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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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Abstract

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 post-operative 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

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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.

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 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 indicates 2 ventricles with no aortic arch obstruction; class 2, 2 ventricles with aortic arch obstruction; class 3, a single ventricle with no arch obstruction; and class 4, a single ventricle with arch obstruction. Patients with tetralogy of Fallot and TGA are class 1, whereas patients with HLHS and variants are class 4.

Subjects were characterized on the basis of occurrence of a postoperative seizure. Ethnicity was classified as Asian/Pacific Islander, African American, Hispanic, Native American, white, or other. *APOE* genotype was coded for presence of the ε2 or ε4 allele. Subjects were

categorized in 3 groups: ε2 (ε2ε2 and ε2ε3), ε3 (ε3ε3), and ε4 (ε3ε4 and ε4ε4). Subjects with the ε2ε4 genotype were excluded from analysis of *APOE* genotype effect. The *APOE* group was coded as a dummy variable, with group ε3 as the reference. Comparisons of covariates between patients with and without a history of seizure were performed using the Fisher exact test or the Student *t* test. Linear regression analysis was used to characterize the relationship between occurrence of a seizure and the ND outcomes. The analyses were adjusted for the covariates listed in Table 1. Ethnicity and surgical class data are coded as dummy variables for the regression analyses, with the most common category being used as the reference group. The analyses were performed for the whole cohort and for the HLHS subgroup. All analyses used STATA 12 software (StataCorp, College Station, Tex).

RESULTS

Between September 1998 and April 2006, 675 eligible infants underwent cardiac surgery. Twenty-three infants died before consent was obtained. Parents of 102 infants declined participation, and 550 (81%) were enrolled. Continuous postoperative EEG monitoring was performed in 183 (88%) of patients between September 2001 and April 2003. All patients enrolled in the APOE study were proposed for enrollment in the EEG study. Reasons for not undergoing the EEG monitoring included parental refusal and unavailability of an EEG monitor. Complete 48-hour EEG studies were obtained in 178 (97%) of patients. Reasons for noncompletion of the EEG included death in 1 patient, parental request in 1 patient, technical issues resulting in loss of the EEG recording in 2 patients, and need for a second period of cardiopulmonary bypass in 1 patient.

In the overall cohort, 486 patients were alive and eligible for the 4-year evaluation, which was completed by 382 (78%) of the eligible patients. There were 151 survivors from the original cohort of 178 infants who underwent continuous EEG monitoring. Developmental evaluations at 4 years of age were performed in 132 (87%) of the survivors, including 39 with HLHS or variant. Postoperative EEG seizures occurred in 14 patients (11%) overall and in 7 (18%) of those with HLHS. Because the genetic evaluations were performed at the time of ND evaluation, patients who did not return were more likely to be classified as “unknown” for genetic anomalies. The only other difference between the returning and nonreturning patients was a smaller birth head circumference for the nonreturners (Table 1).

Baseline variables and operative characteristics are shown in Table 2. Patients with forms of a functional single ventricle were more common in the seizure group. The only significant difference in operative management at the initial operation between patients with and without a history of a seizure was greater duration of DHCA in the patients with a history of a seizure. This is consistent with our previous analysis of risk factors for a postoperative seizure in this cohort. There were no significant differences in unadjusted outcome for any ND measure between the patients with and without a history of seizure for either the entire cohort or the HLHS subgroup (Table 2). In the entire cohort, after adjustment for patient and operative covariates, patients with a history of seizure had worse performance for executive function ($P = .037$) (Table 3). Patients with HLHS had a higher prevalence of deficits in social interactions and repetitive/restricted behaviors ($P = .05$).

DISCUSSION

The current study demonstrates that occurrence of a seizure after cardiac operation is a biomarker of CNS injury. We found that, although the occurrence of a postoperative seizure detected by EEG monitoring was not associated with major deficits in cognition, language, or motor skills, it was associated with worse performance for executive function and a higher prevalence of repetitive/restricted behaviors, compared with those patients in whom seizures did not occur. Our previous evaluation of these patients at 1 year of age did not demonstrate an adverse impact of a postoperative seizure.[5]

Serial evaluations of the patients enrolled in the BCAS have shown that occurrence of a postoperative clinical or electrocardiographic seizure was associated with worse ND outcomes at both 1 and 4 years.[1,2] At the 4-year evaluation, infants who had experienced a postoperative clinical or EEG seizure had lower scores for full-scale, verbal, and performance IQ, and an increased risk of neurologic abnormalities. The cohort recently underwent evaluation at 16 years of age, including assessment of academic achievement, memory, executive function, visual-spatial skills, attention, and social cognition.[3] Interestingly, although there were few significant treatment group differences, the occurrence of seizures in the postoperative period was the variable most consistently related to worse ND outcomes. In regression analyses, a history of a clinical EEG seizure in the postoperative period predicted worse scores on the reading and math achievement, memory, executive function, visual-motor integration, and social cognition.

Andropoulous and colleagues[21] recently evaluated the evidence of postoperative EEG seizures in infants with either 2 ventricles or a single ventricle CHD undergoing neonatal cardiac surgery using a high-flow CPB protocol and cerebral oxygenation. Antegrade cerebral perfusion was used to avoid DHCA. In this cohort of 68 patients, only 1 patient with single-ventricle CHD experienced 2 brief seizures postoperatively. This prevalence of seizures was much lower than that previously recorded in our study and the BCAS. However, the patients were treated with continuous midazolam infusions, and the authors speculate that this may have suppressed postoperative seizures.

Gunn and colleagues[22] evaluated 39 full-term infants undergoing the Norwood procedure with amplitude-integrated EEG monitoring both intraoperatively and for 72 hours postoperatively. However, this technique is less accurate in detecting EEG seizures compared with conventional EEG monitoring.[23] They used a perfusion strategy with full-flow moderately hypothermic CPB with antegrade cerebral perfusion. Overall, 13 infants (33%) had electrical seizures, including 9 with intraoperative seizures and 7 with postoperative seizures. Status epilepticus was pharmacologically treated. Seizures were associated with increased mortality but not with ND abnormalities in the survivors. This study suggests that avoidance of DHCA does not prevent postoperative seizures. In addition, the findings also suggest that prompt identification and treatment may minimize the ND effects of postoperative seizures.

The findings of the current study, compared with those of the BCAS, suggest a less adverse impact of a postoperative seizure. Unlike the BCAS, we did not find that seizures were

associated with worse cognitive, language, or motor skills. It is interesting to speculate on potential reasons for this difference. Our cohort included patients with many types of CHD, including single-ventricle CHD and HLHS, not just TGA. In addition, our cohort included children with genetic anomalies and those undergoing multiple operations. The heterogeneity of our patient population may make it more difficult to identify the impact of a seizure on outcome. In the BCAS study, the EEG monitoring was strictly considered a research tool and the data collected were not used to guide treatment with antiseizure medications. Only clinical seizures were treated, but it is well known that unaided clinical observation grossly underestimates the true number and duration of EEG seizures. Thus, in retrospect, many patients in the BCAS experienced long periods of untreated seizures, lasting cumulatively up to 16.3 hours during 48 hours of monitoring.[24] Indeed, the investigators identified a trend toward worse outcomes at 1 year of age for infants with total seizure duration of longer than 139 minutes.[25] Conversely, in our study, the EEGs were interpreted every 12 hours and the clinical team was notified whenever seizure activity was noted. This prompt identification and treatment may have ameliorated the impact and secondary injury due to untreated seizures.

In multiple clinical settings, seizures defected by visual observation or by EEG are both significantly associated with subsequent adverse outcomes. However, it is not clear if the seizures are only innocent outward signs of brain damage or whether they actively contribute to the final extent and severity of the injury. Recent studies have shown that, in the immature rodent brain, seizures evoke long-lasting disturbances in neuronal structure, synapse formation, network organization, and neurotransmitter subunit composition.[26] Collectively, these changes alter the behavior, memory, and problem-solving skills of affected rodents.[27] In human studies, it has been much more difficult to tease apart the possible adverse effects of the seizures themselves from the underlying conditions that triggered them. In a recent prospective study of neonatal hypoxic-ischemic encephalopathy, all study subjects underwent research protocol brain magnetic resonance imaging shortly after birth, and a seizure burden index was generated.[28] Full-scale IQ was assessed at the age of 4 years in 77 survivors. After adjustment for the extent of anatomic injury detected by the magnetic resonance images, Full-Scale IQ was significantly depressed, with higher seizure burdens. The results of the current study are consistent with the hypothesis that seizures per se are independently associated with some adverse developmental outcomes. In the BCAS, untreated EEG seizures were associated with greater ND impairments than found in the current study. The question must be asked whether all or most infants undergoing infant heart surgery should undergo long-term EEG monitoring to facilitate the prompt detection and early treatment of seizures. Indeed, such a recommendation has recently been made by the American Clinical Neurophysiology Society.[4]

There are several limitations to the current study. Although it is a large overall cohort, the number of patients with EEG seizures is fortunately small. Seizures were treated whenever identified; however, the therapies were not standardized. In addition, the study was not designed or powered to determine if early identification of a seizure and institution of appropriate therapy would improve outcomes. Finally, patterns of developmental disability change as children develop; re-evaluation at an older age may identify additional deficits.

In summary, we found that the occurrence of a postoperative EEG seizure after cardiac surgery in neonates and infants was not associated with deficits in cognitive, language, and motor skills. There is an association with impaired social interactions/restricted behavior and executive function at 4 years of age. The adverse effect of a seizure on ND outcomes may be less than identified in previous studies. Prompt identification and treatment of postoperative seizures may prevent secondary CNS injury due to ongoing seizure activity. A clinical trial is indicated to determine if EEG monitoring and targeted therapy of postoperative seizures will improve ND 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

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TABLE 1

Comparison baseline characteristics and operative variables

Variable	No EEG seizure (N = 118)	EEG seizure (N = 14)	*P* value
Sex			1
Male	67 (56.8)	8 (57.2)	
Female	51 (43.3)	6 (42.9)	
Ethnicity			1
American Indian/Alaska Native	4 (3.4)	0 (0)	
Asian	5 (4.3)	0 (0)	
Black or African American	21 (17.8)	2 (14.3)	
Hispanic	3 (2.6)	0 (0)	
White	85 (72.1)	12 (85.8)	
Maternal education			.6
Less than high school	3 (2.6)	1 (7.2)	
High school/some college	51 (43.3)	7 (50)	
College	44 (37.3)	5 (35.8)	
Graduate	19 (16.2)	1 (7.2)	
Socioeconomic status quintile			.2
1	3 (2.6)	1 (7.2)	
2	10 (8.5)	3 (21.5)	
3	27 (22.9)	1 (7.2)	
4	37 (31.4)	3 (21.5)	
5	40 (33.9)	6 (42.9)	
Genetic anomaly			.8
None 0	87 (73.8)	12 (85.8)	
Suspected 1	14 (11.9)	1 (7.2)	
Confirmed 2	17 (14.5)	1 (7.2)	
APOE genotype*			.85
ε2	15 (12.8)	1 (7.2)	
ε3	64 (54.3)	9 (64.3)	
ε4	37 (31.4)	4 (28.6)	
Birth weight, g			.39
Mean ± SD	3.09 ± 0.62	3.22 ± 0.59	
No.	118	14	
Birth head circumference, cm			.25
Mean ± SD	33.32 ± 2.03	33.97 ± 2.26	
No.	116	14	
Gestational age, wk			.71
Mean ± SD	38.3 ± 2.09	38.5 ± 1.56	
No.	117	14	
Preoperative mechanical ventilation			1

Variable	No EEG seizure (N = 118)	EEG seizure (N = 14)	*P* value
0	95 (80.6)	11 (78.6)	
1	23 (19.5)	3 (21.5)	
Cardiac class			.02
1	62 (52.6)	2 (14.3)	
2	16 (13.6)	3 (21.5)	
3	8 (6.8)	2 (14.3)	
4	32 (27.2)	7 (50)	
Age at first operation, d			.17
Mean ± SD	43.69 ± 52.65	24.29 ± 39.57	
No.	118	14	
Weight at first operation, kg			.73
Mean ± SD	3.84 ± 1.17	3.74 ± 1.14	
No.	118	14	
Total duration CPB at first operation, min			.47
Mean ± SD	57.30 ± 31.90	63.86 ± 24.71	
No.	118	14	
Total duration DHCA at first operation, min			.001
Mean ± SD	21.76 ± 21.23	41.93 ± 22.35	
No.	118	14	
HCT at first operation			.34
Mean ± SD	30.69 ± 3.53	29.71 ± 2.58	
No.	118	14	
Delayed sternal closure			.15
No	108 (91.6)	11 (78.6)	
Yes	10 (8.5)	3 (21.5)	
Preoperative LOS	2.16 ± 3.55	2.14 ± 1.79	1
Mean ± SD			
No.	118	14	
Postoperative LOS			.03
Mean ± SD	10.94 ± 13.30	19.43 ± 15.04	
No.	118	14	
Use of ECMO or VAD			.11
No	118 (100)	13 (92.9)	
Yes	0 (0)	1 (7.2)	
No. of additional operations with CPB			.05
0	73 (61.9)	4 (28.6)	
1	10 (8.5)	2 (14.3)	.02
2	33 (28)	8 (57.2)	
3	2 (1.7)	0 (0)	
Duration cumulative CPB, min			
Mean ± SD	92.31 ± 58.40	132.43 ± 72.04	

Variable	No EEG seizure (N = 118)	EEG seizure (N = 14)	*P* value
No.	118	14	
Any additional DHCA			.02
No	47 (39.9)	1 (7.2)	
Yes	71 (60.2)	13 (92.9)	
Duration cumulative DHCA, min			.003
Mean ± SD	35.93 ± 38.32	66.14 ± 41.41	
No.	118	14	

EEG, Electroencephalographic; *APOE*, apolipoprotein E; *CPB*, cardiopulmonary bypass; *DHCA*, deep hypothermic circulatory arrest; *HCT*, hematocrit; *LOS*, length of stay; *ECMO*, extracorporeal membrane oxygenation; *VAD*, ventricular assist device; *SD*, standard deviation.

*Subjects with the ε2ε4 genotype were excluded.

TABLE 2

Unadjusted neurodevelopmental outcomes

	All				No EEG seizure (n = 118)				EEG seizure (n = 14)				
Outcome	**No.**	**Mean**	**SD**	**Range**	**No.**	**Mean**	**SD**	**Range**	**No.**	**Mean**	**SD**	**Range**	***P* value**
Cognition	130	95.0	18.5	49–137	116	95.2	18.71	49–137	14	93.6	16.7	69–118	.75
Language	132	96.2	18.5	50–131	118	96.7	18.52	50–131	14	92.0	18.4	56–122	.38
Visual-motor integration	131	92.3	18.2	48–136	117	92.6	18.41	48–136	14	89.4	16.8	53–114	.51
Fine motor	131	94.8	19.3	45–132	117	95.1	19.46	45–132	14	92.7	18.1	70–126	.66
Executive function	123	98.4	15.2	60–126	109	99.4	14.84	60–126	14	90.9	15.8	66–112	.07
Memory	115	92.7	17.0	52–133	101	93.5	16.96	52–133	14	87.3	16.5	60–106	.21
Reading skills	128	106.1	17.3	76–190	114	106.3	17.93	76–190	14	103.7	10.2	87–121	.42
Math skills	124	95.6	21.1	40–142	110	96.2	21.18	40–142	14	90.5	20.1	42–121	.33
Impulsivity	131	7.4	6.1	0–22	117	7.3	6.11	0–22	14	8.3	6.0	0–20	.55
Attention	131	6.3	5.3	0–21	117	6.2	5.25	0–21	14	6.4	5.7	0–16	.90
Restricted/repetitive behaviors	131	3.0	3.2	0–18	117	2.7	2.94	0–17	14	5.1	4.5	0–18	.08
Social skills	130	106.2	12.0	56–123	116	106.4	12.10	56–123	14	104.6	11.3	82–120	.60

EEG, Electroencephalographic.

TABLE 3

Linear regression

	All (N = 130)*		HLHS (N = 39)	
Outcome	**β**	***P* value**	**β**	***P* value**
Cognition	−2.138	.648	−7.449	.560
Language	−3.448	.451	−5.500	.589
Visual-motor integration	−2.120	.682	−9.010	.564
Fine motor	1.191	.819	−23.544	.061
Executive function	**−8.977**	**.037**	−12.885	.291
Memory	−3.443	.509	11.409	.271
Reading skills	−2.698	.584	11.924	.347
Math skills	−2.960	.597	−17.430	.226
Impulsivity	1.095	.555	2.51	.699
Attention	0.812	.622	4.256	.364
Restricted/repetitive behaviors	1.984	.057	**6.980**	**.050**
Social skills	−1.814	.632	−17.844	.084

HLHS, Hypoplastic left heart syndrome.

*Regression analyses adjusting for *APOE* status excluded 2 subjects with *APOE* ε2/ε4 genotypes.