which is known to lead to neurological deficits. Four weeks after surgery with CPB that induced hypoxia and inflammation, the team determined that white matter cells were no longer growing and maturing, a finding consistent with the neurological deficits in complex congenital heart

disease patients, who are at higher risk of ischemia and inflammation that often occur after frequent hypoxia.

"Being able to identify the stage in which certain cells are more vulnerable to disruptions brings us much closer to understanding the mechanisms of white matter injury and could eventually help us create strategies and treatment methods to protect those cells in young patients who will need to undergo cardiopulmonary bypass," stated Nobuyuki Ishibashi, MD, lead author of the study and Laboratory Director of Cardiac Surgery. "This study also provides evidence that CPB surgery must be managed precisely to avoid inducing further hypoxia and inflammation in these already fragile patients."

Oligodendrocyte cells are the type of brain cells that make up white matter and serve as the primary messaging "network" that conducts signals rapidly between gray matter areas. Without it, the brain does not function properly. Myelination, or growth of white matter, in humans begins in utero at around 5 months of gestation and continues throughout the first two decades of life. This process involves the maturation of oligodendrocyte cells through different stages; if there is a disruption, for example from a lack of oxygen or inflammation, these cells and the subsequent stages, or lineage, can't develop the way that they should, resulting in neurological deficits.

"Interestingly, the white matter response we saw in the group that experienced hypoxia and inflammation is very similar to what you see in patients with complex congenital heart disease," stated Richard Jonas, MD, Chief of Cardiac Surgery. "If we can start to understand the mechanics of white matter development and how a lack of oxygen and inflammation affects the brain, we will be able to contribute to the treatment strategies for patients with congenital heart disease." Congenital heart disease is the leading birth defect, affecting almost one in every 100 infants each year. For successful white matter development

in congenital heart disease patients, it is imperative to understand how CHD and its treatments affect the growth and repair of white matter.

Director of the Center for Neuroscience Research, Vittorio Gallo, PhD, commented "This study provides us with further evidence of the critical time windows that exist in white matter development and the importance of understanding the mechanisms of white matter development so that we might possibly ease white matter damage in patients."

Myelination, white matter growth and repair, and the study of complex mechanisms of prenatal brain development are a key focus of the Center for Neuroscience Research at Children's National, which also houses the White Matter Diseases Program, one of the largest clinical programs in the country for treating children with disorders that cause the brain's white matter to degenerate. Congenital heart disease and other cardiac conditions are the main priority of the Children's National Heart Institute, an international leader in providing comprehensive care for infants, children, and adults.

More information: www.childrensnational.org/rese … ios/cnr/Gallo_v.aspx

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