injury. So I think it is a complex interplay. If they did not require neonatal surgery or did not have ductal-dependent pulmonary or systemic blood flow, it might be possible to delay until they are out of the neonatal period and the brain is matured. But many of these kids are ductal dependent for either systemic or pulmonary blood flow.

Dr Laks. But you could argue that an off-pump procedure, which would get a similar result, would be better if you could delay the open procedure for at least 5 weeks.

Dr Gaynor. It might be. But again, if you do a shunt off pump, you may introduce a steal. If you do the hybrid procedure for stage 1, there is concern that then cerebral blood flow is retrograde, up a

tiny arch, and it becomes an endartery. So there are competing factors, and I do not think the study has been done that would allow us to answer that question.

Dr Jennifer Hirsch-Romano (*Ann Arbor, Mich*). I just have 1 other question for you. This gets back to what Chuck Fraser brought up about the variation across sites. If you looked at the mortality across those sites, was that associated with worse neurodevelopmental outcomes at long-term follow-up?

Dr Gaynor. We tried to look at that thinking there might be a survivor bias, that some sites could get sicker kids through and they would have worse outcomes, and we could not identify anything like that.

EDITORIAL COMMENTARY

Validation accepted, but look at what else was revealed

Erle H. Austin III, MD

See related article on pages 2560-8.

Cardiac surgery for neonates and infants has evolved substantially in the past several decades with significant improvement in survival for all forms of congenital heart disease. Survival, of course, is only the first objective. Parents want their child to survive, but they also want their child to thrive after recovering from heart surgery. Those of us who care for these patients are paying an increasing amount of attention to neurodevelopmental outcomes.

One of several areas directed at improving neurodevelopmental outcomes is the identification of genetic markers that correlate with neurologic outcome. In 2003, Gaynor and colleagues¹ demonstrated a significant detrimental effect of the apolipoprotein E (APOE) $\epsilon 2$ allele on the neurodevelopmental outcome of patients aged 6 months or less who had undergone cardiac surgery. In this single-center prospective study, neurodevelopmental evaluation was performed using the Bayley Scales of Infant Development assessed at 12 months of age. The presence of the $\epsilon 2$ allele correlated with a 7-point decrease in the Psychomotor Developmental Index (PDI) compared with patients without

that allele. As the apolipoprotein E protein is considered an important factor in repairing injured neural tissue, the presence of the $\epsilon 2$ allele in these patients is believed to adversely affect the ability of the protein to perform such repair after neonatal and infant heart surgery.

As the authors of the accompanying report² indicate, reports of genotype-phenotype associations are rarely validated. The initial report was the product of much work and many resources at a center with a substantial volume of patients. Repeating that process for the sake of validation was unlikely. Fortunately, it was recognized that the Pediatric Heart Network had been independently studying similar patients in 2 multicenter trials (the Infant Single Ventricle [ISV] and the Single Ventricle Reconstruction [SVR] trials). Fortunately, APOE testing had been performed on the SVR patients and DNA had been extracted from blood samples of the ISV patients. Furthermore, in both trials, neurodevelopmental testing (Bayley Scales of Infant Development-II [BSID-II]) had been performed on most patients. Thus, the opportunity to validate or refute the findings of the initial report presented itself.

After appropriate selection of patients, the authors of the current report identified 298 patients with complete APOE and neurodevelopmental data. The presence of the $\epsilon 2$ allele imparted a 6-point decrease in PDI score, almost the same as the 7-point decrement in PDI determined in the primary report. A decrement in the Mental Developmental Index (MDI), the other portion of BSID-II, was also seen at a level just short of significance, but again, similar to what was found in the initial study. I think it is fair to say this genotype-phenotype association has been validated. The authors are to be congratulated for identifying this

From the Department of Surgery, University of Louisville, Louisville, Ky.

Disclosures: Author has nothing to disclose with regard to commercial support.

Received for publication Sept 29, 2014; accepted for publication Oct 1, 2014

Address for reprints: Erle H. Austin III, MD, Department of Surgery, University of Louisville, 201 Abraham Flexner Way #1200, Louisville, KY 40202 (E-mail: eaustin@louisvilleheartsurgery.com).

J Thorac Cardiovasc Surg 2014;148:2568-9

0022-5223/\$36.00

Copyright © 2014 by The American Association for Thoracic Surgery

<http://dx.doi.org/10.1016/j.jtcvs.2014.10.008>

independent population and for performing the secondary analysis to achieve their goal.

But there is more in this report that warrants mention, and hopefully further investigation. Only 1% of the variation in neurodevelopmental outcome in this study population was attributable to the $\epsilon 2$ allele. A much more impressive effect was attributable to the center at which the surgery was performed (11% for PDI and 15% for MDI). This suggests that there was something modifiable occurring at the high-performing centers that resulted in better neurologic outcomes. I hope that this finding is not lost on the authors or on the Pediatric Heart Network. It has already been shown that surgical mortality³ and models for care delivery⁴ can vary significantly among sites. There must be some correlation between processes and outcomes. Is this not an opportunity to identify the centers with the best neurologic outcomes and compare their processes with those of the

centers with the worst? Although the objective of this report was to validate a prior report, the multicenter nature of the data has led to an unanticipated discovery that may have a greater impact on improving neurologic outcome than the initial objective.

References

1. Gaynor JW, Gerdes M, Zackai EH, Bernbaum J, Wernovsky G, Clancy RR, et al. Apolipoprotein E genotype and neurodevelopmental sequelae of infant cardiac surgery. *J Thorac Cardiovasc Surg.* 2003;126:1736-45.
2. Gaynor JW, Kim DS, Arrington CB, Atz AM, Bellinger DC, Burt AA, et al. Validation of the apo-lipoprotein E (APOE) $\epsilon 2$ allele with neurodevelopmental dysfunction after cardiac surgery in neonates and infants. *J Thorac Cardiovasc Surg.* 2014;148:2560-8.
3. Jacobs JP, O'Brien SM, Pasquali SK, Jacobs ML, Lacour-Gayet FG, Tchervenkov CI, et al. Variation in outcomes for benchmark operations: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. *Ann Thorac Surg.* 2011;92:2184-91.
4. Burstein DS, Rossi AF, Jacobs JP, Checchia PA, Wernovsky G, Li JS, et al. Variation in models of care delivery for children undergoing congenital heart surgery in the United States. *World J Pediatr Congit Heart Surg.* 2010;1:8-14.