Cardiopulmonary-Bypass Glial Fibrillary Acidic Protein Correlates With Neurocognitive Skills

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Background. **Neurocognitive deficits at school starting age may affect as many as 50% of children who underwent cardiac surgery for complex congenital heart disease (CHD). The aim of this study was to identify which phases of cardiopulmonary bypass (CPB) are associated with an increased risk of impaired neurodevelopmental skills in children with complex CHD. This was assessed by means of glial fibrillary acidic protein (GFAP) plasma levels during CPB for CHD surgery, as a marker of neurologic insult. We correlated GFAP levels with clinical parameters and neurodevelopmental outcome.**

Methods. **We studied 45 children undergoing surgery for complex CHD. We measured plasma GFAP levels by enzyme-linked immunosorbent assay at the following steps: anesthesia induction, CPB start, end of hypothermia, end of rewarming, and end of CPB. Neurologic assessment and Vineland Adaptive Behavior Scales (VABS-I) were administered to patients at least 18 months after surgery.**

Results. **GFAP was undetectable before surgery and it peaked at the end of hypothermia or rewarming. Multiple regression analyses showed that GFAP peak level and preoperative neurologic comorbidity were significant independent predictors of neurologic impairment, as showed by VABS-I communication domain intelligence quotient (IQ). Receiver operating characteristic curve showed that the model was highly significant.**

Conclusions. **Impaired neurodevelopment was associated with increase of GFAP plasma levels during cardiac surgery in infants. The identification of the neurologic high-risk phases of CPB run could support the application of new neuroprotective strategies for CHD repair.**

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In the last decades, the exponential reduction of the mortality rate in children with congenital heart disease (CHD) has revealed that neurologic and neurodevelopmental complications are key issues in children with CHD, because they may affect functional outcome, peer-interaction, and overall quality of life. Neurocognitive deficits at school starting age affect nearly 50% of children who underwent surgery for complex CHD requiring cardiopulmonary bypass (CPB) and aortic cross clamping (ACC), with or without deep hypothermic circulatory arrest (DHCA) [1]. Altered brain development and newly acquired brain injuries during CHD surgery influence the overall neurologic outcome in a multifactorial, cumulative, and synergistic manner [2]. According to brain magnetic resonance imaging findings, brain injuries occur in 41% of infants preoperatively and in 30% of infants postoperatively [3]. Preoperative brain insults are mainly due to anomalies of cerebral blood flow during pregnancy, and thus they are not preventable. Therefore, research has focused on the potential onset of brain injury during and post cardiac surgery, trying to develop neuroprotective strategies to improve neurologic outcome.

To identify ongoing brain injuries, several biomarkers have been studied [4–8]. Among them, glial fibrillary acidic protein (GFAP), the main intermediate filament in

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mature astrocytes, seems to fit the requirements of specificity, readiness of release, and ease of assaying, all required to identify an acute brain injury [9].

Generally, there is still a lack of data on assessment of the predictive role of such biomarkers. Several methods are available to evaluate neurologic adaptive functioning. This can reveal how individuals are able to apply cognitive skills to everyday tasks and requirements. In particular, this ability can be effectively evaluated in infancy by means of the Vineland Adaptive Behavior Scales (VABS-I) [10].

In this study, we analyzed plasma GFAP concentration during preset phases of CPB in patients undergoing surgery for CHD, to correlate plasma GFAP values to clinical parameters, neurological development, and VABS-I evaluation at follow-up.

Patients and Methods

Patients

This is a prospective, observational, single-center study in children with complex CHD undergoing a cardiac surgical procedure with CPB from 2014 to 2016. The study was approved by the institutional review board and by the ethics committee of the Padova University Hospital. Inclusion criteria were: children with complex CHD requiring elective cardiac surgery; CPB time greater than 60 minutes on hypothermia; ACC greater than 20 minutes, when performed; and written informed consent. All infants underwent a neurological evaluation and head ultrasound before surgery. Exclusion criteria were age greater than 3 years, previous heart surgery, hemodynamic instability, factor V less than 20%, creatinine clearance less than 30%, or chromosomal and neurological abnormalities before surgery. In addition, we excluded patients undergoing a reoperation.

We defined neurological risk time-interval (NRTI) as the timeframe during CPB in which the patient had selective regional cerebral perfusion (RCP) and/or DHCA, whenever performed, as previously reported [11].

For each study infant we collected birth weight, gestational age, sex, weight and age at the time of surgery, presence of preoperative cyanosis (defined as arterial oxygen saturation $< 90\%$), plasma arterial lactate before and during surgery, duration of CPB and of surgical intervention, core temperature, cerebral oxygen saturation, intensive care unit stay, hospital length of stay, survival, and neurological complications during the hospital stay.

Surgery and Sample Collection

Anesthesia and CPB management were described previously [11]. Briefly, after anesthesia induction and heparin administration, patients were cannulated and CPB was initiated with a hematic prime, to keep hematocrit between 25% and 30%. DHCA or selective RCP were applied according to surgeon choice; CPB flows were set according to body surface area, cardiac index, and temperature nadir. Cerebral regional oxygen saturation by near infrared spectroscopy (NIRS; INVOS, Somanetics, Troy, MI) was recorded every minute. A single NIRS probe was positioned on an area of non-hair-bearing scalp, near the right frontal hairline, to encompass both hemispheres. Blood gas analysis and metabolic parameters were measured at least every 20 minutes. At the end of surgery modified ultrafiltration was applied and all patients underwent rewarming to 36°C measured by rectal probe and then they were allowed to rewarm spontaneously in the intensive care unit.

Blood samples were collected in EDTA-containing tubes (1.5 mL) from the superior vena cava at anesthesia induction, CPB start, end of hypothermia, end of rewarming, and end of CPB before modified ultrafiltration.

Sample Analysis

Blood tubes were centrifuged at 1,400 x *g* for 10 minutes to obtain plasma. Plasma was divided in 150-μL aliquots and stored at −80°C until analysis; GFAP was measured using ELISA kit RD192072200R (BioVendor, Brno, Czech Republic).

Calculations

Plasma GFAP was expressed as concentration (ng/mL) at each study point and as the maximum GFAP concentration (GFAP Max) reached by each patient. Lastly, VABS-I scores for each domain were log(10)-transformed prior to the statistical analysis.

Neurologic and Neurodevelopmental Follow-Up

After hospital discharge, all infants received a cardiologic follow-up at least every 6 months. At 18 months after surgery, all study infants underwent neurologic and behavioral assessments. Neurologic evaluation included detailed medical and neurodevelopmental history, evaluation of muscular tone, strength, and position asymmetry, sensory assessment (tactile and vibration), osteotendinous reflexes, cerebellar and cranial nerve integrity, language skills, and head circumference. All neurological items were recorded as normal/not normal when appropriate. We defined neurologic comorbidity as the presence of an abnormal neurologic or neurodevelopmental finding not associated with the cardiac surgery, but with other clinical events or risk factors identified from the child's medical history.

Vineland Adaptive Behavior Scales

Adaptive functioning was assessed by VABS-I [10], a psychometrically validated parent interview administered by a trained psychological examiner who assesses adaptive behaviors at developmental levels from birth through adulthood. Several domains are evaluated, yielding index scores for socialization, communication, daily living, and motor skills (for children up to age 5 years). All index scores have an age-referenced mean of 100 and a SD of 15, where higher scores reflect better skills. Each domain includes several subdomains with developmentally sequenced items, starting with skills typically observed in infancy.

We considered intelligence quotient (IQ) values for each domain as normal when greater than 80, borderline

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