Neurodevelopmental Profiles of Children with Congenital Heart Disease at School Age

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Objectives To assess 6-year neurodevelopmental outcomes in a current cohort of children with congenital heart disease (CHD) who underwent cardiopulmonary bypass surgery (CPB), and to determine risk factors for adverse outcomes.

Study design Outcomes were examined in 233 prospectively enrolled children with CHD (including 64 with a recognized genetic disorder) who underwent CPB between 2004 and 2009. Follow-up assessment included standardized neurologic, motor, and cognitive tests. Variables were collected prospectively, and multiple regression analysis was performed to determine independent risk factors for adverse outcome.

Results The mean patient age at assessment was 6.3 years (range, 5.1-6.8 years). IQ was lower in children with a genetic disorder (median, 55; range, 17-115) compared with children without a genetic disorder (median, 95; range, 47-135; $P < .001$). Cognitive and motor performance also were lower in children without a genetic disorder compared with the norm ($P < .01$ for both). The prevalence of children without a genetic disorder performing below -2 SD (IQ 70) was higher than the norm (5.3% vs 2.3%; $P = .008$), and the prevalence of poor motor performance (<10th percentile) ranged from 21.2% to 41.1% ($P < .01$ for all). Significant independent risk factors for poor neurodevelopmental outcome included a genetic disorder, longer length of intensive care stay, lower birth weight, postoperative seizures, and lower socioeconomic status.

Conclusions Current cohorts of children with CHD undergoing CPB show favorable outcomes but remain at risk for long-term neurodevelopmental impairments, particularly those with a genetic disorder and a complicated postoperative course. Close neurodevelopmental surveillance is necessary to provide early therapeutic support. *(J Pediatr 2017;188:75-81).*

Significant advances in surgical techniques and intensive care management have led to increased survival of children with congenital heart disease (CHD).[1] Children with CHD, including those with the most complex heart defects, now often reach adulthood.[2] Despite these significant advances, children with CHD remain at risk for neurodevelopmental impairments.[3-6] Previous studies have reported outcomes at school age (age 5-9 years)[5,7-9] with a median IQ within the normal range but lower than the norm, with higher rates of motor, language, and behavioral problems.[3,4,6,10,11] There is also evidence of executive function difficulties in children at age 5-7 years.[12]

Often difficulties are seen across several domains,[8] and their coexistence leads to a greater need for therapeutic support.[10] Assessment of neurodevelopmental function at around school entry is critical for counseling regarding educational support. The majority of studies reporting school-age outcomes for children with CHD include children born in the early and late 1990s, whereas studies on recently born children have reported mostly early childhood outcomes.[2,3,7,12] Gaynor et al[2] reported a mild improvement of early development, most likely associated with improved intensive care and surgical management strategies; however, little is known on school-age outcomes. Furthermore, except for a recognized genetic disorder, risk factors for early neurodevelopment might not be the same as for long-term outcomes.[13]

Thus, the goal of the present study was to describe neurodevelopmental outcomes at age 6 years in a cohort of children with various types of CHD who underwent cardiopulmonary bypass (CPB) surgery between 2004 and 2009. We aimed to identify developmental domains that would be particularly affected and to determine risk factors for neurodevelopmental impairment.

CHD	Congenital heart disease
CPB	Cardiopulmonary bypass
ICU	Intensive care unit
K-ABC	Kaufman Assessment Battery for Children
NSS	Neurologic Severity Score
SES	Socioeconomic status
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence, Third Edition
ZNA	Zurich Neuromotor Assessment

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Methods

A total of 368 children with CHD undergoing CPB surgery at the University Children's Hospital Zurich were enrolled prospectively. Children underwent CPB surgery between 2004 and 2009. Neurodevelopmental assessments were performed before surgery, at age 1 year, or at 6 months after surgery (if surgery was performed after age 1 year), and at age 4 and 6 years. Here we report the 6-year outcomes. The Canton of Zurich Ethics Committee approved the study, and written informed consent was obtained from each child's parents.

Twenty-five children (6.8%) died before the 6-year examination (9 postoperatively, 16 before the 6-year examination). Forty-two patients were aged ≥6 years at the time of surgery and thus were too old for the 6-year follow-up, and 27 children were excluded because they had undergone CPB surgery before enrollment. Of 274 eligible children, 41 were lost to follow-up (follow-up, 85%). The children lost to follow-up did not differ from the children followed up in terms of demographic and perioperative variables (**Table I**). Of 233 children examined at age 6 years, 64 had a recognizable genetic or phenotypic syndrome (hereinafter, genetic disorder) (**Table I**). Testing for genetic disorders was performed if a cardiac malformation was known to be associated with a genetic abnormality or if another organ malformation or a significant developmental delay was present. The heart defects were assigned to 1 of 4 cardiac classes according to the classification scheme of Clancy et al.[14]

All patients underwent surgery at the University Children's Hospital Zurich performed by 2 cardiac surgeons. In most of the cardiac surgeries, normothermic or mild hypothermic CPB (rectal temperature >32°C) was maintained, whereas in Norwood I procedures and other aortic arch repairs, moderate hypothermia (nasopharyngeal temperature 22-28°C) was maintained. During a normal CPB with whole-body perfusion, a pump flow rate at 100-150 mL/kg/minute was targeted. In patients undergoing arch repair operations, antegrade cerebral perfusion was used, with a pump flow rate of ~50 mL/kg/minute and a target mean arterial pressure of ~40-50 mmHg measured in the right radial artery. Modified ultrafiltration and alpha-stat blood gas management was provided for all patients. First-line postoperative catecholamine therapy was provided with norepinephrine, and second-line was provided with epinephrine. All patients received milrinone in the early postoperative period.

In general, cognition was assessed with the German version of the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III). This was possible for 183 children. In 28 children, a specific language disorder was

Table I. Demographic and cardiac variables of children with CHD (n = 233)

Variables	Non–genetic disorder (n = 169)	Genetic disorder (n = 64)	*P* value, non–genetic disorder vs genetic disorder
Male sex, n (%)	104 (61.5)	30 (46.9)	.04
SES (range, 2-12), median (range)	8 (2-13)	8 (4-12)	.71
Gestational age, wk, median (range)	39.4 (30.4-43)	38.35 (27-42.6)	.001
Prematurity (<37 wk), n (%)	18 (10.7)	16 (25)	.008
Birth weight, kg, median (range)	3.27 (1.34-5.3)	2.66 (0.79-4.3)	<.001
5-minute Apgar score, median (range)	9 (1-10)	9 (2-10)	.07
Cardiac class, n (%)			
1: 2 ventricle/no arch obstruction	123 (72.8)	55 (85.9)	
2: 2 ventricle/arch obstruction	14 (8.3)	6 (9.4)	.06
3: 1 ventricle/no arch obstruction	14 (8.3)	2 (3.1)	
4: 1 ventricle/arch obstruction	18 (10.7)	1 (1.6)	
Cyanotic heart defect, n (%)	107 (63.3)	15 (23.4)	<.001
Genetic disorder, n (%)			
Trisomy 21 syndrome		22 (34.4)	
Microdeletion 22 syndrome		8 (12.5)	
VACTERL association		4 (6.3)	
CHARGE syndrome		4 (6.3)	
Other*		13 (20.3)	
Unknown syndrome		13 (20.3)	
Feeding difficulties, preoperative, n (%)	37 (21.9)	24 (37.5)	.02
Preoperative neurologic severity score, median (range)	2.5 (0-11)	7 (1-18)	<.001
Age at first surgery, mo, median (range)	2.7 (0.1-56.9)	4.2 (0.16-33.1)	.007
Weight at surgery, kg, median (range)	4.30 (1.5-19.8)	4.66 (1.97-16.5)	.73
Lowest temperature during first surgery, °C, median (range)	30 (16-37)	28 (16-37)	.11
ECC time during first surgery, min, median (range)	150 (25-405)	134.5 (55-307)	.36
Cumulative ECC time, min, median (range)	182 (40-818)	157.5 (55-538)	.33
Cumulative aortic cross-clamping time, min, median (range)	95 (9-333)	79 (32-271)	.27
Length of ICU stay after first surgery, d, median (range)	6 (1-232)	6 (2-117)	.48
Clinical seizures after first surgery, n (%)	2 (1.2)	3 (4.7)	.10

CHARGE, Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies/deafness; *ECC*, extracorporeal circulation; *VACTERL*, vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities.
Differences between children with and without a genetic disorder were calculated using the Mann-Whitney *U* test or the χ^2 test.
*Each syndrome is represented by 1 case: oculocutanean albinism, alcohol fetopathy, galactosomy, balanced translocation t(5;9), hypertelorism, Albright hereditary osteodyspathy, 3C(cranio-cerebello-cardial dysplasia), deletion (del) exon MED13L, chromosomal aberration del-8p, cri-du-chat, Ellis-van-Crefeld syndrome, del-15p, and Kabuki syndrome.