Association of intraoperative circulating-brain injury biomarker and neurodevelopmental outcomes at 1 year among neonates who have undergone cardiac surgery

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ABSTRACT

Background: Neurodevelopmental disability is the most significant complication for survivors of infant surgery for congenital heart disease. In this study we sought to determine if perioperative circulating brain injury biomarker levels are associated with neurodevelopmental outcomes at 12 months.

Methods: A secondary analysis of a randomized controlled trial of neonates who underwent cardiac surgery was performed. Glial fibrillary acidic protein (GFAP) was measured: (1) before skin incision; (2) immediately after bypass; (3) 4 and (4) 24 hours postoperatively. Linear regression models were used to determine an association with the highest levels of GFAP and Bayley Scales of Infant and Toddler Development third edition (BSID) composite scores.

Results: There were 97 subjects who had cardiac surgery at a mean age of 9 ± 6 days and completed a BSID at 12.5 ± 0.6 months of age. Median (25th-75th percentile) levels of GFAP were 0.01 (0.01-0.02), 0.85 (0.40-1.55), 0.07 (0.05-0.11), and 0.03 (0.02-0.04) ng/mL at the 4 time points, respectively. In univariate analysis GFAP was negatively associated with cognitive, language, and motor composite scores. GFAP levels immediately after bypass differed between institutions; 1.57 (0.92-2.48) versus 0.77 (0.36-1.21) ng/mL ($P = .01$). After adjusting for center and potential confounders, GFAP was independently associated with BSID motor score ($P = .04$).

Conclusions: Higher GFAP levels at the time of neonatal cardiac operations were independently associated with decreased BSID motor scores at 12 months. GFAP might serve as a diagnostic means to acutely identify perioperative brain-specific injury and serve as a benchmark of therapeutic efficacy for investigational treatments, discriminate center-specific effects, and provide early prognostic information for intervention. (J Thorac Cardiovasc Surg 2019;157:1996-2002)

Post-bypass GFAP differs according to site and is associated with worse neurodevelopment at 12 months.

Central Message

In this multicenter study, higher plasma glial fibrillary acidic protein level at the time of neonatal cardiac operations was associated with worse 1-year neurodevelopmental assessment.

Perspective

Neurodevelopmental disability is the most significant complication for survivors of infant surgery for congenital heart disease. Higher plasma glial fibrillary acidic protein level at the time of neonatal cardiac operations is associated with worse neurodevelopmental assessment at 12 months of age. Glial fibrillary acidic protein might serve as a diagnostic means to acutely identify perioperative brain injury.

See Commentary on page 2003.

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Neurodevelopmental disability is the most significant complication for survivors of infant surgery for congenital heart disease.¹⁻³ Children who have undergone cardiac surgery as an infant have been found to have more problems with motor, language and social skills, reasoning, executive function, inattention, and impulsive behavior than their peers without heart disease.⁴⁻⁷ These disabilities can ultimately limit educational and employment opportunities, challenge interpersonal relationships, and diminish quality of life. Neurodevelopmental and behavioral impairment have become so pervasive that in 2012 the American Heart Association and the American Academy of Pediatrics issued a joint scientific statement on guidelines for systematic surveillance, screening,

Abbreviations and Acronyms

BSID	= Bayley Scales of Infant and Toddler Development third edition
CPB	= cardiopulmonary bypass
GFAP	= glial fibrillary acidic protein
NIRS	= near-infrared spectroscopy
STAT	= Society of Thoracic Surgery-European Association for Cardio-Thoracic Surgery

evaluation, and management of developmental disabilities in an effort to optimize neurodevelopmental outcomes in this population.⁷

The cause of this disability is multifactorial including innate patient, sociodemographic, and perioperative factors known and unknown and as a result the ability to detect brain injury in real time remains elusive.^{2,4} There is a need to develop simple, objective, point of care diagnostic brain injury biomarkers to predict neurodevelopmental outcomes and provide a possible outcome variable to test new neuroprotection therapies. One candidate biomarker is glial fibrillary acidic protein (GFAP), an astrocyte intermediate filament protein, normally absent in blood and released as a result of astrocyte injury or necrosis.⁸ GFAP levels measured acutely in adults with traumatic brain injury and those surviving cardiac arrest have been associated with neurological disability.⁹⁻¹¹ The US Food and Drug Administration recently approved (February 14, 2018) the Banyan Brain Trauma Indicator, which measures the levels of 2 brain injury biomarkers, one of which is GFAP (<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm596531.htm>). This provides the first commercially available blood test to detect brain injury during concussions. However, an association of GFAP with longer-term neurodevelopmental outcomes specifically in neonates undergoing cardiac surgery has not been explored. Accordingly the objective of this study was to determine if perioperative circulating GFAP levels in neonates undergoing cardiac surgery with cardiopulmonary bypass (CPB) were associated with neurodevelopmental outcomes at 12 months of age.

METHODS

Subjects

Patients were recruited from 2 centers in North America participating in the National Heart, Lung, and Blood Institute-funded Corticosteroid Therapy in Neonates Undergoing Cardiopulmonary Bypass randomized controlled trial of the use of intraoperative methylprednisolone compared with placebo (the study is registered at ClinicalTrials.gov: NCT01579513).

Inclusion criteria for the parent study consisted of infants younger than 1 month of age undergoing cardiac surgery with CPB. Exclusion criteria included prematurity defined as <37 weeks post gestational age at the time of surgery, steroids within the 2 days before surgery, suspected infection, or a hypersensitivity that would be a contraindication to

methylprednisolone or use of mechanical circulatory support or active resuscitation at the time of proposed randomization. The protocol was approved by the institutional review board at each center, and written informed consent was obtained from a parent/guardian before randomization.

Neurodevelopmental Assessment

The primary measure of neurodevelopment was assessed at 12 months of age with an in-person evaluation by a trained psychologist experienced with the Bayley Scales of Infant and Toddler Development third edition (BSID).¹² The BSID is a standardized test for children aged 1 through 42 months and is widely accepted to have good inter-rater reliability. The BSID yields cognitive, language, and motor composite scores. The mean $\pm$ standard deviation for each of the composite scores in the normative population is 100 ± 15 . Administration of the BSID followed manual guidelines.¹² The BSID was only administered in English or Spanish, and it was administered in the dominant language spoken in the home. Testing personnel were blinded to the treatment assignment and biomarker results of the subjects.

Study Design and Measurements

Subjects were randomly assigned to either methylprednisolone at 30 mg/kg of body weight or placebo at the induction of anesthesia within strata according to planned corrective or palliative operation, with dynamic balancing within surgeon. Whole-blood samples were collected in ethylenediaminetetraacetic acid tubes at 5 perioperative time points. Plasma was isolated by centrifugation, decanted into aliquots, and stored at -80°C until processed for immunoassays. Extensive peri- and postoperative variables were recorded. In all other respects, subjects were managed according to the usual practices at each center. At site 1, full-flow bypass was considered 200 mL/kg/min at 36°C and flow is decreased as patient temperature decreases to meet mean arterial pressure goals of 30 to 35 mm Hg. Generally this resulted in a flow of 80 to 100 mL/kg/min at 18°C . Regional antegrade cerebral perfusion was used during arch reconstructions either at 18°C at a flow of 30 mL/kg/min with monitoring of cerebral near-infrared spectroscopy (NIRS) with a target goal of $>90\%$; or at 25°C at a flow of 60 to 80 mL/kg/min with monitoring of cerebral NIRS, but without a specific target depending on the surgeon. Circulatory arrest was performed at moderate hypothermia (at approximately 25°C), typically for very brief periods, when needed. Cold-blood cardioplegia was given at 45- to 90-minute intervals during periods of aortic cross-clamping. Acid-base management was a pH-stat strategy with a hematocrit goal of 30% during CPB at 20°C or lower. Alpha-stat management was used for periods of warming. Conventional ultrafiltration was used in all cases. Modified ultrafiltration was used in most cases. At site 2, general perfusion strategies included full-flow bypass at 2.6 L/min/ m^2 at 32°C , or low-flow bypass at 1.3 L/min/ m^2 between 20°C and 25°C . Regional antegrade cerebral perfusion was used during aortic arch reconstructions, generally carried out at a temperature of 20°C and a flow of 50 mL/kg/min, with monitoring of cerebral NIRS with a target goal of $>90\%$. Cold-blood cardioplegia was given at 20-minute intervals during periods of aortic cross-clamping. Deep hypothermic circulatory arrest was performed at 20°C , when necessary. Acid-base management was by a pH-stat strategy with a hematocrit goal of 28% during CPB. Conventional and modified ultrafiltration were used in all cases.

Subjects enrolled in this secondary analysis were included if they completed a BSID and had adequate volume of plasma for measurement of GFAP at the time of this study. GFAP was measured in blood at 4 time points: (1) before skin incision; (2) immediately after the completion of modified ultrafiltration at the end of CPB; (3) at 4 and (4) at 24 hours postoperatively. All samples were batched and assayed simultaneously to avoid potential laboratory assay variance. GFAP was assayed at Johns Hopkins University using an electrochemiluminescent sandwich immunoassay

as previously described.¹³⁻¹⁷ The lower limit of quantification for the assays was 0.008 ng/mL. The interassay variance at the lower limit of quantification was 11.5% over the 6 assay plates.

Statistical Analysis

Standard descriptive statistics were used to summarize the general demographic and clinical data. Continuous demographic characteristics are listed as means and associated standard deviations. Categorical characteristics are expressed as number and percentage of subjects. Simple linear regression models were used to determine an association with highest level of GFAP and BSID cognitive, language, and motor composite scores and between demographic and operating characteristics (age, sex, race, ethnicity, presence of a genetic syndrome, use of deep hypothermic circulatory arrest, duration of CPB, and cross-clamp time) with highest level of GFAP. Linear regression models were developed that adjusted for potential cofounders including center, CPB duration, aortic cross-clamp time, use of deep hypothermic circulatory arrest, and Society of Thoracic Surgery-European Association for Cardio-Thoracic Surgery (STAT) category.¹⁸ To test differences between centers an independent *t* test was performed for continuous variables and a χ^2 or Fisher exact test for categorical

variables. Statistical analyses were performed with SAS, version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Between June 2012 and June 2017, 97 subjects were enrolled in the primary study and completed a BSID. All 97 subjects had adequate samples for GFAP analysis and comprise this study cohort. Preoperative demographic and operative characteristics are shown in Table 1. There was a slight male predominance. Mortality risk categories as defined according to STAT categories showed that just over half were STAT 4 with the remaining almost equally divided between STAT 3 and 5 categories. Neurodevelopmental assessment occurred at a mean age of 12.5 ± 0.6 months. Mean BSID cognitive composite scores were 105 ± 15 , for language 101 ± 13 , and motor scores were 92 ± 17 .

TABLE 1. Preoperative demographics and operative characteristics

Variable	Overall cohort (n = 97)	Site 1 (n = 23)	Site 2 (n = 74)	P value
Age/sex				
Mean gestational age at birth, wk	38.9 $\pm$ 1.3	38.5 $\pm$ 1.4	39.0 $\pm$ 1.2	NS
Male sex	56 (58)	14 (61)	42 (57)	NS
Race/ethnicity				.05
Asian	2 (2)	0	2 (3)	
Black or African American	24 (25)	2 (9)	22 (30)	
Caucasian	66 (68)	21 (91)	45 (61)	
Other	5 (5)	0	5 (7)	
Hispanic or Latino	6 (6)	1 (4)	5 (7)	
Diagnosis/procedure				
Corrective procedure	67 (69)	16 (70)	51 (69)	NS
Aortic arch hypoplasia	11 (11)	1 (4)	10 (13)	
Transposition of the great arteries	34 (35)	7 (30)	27 (37)	
Truncus arteriosus	6 (6)	2 (9)	4 (5)	
Other biventricular repair	16 (17)	6 (26)	10 (14)	
Palliative procedure	30 (31)	7 (30)	23 (31)	NS
Hypoplastic left heart syndrome	14 (14)	4 (17)	10 (14)	
Other single ventricle lesions	7 (7)	0	7 (10)	
Tetralogy of Fallot pulmonary atresia	3 (3)	0	3 (4)	
Other palliative procedure	6 (6)	3 (13)	3 (4)	
Operative characteristics				
Age at surgery, d	9.1 $\pm$ 5.6	7.2 $\pm$ 4.6	9.7 $\pm$ 5.7	.06
Weight at surgery, kg	3.3 $\pm$ 0.5	3.3 $\pm$ 0.5	3.3 $\pm$ 0.5	NS
STAT 1	1 (1)	0	1 (1)	NS
STAT 2	2 (2)	0	2 (3)	NS
STAT 3	23 (24)	6 (26)	17 (23)	NS
STAT 4	52 (54)	11 (48)	41 (55)	NS
STAT 5	19 (20)	6 (26)	13 (18)	NS
Cardiopulmonary bypass duration, minutes	185 $\pm$ 62	143 $\pm$ 38	198 $\pm$ 63	<.0001
Aortic cross clamp, minutes	82 $\pm$ 42	83 $\pm$ 26	82 $\pm$ 47	NS
Circulatory arrest	26 (27)	8 (35)	18 (24)	NS
Circulatory arrest duration, minutes	5 (0.2-60)	2 (0.2-18)	8 (2-60)	.006

Values are mean $\pm$ standard deviation, median (range), or number (%) as appropriate. NS, Not significant; STAT, Society of Thoracic Surgery-European Association for Cardio-Thoracic Surgery mortality risk category.

GFAP levels are depicted in Figure 1. Before skin incision GFAP levels were low. Immediately after completion of CPB there was an almost 100-fold increase. Subsequently there was a 10-fold decline by 4 hours with a continuing decline at 24 hours postoperatively. In simple linear regression models GFAP at the cessation of CPB was inversely associated with cognitive ($R^2 = 0.07$; $P = .01$), language ($R^2 = 0.05$; $P = .03$), and motor ($R^2 = 0.09$; $P < .01$) composite scores (Table 2). When the models were adjusted for clinical center, STAT category, CPB duration, aortic cross-clamp time, and use of deep hypothermic circulatory arrest, GFAP at the cessation of CPB was independently associated with motor composite scores ($R^2 = 0.22$; $P = .04$; Figure 2). Cognitive and language composite scores were not independently associated with GFAP levels (Table 2). In simple linear regression models age at surgery was inversely associated with GFAP at the cessation of CPB ($P = .02$), but sex, race, ethnicity, presence of a genetic syndrome, use of deep hypothermic circulatory arrest, duration of CPB, and cross-clamp time were not (data not shown).

Center Differences

Knowing that recent studies have described center variation in neurodevelopmental outcomes, we examined the relationship between GFAP levels at the cessation of CPB and BSID composite scores according to enrolling site. Figure 3 shows the median (25th-75th percentile) GFAP level was twice as high at one site compared to the other: 1.57 (0.92-2.48) versus 0.77 (0.36-1.21) ng/mL ($P = .01$).

This corresponded to lower BSID cognitive (92 ± 12 vs 109 ± 13 ; $P < .0001$), language (88 ± 12 vs 105 ± 11 ; $P < .0001$), and motor composite scores (81 ± 16 vs 95 ± 16 ; $P = .0006$) at site 1 compared with site 2, respectively. Preoperative demographic and operative characteristics between centers were similar with the exception of a higher percentage of Caucasian infants, younger age at surgery, and shorter CPB and circulatory arrest times at site 1 (Table 1).

DISCUSSION

Blood-Based Biomarkers and Neurologic Injury

Blood-based brain biomarkers represent a potentially rapid means of diagnosing neurological injury and GFAP was recently approved by the US Food and Drug Administration as a blood test for concussive brain injury. GFAP is an astrocyte intermediate filament protein, not normally present in blood and represents astrocyte injury or necrosis. Astrocyte foot processes make up the subendothelial component of the blood-brain barrier, thus astrocyte injury biomarkers will also reflect loss of blood-brain barrier integrity.⁸ Elevations in levels of GFAP are detectable within 30 minutes of CPB and are not affected by ultrafiltration.¹⁹ GFAP levels have been associated with neurological disability in adults with traumatic brain injury and those surviving cardiac arrest.⁹⁻¹¹ In the pediatric population, circulating GFAP has been shown to be a significant predictor of neurologic injury and hospital survival in children receiving extracorporeal membrane oxygenation, of abnormal magnetic resonance imaging and functional

FIGURE 1. Perioperative GFAP levels. Before skin incision GFAP levels were low. Immediately after completion of CPB there was an almost 100-fold increase, followed by a rapid tapering by 4 hours. The upper and lower borders of the box represent the upper and lower quartiles. The middle horizontal line represents the median. The upper and lower whiskers represent the maximum and minimum values of nonoutliers. Extra dots represent outliers. GFAP, Glial fibrillary acidic protein; CPB, cardiopulmonary bypass; POST OP, postoperative.

TABLE 2. Linear regression models for GFAP and Bayley composite scores

BSID	Unadjusted					Adjusted				
	Parameter estimate	Standard error	T value	R ²	P value	Parameter estimate	Standard error	T value	R ²	P value
Cognitive	−3.03	1.18	−2.62	0.07	.01	−1.43	1.15	−1.24	0.34	.22
Language	−2.50	1.13	−2.23	0.05	.03	−0.58	1.09	−0.53	0.35	.60
Motor	−4.07	1.38	−3.04	0.09	.003	−3.24	1.52	−2.13	0.22	.04

Adjusted models include center, cardiopulmonary bypass duration, aortic cross-clamp time, use of deep hypothermic circulatory arrest, and Society of Thoracic Surgery-European Association for Cardio-Thoracic Surgery category. BSID, Bayley Scales of Infant and Toddler Development third edition.

outcomes at discharge in neonates with birth-related hypoxic ischemic encephalopathy, and of periventricular white matter injury on 6-week head ultrasound imaging in premature infants.^{13,14,20} This study builds on the current literature by showing an association with circulating GFAP at the time of neonatal cardiac operations and neurodevelopmental assessment at 1 year.

Congenital Heart Disease and Neurodevelopmental Outcomes

The prevalence and severity of developmental disabilities increases with the complexity of congenital heart disease. Neonates and infants requiring open heart surgery for cyanotic or acyanotic defects are categorized as high risk for developmental disorders or disabilities.^{3,7} Etiologies postulated to explain such neurodevelopmental sequelae are diverse and include genetic syndromes, brain malformations, brain maturity, hypoxemic-ischemic insults, brain injury prenatally, during or after surgery, and socioeconomic and environmental factors.^{2,4,21,22}

Although intraoperative factors receive the most attention, and would be the easiest to modify, it would be naive to place

all the blame on events in the operating room. Large studies involving infants with congenital heart disease show neurodevelopmental impairments are most highly associated with innate patient factors and general medical morbidities rather than specific techniques used intraoperatively.^{1,22,23} Despite this, in the Single Ventricle Reconstruction Trial, the largest prospective study to date of children undergoing the Norwood procedure at 15 centers in North America, the clinical center at which the Norwood procedure was performed emerged as an independent predictor of neurodevelopmental impairment.²³ Clinical center remained an independent predictor although data on many potential risk factors, including details of perfusion techniques were included in their analysis and when centers were eliminated from the multivariable models one at a time. The authors opined that it was possible these differences were unmeasured variables in patient characteristics or perioperative management such as anesthetic agents.²³ This highlights the need for a diagnostic means to acutely identify perioperative brain-specific injury to discriminate center-specific effects. Although not an objective of the current study we found a significant site-specific inverse relationship between higher post CPB GFAP values and lower BSID mean cognitive, language, and motor composite scores. Although many of the demographic characteristics and operating room procedures were similar there are some perfusion strategy differences between sites that could contribute. We have previously shown in a larger cohort, not exclusively focused on neonates, that perioperative GFAP was negatively associated with nadir oxygen delivery during CPB.¹⁷ The amount of support or “flow” during CPB is empiric and immediately amenable as an actionable trial intervention, but was not recorded in this or many other cohorts. The centers also use different manufacturers for the bypass circuits and oxygenators. However, there are many other potential confounders that were not recorded including anesthetic, pain, and anxiolytic medications, socioeconomic status, and available health resources and early intervention programs that could contribute to these differences.

A metanalysis, including several interventional studies aimed at improving neurodevelopmental outcomes, showed that infants receiving cardiac surgery at younger than 6 months of age had cognitive and motor developmental

FIGURE 2. GFAP and Bayley Motor Score. Linear regression model showing the inverse association between GFAP levels (ng/mL) immediately after cardiopulmonary bypass on the x-axis and BSID motor composite score at 12 months on the y-axis.

FIGURE 3. GFAP and Bayley Motor Score according to site. A, GFAP levels immediately after cardiopulmonary bypass and (B) BSID motor composite scores were different between the 2 sites. Patients from the institution (site 1) with higher GFAP levels had significantly lower BSID scores than the institution where patients had lower GFAP levels. The *upper* and *lower borders* of the *box* represent the upper and lower quartiles. The *middle horizontal line* represents the median. The *upper* and *lower whiskers* represent the maximum and minimum values of nonoutliers. *Extra dots* represent outliers. GFAP, Glial fibrillary acidic protein; BSID, Bayley Scales of Infant and Toddler Development third edition.

domains that were below the expected mean at all ages studied. The authors concluded that “more definitive outcomes are critical for parent counseling and the provision of timely intervention for the individual.”³ Taken in whole one could envision a complex intertwined relationship in which genetics and innate patient factors result in brain vulnerability to the hemodynamic and physiologic stresses of the perioperative period. Therefore, the need to determine brain injury in real time to tease apart causal injury pathways for patient-specific interventions to improve outcome is paramount. If these findings can be confirmed by future studies GFAP could provide an invaluable tool as a means to focus, shorten, and decrease cost for interventional trials and ultimately reduce neurodevelopmental insult associated with the perioperative management of congenital heart disease.

Limitation

The results of this study must be viewed in light of its limitations. By design this study only included infants who completed a neurodevelopmental assessment at 12 months and therefore did not include children who died in the first year of life. This study included 2 institutions and although the BSID is a standardized test widely accepted to have good inter-rater reliability, we could not examine inter-rater reliability for individual testers for this study. There are growing concerns that the BSID underestimates neurodevelopmental disabilities with the greatest discrepancy in cognitive scores.²⁴ This might explain this cohort’s cognitive and language scores being slightly above the general population norm. Neurodevelopmental assessment at age 12 months might not be predictive of later outcomes and longer follow-up is necessary.²² These subjects were randomized to intraoperative steroid therapy as part of an

interventional clinical trial. Because data collection is still ongoing we do not know if the trial intervention could have had an effect on GFAP levels and outcomes. Finally, although these findings are compelling and might constitute the basis for clearer exploration of neuroprotection going forward, a detailed determination of how patient- and center-specific perioperative factors contribute to elevated GFAP levels was beyond the scope of this work.

CONCLUSIONS

In summary, higher circulating GFAP levels at the time of neonatal cardiac surgery are independently associated with decreased BSID motor composite scores at 12 months. GFAP might serve as a diagnostic means to acutely identify perioperative brain-specific injury and serve as a benchmark of therapeutic efficacy for investigational treatments, provide early prognostic information for intervention, and discriminate center-specific effects for possible quality improvement initiatives. If these findings can be confirmed by future studies GFAP could provide an invaluable tool for reducing neurodevelopmental insult.

Conflict of Interest Statement

Dr Graham is a consultant for Bayer. Dr Everett is a consultant for Immunarray Inc. Immunarray Inc has licensed brain injury biomarkers from Johns Hopkins with Dr Everett as an inventor. All other authors have nothing to disclose with regard to commercial support.

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