Commentary: What in the world is glial fibrillary acidic protein?

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Brain injury associated with congenital heart surgery has been recognized since, well, since the beginning of congenital heart surgery, as described by one of the pioneers of our specialty.¹ The first few years of open cardiac repairs for congenital heart disease were primarily focused on survival. The past 4 decades have seen a greater focus on neurodevelopmental (ND) outcomes as it became apparent that those children surviving complex operations performed during infancy were not normal from an ND point of view. This was especially true when deep hypothermic circulatory arrest was a part of the operative strategy² and increased with the complexity of the procedure (Figure 1). One difficulty with sorting out cause and effect of the ND outcomes is that these issues may not be readily apparent during the early postoperative course of a small infant and can only be seen once the child is old enough to be formally tested for intelligence quotient or somewhat complex developmental tests. This might be as much as 5 years after the sentinel event. Any evaluation of the impact of changes in the conduct of operations with the technique of the procedure or cardiopulmonary bypass would require a patient investigator to follow these patients for several years before being able to assess the impact of the changes. The Boston Circulatory Arrest study is one of these investigations, and those involved are to be congratulated for this work, which continues to provide ND information about those children undergoing the arterial switch procedure.³

The study by Graham and colleagues⁴ evaluated the predictive power of serum levels of glial fibrillary acidic protein (GFAP) as a marker of brain injury. This was then correlated with evidence of abnormalities in ND outcomes when these children reach 1 year of age.⁴ Their study suggests that elevated GFAP levels measured in the perioperative period are predictive of poor ND outcomes as assessed using cognitive, language, and intellectual scores on standardized tests performed at 1 year of age. This would allow an earlier intervention into various developmental therapies that could affect the longer-term outcomes in these patients.

ND impairment is related to the complexity of the congenital heart lesion.

Central Message

GFAP levels after neonatal cardiac surgery may predict ND outcomes at 1 year of age. Outcomes beyond that are unknown.

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In addition, this finding would aid the study of cardiac surgery and brain injury by shortening the interval between changes in therapy and evaluation of results so that we could create new information in this realm over a shorter duration. The study has flaws that the authors list in the obligatory "Limitations" section of the article. The major flaw in my view was that these patients were part of another randomized study involving the use of steroids in congenital heart surgery. Other additional important limitations include the lack of a specific protocol for the conduct of cardiopulmonary bypass, nonuniform neuroprotective strategies, and the variety of operations performed between both institutions. Those issues are of less concern. I believe that the study should just be viewed as a simple examination of what happens in ND of an infant when postoperative GFAP levels are elevated. Whether their results at 1 year will hold up in the longer term has yet to be determined.

What in the world is GFAP? GFAP is a protein located in neurons and plays a role in cell-cell communication within the central nervous system. It is an important component of maintaining the blood-brain barrier. It was discovered by Amico Bignami and colleagues⁵ (which I think is Italian for friend with big name, ie, famous friend) when researching the plaques found in the central nervous system of patients with multiple sclerosis. The normal serum level is zero, but it is released when there is damage to a neuron, specifically astrocytes, in the central nervous system. It

FIGURE 1. This relates the degree of neurodevelopmental delay to the complexity of the congenital heart disease. *ND*, Neurodevelopmental; *SV*, single ventricle.

became popular years ago as a potential marker for the severity of traumatic brain injuries, such as concussions. Its use in this area has waned primarily because its correlation with longer-term (6 months postinjury) neurologic outcomes has been inconsistent.⁶ It is not a blood test that is available in most medical centers, although there are kits available to run this at approximately \$500 per sample. Imaging studies of the brain have been the mainstay of neurologic evaluations early in the course of congenital heart disease and surgical treatment thereof. A recent study by

Peyvandi and colleagues⁷ was devoted to the correlation of magnetic resonance imaging findings and long-term ND outcomes. They found that the Bayley Scales of Infant Development scores were not associated with white matter injury on magnetic resonance imaging at 12 months but did at 30 months of age. Why there was a lack of association that did not manifest early on is unclear. There is also appropriate emphasis on the other factors that play a role in ND development, including maternal education, socioeconomic status, and the presence of genetic abnormalities. This must give us pause in how we view the work by Graham and colleagues⁴ on GFAP. Nonetheless, the results of this study are compelling and may offer an additional tool in this area of research.

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