Postoperative electroencephalographic seizures are associated with deficits in executive function and social behaviors at 4 years of age following cardiac surgery in infancy

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Objective: The occurrence of an electroencephalographic (EEG) seizure after surgery for complex congenital heart defects has been associated with worse neurodevelopmental (ND) outcomes. We previously identified postoperative seizures documented by 48-hour EEG monitoring in 11% of 178 neonates and infants. Evaluation at 1 year of age did not identify an adverse effect of an EEG seizure on ND outcomes. The current study was undertaken to determine if testing in the preschool period would identify deficits that become apparent as children develop.

Methods: The ND outcomes assessed at 4 years of age included cognition, language, attention, impulsivity, executive function, behavior problems, academic achievement, and visual and fine motor skills.

Results: Developmental evaluations were performed in 132 (87%) of 151 survivors. For the entire cohort, the Full-Scale IQ was 95.0 ± 18.5. IQ was 95.1 ± 18.7 for patients without a history of seizure and 93.6 ± 16.7 for those with a history of seizure. After covariate adjustment, occurrence of an EEG seizure was associated with worse executive function ($P = .037$) and impaired social interactions/restricted behavior ($P = .05$). Seizures were not significantly associated with worse performance for cognition, language, attention, impulsivity, academic achievement, or motor skills (all $P > .1$).

Conclusions: The occurrence of a postoperative seizure is a biomarker of brain injury. This study confirms that postoperative EEG seizures are associated with worse ND outcomes, characterized by impairments of executive function and a higher prevalence of deficits in social interactions and repetitive/restricted behaviors in preschool survivors of cardiac surgery in infancy. However, EEG seizures were not associated with worse cognitive, language, or motor skills. (J Thorac Cardiovasc Surg 2013;146:132-9)

CHD

The occurrence of a seizure in the early postoperative period after repair or palliation of congenital heart defects (CHDs) is a marker for a central nervous system (CNS) injury and has been associated with adverse neurodevelopmental (ND) sequelae.[1-3] The research standard for detection and quantification of postoperative seizures remains continuous electroencephalographic (EEG) monitoring.[4] In the Boston Circulatory Arrest Study (BCAS) conducted between 1988 and 1992, continuous EEG monitoring in the first 48 hours after the arterial switch operation for transposition of the great arteries (TGA), with or without a ventricular septal defect, demonstrated seizures in 27 (20%) of 136 neonates and infants. Follow-up evaluation of these patients demonstrated that the occurrence of a postoperative EEG seizure, identified either clinically or by EEG monitoring, was associated with worse ND outcomes at 1, 4, and 16 years of age.[1-3]

We previously evaluated the incidence of perioperative seizures in a heterogeneous cohort of 178 patients with complex CHD, including hypoplastic left heart syndrome (HLHS).[5,6] Early postoperative seizures were identified in 11.2% of these neonates and infants. All of the seizures were subclinical. The ND evaluation was performed at 1 year of age in 114 of 164 survivors, of whom 15 (13%) had had seizures. In this cohort of neonates and infants, the occurrence of a seizure was not predictive of an adverse ND outcome, as assessed by the Bayley Scales of Infant Development-II. However, ND assessment at 1 year of age has limited predictive validity for later outcomes

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Abbreviations and Acronyms

APOE = apolipoprotein E
BCAS = Boston Circulatory Arrest Study
CHD = congenital heart defect
CNS = central nervous system
CPB = cardiopulmonary bypass
DHCA = deep hypothermic circulatory arrest
EEG = electroencephalographic
HLHS = hypoplastic left heart syndrome
ND = neurodevelopmental
PDP = pervasive developmental problem
TGA = transposition of the great arteries

and does not assess higher functions, such as executive function and memory.[7] The current study was undertaken to determine if testing in the preschool period would identify deficits that had become apparent as children developed.

METHODS

Sample

A subgroup of children enrolled in a prospective study evaluating polymorphisms of apolipoprotein E (APOE) as a risk factor for ND dysfunction also underwent continuous video-EEG monitoring in the early postoperative period. Patients who were 6 months of age or younger and underwent cardiopulmonary bypass (CPB), with or without deep hypothermic circulatory arrest (DHCA), for repair of CHD were eligible for enrollment. Exclusion criteria included (1) multiple congenital anomalies, (2) a recognizable genetic or phenotypic syndrome other than chromosome 22q11 microdeletions, and (3) a language other than English spoken in the home. The study was approved by the Institutional Review Board at The Children's Hospital of Philadelphia (Philadelphia, Pa). Informed consent was obtained from the parent or guardian.[8,9]

Operative Management

Operations were performed by 5 cardiac surgeons with a dedicated team of cardiac anesthesiologists. α-Stat blood gas management was used. Pump flow rates were not standardized for this study. DHCA was used at the surgeon's discretion. Before DHCA, patients underwent core cooling with topical hypothermia of the head to a nasopharyngeal temperature of 18°C. Modified ultrafiltration was performed in all patients.

Video-EEG Examination

Details of the video-EEG evaluation have been previously published.[5,6,10] Video-EEGs were recorded on 1 of 3 identical, dedicated, portable Telefactor Millenium Beehive machines (Conshohocken, Pa), which capture time-synchronized video images and digital EEG data. A brief 15-minute preoperative baseline study was recorded. Recording was reinitiated after surgery immediately after admission to the cardiac intensive care unit. Video-EEGs were recorded continuously for the first 48 hours after surgery. Studies were terminated early only for death or at parental request. Each record was visually reviewed in its entirety every 12 hours by the recording EEG technologist and independently by a pediatric neurologist (R.R.C.). The number of seizures during the study period was recorded. In addition, the sites of origin of the seizures were recorded and classified as frontal or nonfrontal. After confirmation of the presence of seizures, the attending physician was informed of the occurrence of a seizure. All treatment decisions, including the institution of antiepileptic drug therapy, were made at the discretion of the attending physician.

Data Collection

Preoperative factors, including gestational age, birth head circumference, birth weight, Apgar scores, and preoperative intubation, were obtained from birth and hospital records. Weight, age at operation, and type of operation were recorded, along with perfusion data, including CPB time, aortic cross-clamp time, and duration of DHCA. Total support time was calculated as CPB time plus DHCA time. Total DHCA time was calculated as the sum of the duration of each episode of DHCA.

Four-Year Evaluation and ND Testing

Children were evaluated between their fourth and fifth birthdays. Growth measurements were obtained, including weight, length, and head circumference. Maternal education and the child's ethnicity were assessed by parental report. The familial socioeconomic status was assessed by parental report, according to the Hollingshead scale.[11] A health history was obtained, focusing on the incidence of interim illnesses, rehospitalizations, neurologic events or interim evaluations, current medication use, and parental concerns about health. Parents completed behavior questionnaires and rating scales.

To provide a broad assessment of ND status, multiple domains were tested, including cognition, language, fine and visual motor skills, executive function, inattention and impulsivity, and social skills. Quantitative testing was used to assess cognition, core language skills, fine and visual motor skills, and executive function. Cognitive skills were assessed with a Full-Scale IQ from the Wechsler Preschool and Primary Scale of Intelligence-3rd Edition.[12] Core language competence was assessed using the Preschool Language Test-4 Total Language Score.[13] Fine motor skills were tested with the Wide Range Assessment of Visual Motor Abilities pegboard, a manipulative dexterity test.[14] Visual-motor integration was assessed with the Developmental Test of Visual Motor Integration, a simple copying task that assesses the child's fine motor and visual motor coordination skills.[15] Academic achievement (school readiness for reading and math) was tested using the reading and math clusters of the Woodcock-Johnson III, a standardized achievement test for children from the age of 2 years to adulthood.[16] Executive function was assessed with the NEPSY (NEuro-PSYchology) Attention/Executive Functions Core Domain Score, which reflects performance on measures of selective attention and executive functions, including motor and task persistence, inhibition, planning, and mental flexibility.[17] If a child was judged to be too developmentally impaired to complete the tasks, a score was imputed by assigning them the lowest possible score for the specific test.

Inattention, impulsivity, and social skills were assessed by parental report. Inattention and impulsivity were also assessed by the Impulsivity and Inattention Scales of the Attention Deficit/Hyperactivity Disorder Rating Scale-IV Preschool Version.[18] Social competence was assessed by the Preschool and Kindergarten Behavior Rating Scales Social Skills Total Score, which details social cooperation, social interaction, and social independence, as reported by parents.[19] Other behavioral skills were assessed using the Child Behavior Checklist for ages 1.5 to 5 years.[20] The Child Behavior Checklist for ages 1.5 to 5 years is a questionnaire used to obtain parental reports of behavior problems and prosocial adaptive skills demonstrated within the previous 6 months. Specifically, the pervasive developmental problem (PDP) scale was used to assess the prevalence of problems in the area of reciprocal social interactions and restricted behaviors (eg, repetitive behavior or disturbed by change). The PDP scale was developed to incorporate some of the behavioral symptoms that the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, lists as criteria for the diagnosis of an autism spectrum disorder (autism, Asperger syndrome, or pervasive developmental disorder not otherwise specified). High scores on the PDP scale do not confirm the diagnosis of an autism spectrum disorder, but suggest that further evaluation is warranted.

Data Analysis and Statistical Methods

Patients were coded according to a previously described classification that incorporates cardiac anatomy and perioperative physiology and that has been shown to be predictive of perioperative mortality. Class 1