ORIGINAL RESEARCH

Neuropsychological Status and Structural Brain Imaging in Adolescents With Single Ventricle Who Underwent the Fontan Procedure

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***Background*—**Few studies have described the neuropsychological outcomes and frequency of structural brain or genetic abnormalities in adolescents with single ventricle who underwent the Fontan procedure.

***Methods and Results*—**In a cross-sectional, single-center study, we enrolled 156 subjects with single ventricle, mean age 14.5±2.9 years, who had undergone the Fontan procedure. Scores in the entire cohort on a standard battery of neuropsychological tests were compared with those of normative populations or to those of a group of 111 locally recruited healthy adolescents. They also underwent brain magnetic resonance imaging and were evaluated by a clinical geneticist. Genetic abnormalities were definite in 16 subjects (10%) and possible in 49 subjects (31%). Mean Full-Scale IQ was 91.6±16.8, mean Reading Composite score was 91.9±17.2, and mean Mathematics Composite score was 92.0±22.9, each significantly lower than the population means of 100±15. Mean scores on other neuropsychological tests were similarly lower than population norms. In multivariable models, risk factors for worse neuropsychological outcomes were longer total support and circulatory arrest duration at first operation, presence of a genetic abnormality, more operations and operative complications, more catheterization complications, and seizure history. The frequency of any abnormality on magnetic resonance imaging was 11 times higher among Fontan adolescents than referents (66% versus 6%); 19 (13%) patients had evidence of a stroke, previously undiagnosed in 7 patients (40%).

***Conclusions*—**The neuropsychological deficits and high frequencies of structural brain abnormalities in adolescents who underwent the Fontan procedure highlight the need for research on interventions to improve the long-term outcomes in this high-risk group. **(*J Am Heart Assoc*. 2015;4:e002302 doi: 10.1161/JAHA.115.002302)**

Key Words: congenital heart defects • Fontan procedure • genetics • magnetic resonance imaging

In recent decades, there has been improvement in both survival and neurodevelopment of children with single ventricle who have been palliated with use of the Fontan procedure. Nonetheless, these patients remain at increased risk of cognitive and behavioral impairments.[1–11] Although in some studies the deficits are modest in severity,[12,13] they are broad-based and include reduced IQ scores, learning disorders, visuomotor integration deficits, attention deficit hyperactivity disorder (ADHD), and reduced quality of life.[14,15] The reported deficits have tended to be greater among patients with hypoplastic left heart syndrome (HLHS) than in those with other forms of univentricular heart,[16–18] with occasional exceptions.[19]

Longitudinal studies of children with other forms of congenital heart disease (CHD) have shown that the full range of their neurodevelopmental morbidity can be appreciated only if follow-up extends at least into adolescence, when patients face the complex academic and social challenges associated with this developmental epoch.[20,21] This period, with its greater demands for self-regulation and self-organization, may be particularly challenging for Fontan patients.

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We report here on a cross-sectional study of adolescents who underwent the Fontan procedure to palliate complex CHD. Neurodevelopmental outcomes and anatomic brain magnetic resonance imaging (MRI) at 10 to 19 years of age are compared with those of normative populations or those of a locally recruited healthy adolescent referent group. We hypothesized that patients whose first operation was a Norwood procedure versus another operation would have worse neurodevelopmental outcomes because of a greater likelihood of disturbed cerebral perfusion in utero and of neonatal open heart surgery. In addition, we report on operative, medical, and genetic risk factors for worse neurodevelopmental outcomes in these patients.

Methods

Subjects

We enrolled Fontan subjects from 2010 to 2012 at a single institution. Inclusion criteria were (1) age 10 to 19 years at the time of enrollment, (2) diagnosis of single ventricle lesion, and (3) history of Fontan procedure. We excluded patients who met any of the following criteria: (1) disorders that would prevent successful completion of the planned study testing (eg, pacemaker, metal implants preventing MRI); (2) lack of reading fluency by primary caregiver in English, which is the only language for which questionnaires have been validated; (3) foreign residence; (4) cardiac transplantation; and (5) cardiac surgery within 6 months of testing. The study was approved by the institutional review board, and we obtained informed consent of parent or guardian (for subjects aged <18 years) or of subjects (aged ≥18 years), as well as assent of study participants aged <18 years. A separate informed consent was obtained from parents to obtain their DNA.

We also recruited healthy referent subjects of a similar age from local pediatric practices, from our institutional adolescent clinic, and through posted notices. Because these subjects were recruited primarily for the purpose of comparing brain MRI, we applied exclusion criteria derived from the National Institutes of Health's MRI study of normal brain development.[22] Data from these referent subjects were also used for comparison with Fontan subjects on psychometric tests for which normative data are not available.

Medical Data Obtained

By using medical record reviews, questionnaires, and family interviews, we recorded data on family history, events before the first operation, the number and types of cardiovascular interventions, intraoperative variables for all operations (eg, total support and circulatory arrest times), and major postoperative or postcatheterization complications (eg, cardiac arrest, need for extracorporeal membrane oxygenation, mediastinitis, necrotizing enterocolitis, prolonged intensive care unit course [>1 week], renal failure [serum creatinine >1.5 mg/dL], reoperation/exploration, seizure, stroke, and ventricular tachycardia). We also recorded concurrent comorbidities, including but not limited to ventricular and atrial arrhythmia, New York Heart Association (NYHA) functional class, thrombosis, stroke, seizure, protein-losing enteropathy, cirrhosis, and plastic bronchitis. Subjects with single-ventricle lesions were classified into those who had or had not undergone the Norwood procedure before the Fontan procedure.

Neuropsychological Assessment

The assessment battery included tests of general intelligence, academic achievement, memory, executive functions, visuospatial skills, attention, and social cognition. The specific assessments administered, and the scores derived from each, are described next.

General intelligence

The Wechsler Intelligence Scale for Children–Fourth Edition[23] was administered to adolescents <17 years old, and the Wechsler Adult Intelligence Scale–Fourth Edition[24] to adolescents 17 to 19 years of age. The end points considered were the 5 composite scores of Full-Scale IQ, Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed (all with an expected mean 100, SD 15).

Academic achievement

Each adolescent's Reading and Mathematics Composite scores (expected mean 100, SD 15 for both) of the Wechsler Individual Achievement Test–Second Edition[25] were calculated. Tables provided in the Wechsler Intelligence Scale for Children–Fourth Edition Technical Manual were used to identify individuals for whom a Wechsler Individual Achievement Test–Second Edition score was significantly higher or lower than would be predicted based on the Full-Scale IQ score.

Memory

For adolescents <17 years of age, scores on the core subtests (Dot Locations, Stories, Faces, and Word Pairs) of the Children's Memory Scale[26] were combined to obtain the General Memory Index (expected mean 100, SD 15). For adolescents who were at least 17 years of age, the core subtests (Logical Memory, Verbal Paired Associates, Designs, and Visual Reproduction) and 2 additional subtests (Spatial Addition and Symbol Span) of the Wechsler Memory Scale–Fourth Edition[27] were administered. Scores were combined to

calculate an overall memory score (expected mean 100, SD 15).

Executive functions

An executive function summary score was calculated by averaging an adolescent's scores on 5 subtests of the Delis–Kaplan Executive Function System[28]: Verbal Fluency (mean score on the letter and semantic fluency trials), Design Fluency (primary combined measure), Sorting (combined conditions score), Word Context (consecutively correct score), and Tower (total achievement score). The expected mean score is 10. Three informants (parent, teacher, self) completed the Behavior Rating Inventory of Executive Function (BRIEF).[29,30] For each informant, the General Executive Composite score was analyzed. The expected mean score is 50 (SD 10), with a higher score indicating less optimal function.

Visuospatial skills

A visuospatial composite score was calculated by averaging an adolescent's scores on 3 subscales (Memory, Sequential Memory, and Closure) of the Test of Visual-Perceptual Skills (nonmotor) (Upper Level)–Revised.[31] The expected mean score is 100 (SD 15). In addition, the copy and immediate recall trials of the Rey–Osterrieth Complex Figure were administered to each adolescent. For each trial, an overall Organization score and scores for Structural Elements and Incidental Elements were derived by using the Developmental Scoring System.[32] Each adolescent also completed the Sense of Direction Scale, which assesses environmental spatial ability.[33]

Attention

The ADHD Index T score yielded by the parent-completed Conners' ADHD/Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition[34] served as the primary measure of attention. The expected mean is 50 (SD 10), with higher scores indicating greater attention problems.

Social cognition

Three assessments of social cognition were administered. The Reading the Mind in the Eyes Test–Revised[35] indicates skill at identifying others' emotional states (higher score is better). The Toronto Alexithymia Scale[36] assesses the ability to identify and label one's own emotions. A total score is calculated from 3 subscales: Difficulty Identifying Feelings, Difficulty Describing Feelings, and Externally-Oriented Thinking. Higher scores suggest greater difficulties. The Autism Spectrum Quotient[37] indicates autistic tendencies (higher score is worse, ie, greater autistic tendencies).

Magnetic Resonance Imaging

MRI was performed on 1 of 2 systems: a 3-T General Electric system (General Electric Medical Systems) or, for patients in whom cardiovascular devices or coils had been implanted, a 1.5-T General Electric Twinspeed magnetic resonance scanner. MRI methods using the 1.5-T scanner have previously been described.[20,21] Subjects were scanned without the use of sedation. The T1-weighted acquisition used a 3-dimensional spoiled gradient recalled steady state sequence with the following parameters: repetition time/echo time=7/2.8 ms; flip angle=8°; and voxel size=1 mm^3 isotropic. The susceptibility sensitive T2-weighted acquisition consisted of multiplanar gradient recalled axial sequences with repetition time/echo time=600/40 ms; flip angle=30°; slice thickness=5 mm (with 1-mm gap); and voxel size=$0.8594\times0.8594\times6$ mm^3 chosen to maintain a streamlined total scan time.

Brain MRI results were read by a single blinded neuroradiologist (R.L.R.). Images were assessed by visual inspection to rate the quality of data and to identify abnormalities. Abnormalities were classified by origin (acquired or developmental), type (infarction, mineralization, iron deposition, myelination delay, ventriculomegaly, or abnormal T2-weighted signal hyperintensity), extent (focal or diffuse), and anatomic location.

Genetics Evaluation

Genetics evaluation of the Fontan patients included examination by a clinical geneticist (A.E.R.), medical record review, and blood sampling for a chromosomal microarray, performed on an oligonucleotide-based Agilent 244k platform array that detected deletions or duplications at multiple targeted sites throughout the genome. It contained probes to detect copy number changes as small as 150 kb between the target regions. We classified subjects as having a possible or definite genetic abnormality if they met $\geq$1 of the following criteria: a relevant known genetic diagnosis at time of enrollment, a pathogenic variant on array, a variant of unknown significance on array, and/or syndromic presentation (defined as dysmorphic features and/or extracardiac birth defects).

Statistical Methods

Comparisons of operative and medical risk factors, special services, and MRI findings were performed by using Fisher's exact tests for categorical measures and either ANOVA for continuous measures (when normally distributed) or Kruskal–Wallis tests (when non-normal). Comparisons of NYHA functional class were made with Cochran–Armitage trend tests. Neuropsychological outcomes of Fontan adolescents,

collectively and stratified by Norwood procedure, were compared with available expected population means by using 1-sample *t* tests. Linear regression with adjustment for concurrent family social status (ie, Hollingshead Four-Factor Index of Social Status) was used to compare neuropsychological outcomes of Fontan adolescents with those of the referent group when a population mean was not available (ie, Rey–Osterrieth Complex Figure, Sense of Direction Scale, Reading the Mind in the Eyes Test–Revised, Toronto Alexithymia Scale, Autism Spectrum Quotient), as well as for comparisons between Norwood groups.

We used linear regression analyses to identify earlier risk factors for neuropsychological outcomes in Fontan adolescents among the predictors listed in Table 1 (except cardiac diagnosis, continuous age at operation, indicator for use of deep hypothermic circulatory arrest at first operation, NYHA functional class, and use of special services) after adjusting for family social status and Norwood procedure. We did not adjust for the large number of types of anatomic heart disease because, with the exception of HLHS, the number of patients in each category was small, and the type of heart lesion and surgical variables were collinear. For closed procedures, values of deep hypothermic circulatory arrest and total support duration were set to 0. Predictors associated with neuropsychological outcomes at a level of $P<0.20$ were considered for stepwise backward regression, for which $P<0.05$ served as the significance criterion while adjusting for family social status and Norwood procedure. A similar procedure was used to identify factors predicting MRI outcomes by using logistic regression while adjusting for genetic abnormality.

Results

Cardiac Status and History

Among 362 Fontan adolescents who met the eligibility criteria, 116 (32%) were followed at other institutions or lost to follow-up. Of the 246 invited to participate, 90 (35%) declined to participate. Patients who consented versus declined did not differ in sex, race, or diagnosis of HLHS. Our study cohort consisted of the remaining 156 adolescents, as well as 111 referent subjects. Table 1 summarizes the medical histories of the Fontan adolescents. Most (64%) had undergone staged palliation, with a median of 3 operations (range 1–5), and 40% had HLHS or another single right ventricle anomaly requiring the Norwood procedure.

Compared with referent subjects, Fontan subjects had lower birth weight (3.3±0.6 versus 3.5±0.6 kg, $P=0.01$), were of younger gestational age (38.9±2.2 versus 39.6±1.3 weeks, $P=0.007$), were more likely to be white (93% versus 83%, $P=0.03$), had lower concurrent family social status (50±13 versus 53±10, $P=0.02$), and were significantly younger at developmental testing (14.5±2.9 versus 15.3±1.8 years, $P=0.008$), but they had similar distributions of sex and ethnicity. Fontan adolescents who underwent the Norwood procedure, compared with those who did not, were less likely to have genetic abnormalities ($P=0.02$), were more likely to have had neonatal heart surgery ($P<0.001$), were more likely to have had a first operation that was performed on bypass ($P<0.001$), had longer deep hypothermic circulatory arrest and total support durations at first operation ($P<0.001$ each), and had more operative complications ($P<0.001$).

Most Fontan adolescents were in NYHA functional class II (63%), while 29% were in class I, and 8% were in class III. None were in class IV. In contrast, most referent subjects were in NYHA functional class I (95%), with the remaining 5% in class II ($P<0.001$). NYHA functional class did not differ between Fontan patients who had undergone the Norwood procedure versus those who had not.

Among Fontan adolescents, medical histories included seizures (n=23, 15%), stroke (n=19, 12%), choreoathetosis (n=1, 1%), and meningitis (n=1, 1%). Parents reported that 22% (n=34) had been diagnosed with ADHD and 37% (n=57) with a learning disability. Medications in the Fontan group included therapies for attention-deficit disorder or ADHD (n=15, 10%) and psychotropic agents (n=13, 8%). Three Fontan adolescents (2%) reported use of both ADHD and psychotropic medications.

Genetics Evaluation

Of 156 enrolled subjects, 6 had a genetic diagnosis at the time of enrollment (22q11 deletion, CHARGE syndrome [represents coloboma, heart defect, atresia choanae (also known as choanal atresia), retarded growth and development, genital abnormality, and ear abnormality], hyperphenylalaninemia, Kartagener syndrome, and 2 cases of VACTERL [vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities]), and 134 had a physical examination completed by a medical geneticist (A.E.R.) and array comparative genomic hybridization (CGH) analysis. Ten percent were classified as having a definite genetic abnormality (6 subjects with a genetic diagnosis at the time of enrollment and 10 subjects with a pathogenic variant on array CGH). An additional 31% were classified as having a possible genetic abnormality (17 with a variant of unknown significance on array CGH and 32 with normal array but syndromic features). The Norwood and non-Norwood groups did not differ significantly with respect to genetic diagnosis at the time of enrollment or abnormal array CGH. However, the Norwood group was less likely to have

Table 1. Characteristics of Fontan Adolescents

Variable	All (N=156)	Norwood (n=63)	Non-Norwood (n=93)	*P* Value
	Percent, Mean±SD, or Median (IQR)			
Preoperative characteristics				
Birth weight, kg	3.3±0.6	3.4±0.6	3.2±0.7	0.09
Gestational age, wk	38.9±2.2	39.2±2.0	38.8±2.4	0.27
Male	61	67	57	0.25
Race				0.15
Asian	3	0	4	
Black	4	6	3	
White	93	94	92	
Hispanic ethnicity	12	10	14	0.46
Cardiac diagnosis				<0.001
HLHS	26	65	0	
Tricuspid atresia	19	14	23	
DORV	12	6	16	
DILV	12	13	11	
Heterotaxy syndrome	11	2	17	
Complex TGA	8	0	13	
PA/IVS	6	0	11	
Unbalanced AV canal	3	0	4	
Mitral atresia	1	0	2	
Other	2	0	3	
Genetic abnormality	42	30	49	0.02
Status at first operation				
Age, d	6 (3–22)	5 (3–8)	7 (3–87)	0.01
Neonatal status, age ≤30 d	78	95	67	<0.001
Open procedure	59	100	31	<0.001
Patients undergoing DHCA (if open)	71	91	15	<0.001
DHCA duration, min (if open)	42 (0–56)	49 (33–58)	0 (0–0)	<0.001
Total support duration, min (if open)	121 (99–141)	125 (115–150)	81 (66–107)	<0.001
No. of operative complications				<0.001
0	43	17	61	
1	22	22	22	
≥2	35	60	16	
Medical history				
Total No. of operations				<0.001
1 or 2	18	3	28	
3	64	84	51	
4 or 5	18	13	22	
Total No. of open operations				<0.001
1	9	0	15	
2	39	3	63	
≥3	52	97	22	

Continued

Table 1. Continued

Variable	All (N=156)	Norwood (n=63)	Non-Norwood (n=93)	*P* Value
	Percent, Mean±SD, or Median (IQR)			
Total No. of operative complications				<0.001
0	15	5	23	
1 to 5	67	67	68	
≥6	17	29	10	
Total No. of catheterizations				0.56
1 or 2	11	14	9	
3 to 5	69	67	70	
≥6	21	19	22	
Total No. of catheterization complications				0.97
0	49	51	48	
1 or 2	40	40	41	
≥3	10	10	11	
New York Heart Association functional class				0.16
I	29	25	31	
II	63	62	63	
III	8	13	5	
Seizure	15	24	9	0.01
Any neurological event*	25	31	22	0.26
Use of special services	86	90	83	0.24
Tutoring	56	65	49	0.07
Grade retention	23	21	25	0.70
Early intervention	57	60	55	0.51
Occupational therapy	54	62	48	0.10
Physical therapy	51	62	44	0.03
Special education	35	44	29	0.06
Psychotherapy and counseling	45	49	42	0.41
Family social status†	50±13	48±13	51±13	0.09
Age at developmental testing, y	14.5±2.9	14.1±2.8	14.7±3.1	0.22

Values are represented as percentages, mean±SD, or median (IQR). *P* values are determined by Fisher's exact tests for categorical variables (except for New York Heart Association class, which used a Cochran–Armitage trend test), analysis of variance for variables with means reported, and Kruskal–Wallis tests for variables with medians reported. AV indicates atrioventricular; DHCA, deep hypothermic circulatory arrest; DILV, double inlet left ventricle; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; PA/IVS, pulmonary atresia with intact ventricular septum; TGA, transposition of the great arteries.

*Includes stroke, seizure, choreoathetosis, and meningitis.

†Score on Hollingshead Four Factor Index of Social Status, with higher scores indicating higher social status.

syndromic features than were the non-Norwood group (18% versus 42%, *P*=0.003).

On array CGH, 7 Fontan subjects had 2 abnormalities, 2 subjects had 3 abnormalities, and 1 subject had 4 abnormalities, for a total of 55 variants in 41 probands (Table 2). Of the variants, 25% were judged to be pathogenic (3 syndromic subjects and 7 nonsyndromic subjects); 44% were variants of unknown significance (7 syndromic subjects and 12 nonsyndromic subjects); and 31% were thought to be likely benign (5 syndromic subjects and 12 nonsyndromic subjects). The overall rate of pathogenic copy number variant (CNV) detection was 7% (10/134). Of the pathogenic variants, 7 were thought to explain the CHD (3 cases of hypoplastic right ventricle, 3 cases of hypoplastic left ventricle, and 1 case of tricuspid atresia). The remaining 3 CNVs were clinically significant for extracardiac anomalies but without a clear association to CHD based on the published literature and what is known biologically about the genes in the region. The

Table 2. Abnormalities of Fontan Subjects Who Completed Array Comparative Genomic Hybridization Analysis

Proband	Cardiac Diagnosis	Array Result	Size	Syndromic
Variant known to be pathogenic for congenital heart disease (7 probands, 11 variants)				
1a	PA/IVS	2p16.2-p14 LOH	12.6 Mb	Y
1b		5q14.1-q22.1 LOH	30.2 Mb	
1c		12p13.1-p12.1 LOH	11.3 Mb	
1d		13q12.13-q13.3 LOH	9.8 Mb	
2a	DILV	4q35.1q35.2 del	4.6 Mb	N
2b		4q35.1 dup	509 kb	
3	HLHS	2q13 dup	2.2 Mb	N
4	PA/IVS	3q28 del	313 kb	N
5a	HLHS	7q36.3 del	2.4 Mb	N
6a	Tricuspid atresia	9q31.2 dup	219 kb	Y
7	HLHS	15q11.2 del	257 kb	N
Variant known to be pathogenic for extracardiac disease (3 probands)				
8	Complex TGA	15q13.2-q13.3 dup	1.5 Mb	N
9a	Complex TGA	16p11.2 del	220 kb	Y
10a	HLHS	17p13.2 del	76 kb	N
Benign variant (inherited, no family history of congenital heart disease; 17 probands)				
11	DORV	2p16.3 dup	75 kb	N
12	HLHS	2p24.3 del	210 kb	N
5b	HLHS	3p11.1 dup	983 kb	N
13	Tricuspid atresia	6q21 dup	438 kb	Y
14	Heterotaxy syndrome	8p22 dup	249 kb	Y
15	PA/IVS	8q24.21 dup	274 kb	Y
6b	Tricuspid atresia	9q33.1 dup	672 kb	Y
16	HLHS	10q21.3 dup	1.9 Mb	N
17	Tricuspid atresia	10q24.2 del	251 kb	N
18	DILV	14q11.2 dup	12 kb	N
10b	HLHS	15q15.3 del	248 kb	N
19	HLHS	15q21.2 dup	308 kb	Y
20	Tricuspid atresia	16p13.2 dup	159 kb	N
21	HLHS	16p13.3 del	265 kb	N
22	HLHS	20p11.23 dup	453 kb	N
22sib	HLHS	20p11.23 dup	453 kb	N
23	HLHS	Xp11.4 dup	191 kb	N
24	HLHS	Xq21.1 dup	105 kb	N
Variant of unknown significance (19 probands. 24 variants)				
25a	DORV	6q26 dup	98 kb	Y
25b		Yq11.21 dup	126 kb	
25c		Yq11.21 dup	290 kb	
26a	DORV	1q21.3 dup	728 kb	N
26b		11p11.2 del	19 kb	

Continued

Table 2. Continued

Proband	Cardiac Diagnosis	Array Result	Size	Syndromic
27a	Complex TGA	2p22.1 dup	361 kb	N
27b		7q36.3 dup	323 kb	
28a	Heterotaxy syndrome	11q14.1-q14.2 del	1.2 Mb	Y
28b		22q13.2	52 kb	
29	Tricuspid atresia	1q42.2 dup	89 kb	N
30	Heterotaxy syndrome	2q31.2 dup	627 kb	Y
31	DORV	3p21.31 dup	251 kb	Y
32	Tricuspid atresia	3p26.1 dup	68 kb	N
9b	Complex TGA	4p15.2 del	375 kb	Y
33	Mitral atresia	6q24.3 del	58 kb	N
34	HLHS	7p14.1 dup	271 kb	N
35	HLHS	8q22.1 del	412 kb	N
36	HLHS	10q26.2 del	127 kb	N
37	Heterotaxy syndrome	15q23 dup	276 kb	Y
38	Mitral atresia	15q25.2 del	105 kb	N
39	Tricuspid atresia	18p11.31 dup	421 kb	N
40	DILV	18p11.32-p11.31 del	3.7 Mb	Y
2c	DILV	21q22.11 dup	112 kb	N
41	Tricuspid atresia	Xp22.31 dup	1.6 Mb	N

DILV indicates double inlet left ventricle; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; LOH, loss of heterozygosity; PA/IVS pulmonary atresia with intact ventricular septum; TGA, transposition of the great arteries.

syndromic and nonsyndromic groups did not differ significantly in their prevalence of CNVs (any type) or pathogenic CNVs. There were 20 deletions reported, none recurrent, ranging in size from 19 kb to 4.6 Mb. There were 31 duplications reported, none recurrent, ranging in size from 12 kb to 2.2 Mb.

Compared with Fontan adolescents without genetic abnormalities, those with definite or possible genetic abnormalities were more likely to have received special services, including early intervention, occupational therapy, physical therapy, special education, and psychotherapy or counseling (data not shown). Because we grouped those with definite and possible genetic abnormalities together in the "genetic abnormality group," our analysis may underestimate the effect of a genetic diagnosis on neuropsychological outcomes.

Neuropsychological Assessment

Table 3 presents the neuropsychological scores of all Fontan adolescents, collectively and stratified by Norwood procedure, along with the results of comparisons with the expected population mean scores and the scores of the referent group. Table 4 presents the percentages of adolescents in the Norwood and non-Norwood groups with neuropsychological scores that were >1 or >2 SDs below the expected mean and parent or teacher ratings of executive function that were in the range considered to be clinically significant. As the tables illustrate, the scores of the Fontan group as a whole on most tests were significantly worse than the expected population means or the scores of the referent group. Therefore, the following section focuses on comparisons of the scores of the Norwood and non-Norwood groups.

General Intelligence

The Norwood group scored lower than the non-Norwood group on all composites except Working Memory. More than 2 (43%) in 5 of the Norwood group had a Full-Scale IQ score ≤85 (compared with an expected frequency in the general population of 16%) and 17% scored ≤70 (compared with the expected 2%). One (24%) in 4 adolescents in the non-Norwood group had a Full-Scale IQ score ≤85 and 8% scored ≤70.

Academic Achievement

Reading and Mathematics Composite scores were significantly lower for the Norwood group than for the

Table 3. Neuropsychological Outcomes of Fontan Adolescents

Variable	All (N=156) Mean±SD	Norwood (n=63) Mean±SD	Non-Norwood (n=93) Mean±SD	*P* Value, All Fontan Versus Referent*	*P* Value, Norwood Versus Non-Norwood*	*P* Value, Norwood Versus Expected Population Mean†	*P* Value, Non-Norwood Versus Expected Population Mean†
Wechsler Intelligence Scales, Combined							
Full-Scale IQ	91.6±16.8	86.0±17.6	95.5±15.2	<0.001	0.001	<0.001	0.005
Verbal Comprehension	97.6±15.4	91.1±15.7	101.9±13.6	<0.001	<0.001	<0.001	0.17
Perceptual Reasoning	92.6±16.3	88.6±17.4	95.3±15.1	<0.001	0.02	<0.001	0.004
Working Memory	92.7±15.8	89.8±15.9	94.7±15.5	<0.001	0.12	<0.001	0.001
Processing Speed	87.4±16.4	83.0±16.7	90.4±15.5	<0.001	0.009	<0.001	<0.001
Wechsler Individual Achievement Test							
Reading Composite	91.9±17.2	87.3±18.0	95.0±16.1	<0.001	0.02	<0.001	0.004
Mathematics Composite	92.0±22.9	85.8±22.9	96.1±22.1	<0.001	0.02	<0.001	0.09
Children's Memory Scale General Memory Index‡	93.9±21.5	89.3±23.4	97.3±19.3	0.001	0.10	0.002	0.25
Wechsler Memory Scale Composite§	87.4±16.1	80.7±17.6	90.3±14.8	<0.001	0.09	0.005	0.003
Executive Function Summary Score	8.6±2.2	8.1±2.3	8.9±2.1	<0.001	0.0499	<0.001	<0.001
Behavior Rating Inventory of Executive Function							
Parent	57.6±12.1	58.7±11.8	56.8±12.3	<0.001	0.46	<0.001	<0.001
Teacher	60.9±16.0	63.6±16.1	58.9±15.8	0.003	0.17	<0.001	<0.001
Self-report‖	49.9±11.4	51.1±11.9	49.2±11.1	<0.001	0.48	0.53	0.53
Test of Visual-Perceptual Skills Composite¶	85.2±17.9	81.9±18.3	87.5±17.4	<0.001	0.20	<0.001	<0.001
Rey–Osterrieth Complex Figure#							
Copy: Organization	6.7±3.3	5.8±3.0	7.4±3.4	<0.001	0.007	<0.001	<0.001
Structural Element	24.0±2.4	23.2±3.5	24.6±1.1	<0.001	0.001	<0.001	0.01
Incidental Element	37.2±3.6	36.2±4.5	37.8±2.7	<0.001	0.006	<0.001	<0.001
Immediate Recall: Organization	5.6±3.5	4.5±3.3	6.4±3.5	<0.001	0.003	<0.001	<0.001
Structural Element	19.3±5.4	17.5±6.4	20.5±4.3	<0.001	0.001	<0.001	<0.001
Incidental Element	24.6±8.5	22.1±8.8	26.2±8.0	<0.001	0.002	<0.001	0.004
Sense of Direction Scale#	44.6±10.7	43.6±11.4	45.3±10.2	0.002	0.29	0.003	0.02
Parent Conners' ADHD Index T Score	60.0±13.4	61.6±13.7	58.9±13.2	<0.001	0.34	<0.001	<0.001
Reading the Mind in the Eyes Test Score#	18.6±5.9	16.9±5.8	19.6±5.8	<0.001	0.02	<0.001	<0.001
Toronto Alexithymia Scale Total Score#	50.8±10.9	52.2±12.2	50.0±10.0	0.02	0.24	0.04	0.07
Autism Spectrum Quotient#	17.5±5.2	18.8±5.7	16.7±4.6	<0.001	0.03	<0.001	0.02

Values are mean±SD. Missing <10% of outcomes except for Behavior Rating Inventory of Executive Function–Teacher (Fontan: n=90; referent: n=42), Test of Visual-Perceptual Skills (Fontan: n=93; referent: n=96), Reading the Mind in the Eyes (Fontan: n=140; referent: n=98), and the Toronto Alexithymia Scale (referent: n=66) tasks. ADHD indicates attention-deficit/hyperactivity disorder.

**P* values are determined by linear regression with adjustment for concurrent family social status.

†*P* values are determined by 1-sample *t* tests comparing the Fontan group with expected population means of 100, 10, or 50, as appropriate.

‡Outcomes are based on those Fontan subjects (n=120) and referents (n=97) aged <17 years.

§Outcomes are based on those Fontan subjects (n=36) and referents (n=14) aged ≥17 years.

‖Outcomes are based on those Fontan subjects (n=134) and referents (n=109) aged ≥11 years.

¶Outcomes are based on those Fontan subjects (n=119) and referents (n=105) aged ≥12 years.

#Expected population means are not available; *P* values are determined by linear regression comparing the Fontan group and the referent group with adjustment for concurrent family social status.

Table 4. Percentages of Fontan Adolescents With Extreme Scores

Variable	All (N=156)	Norwood (n=63)	Non-Norwood (n=93)	*P* Value, Norwood Versus Non-Norwood*
	%			
Wechsler Intelligence Scales, Combined: Full-Scale IQ				
≤85	31	43	24	0.01
≤70	12	17	8	0.07
Wechsler Individual Achievement Test				
Reading Composite				
≤85	29	42	20	0.006
≤70	12	18	8	0.07
Mathematics Composite				
≤85	35	47	27	0.02
≤70	19	23	17	0.41
Children's Memory Scale General Memory Index†				
≤85	34	41	28	0.17
≤70	18	25	12	0.09
Wechsler Memory Scale Composite‡				
≤85	39	64	28	0.07
≤70	14	27	8	0.15
Executive Function Summary Score				
≤7	23	35	14	0.003
≤4	5	5	4	1.0
Behavior Rating Inventory of Executive Function				
Parent, ≥65	33	35	32	0.73
Teacher, ≥65	34	44	27	0.12
Self-Report, ≥65	11	12	10	1.0
Parent Conners' ADHD Index T Score, >65	33	40	29	0.16

Values are percentages. Missing <10% of outcomes except for Behavior Rating Inventory of Executive Function–Teacher (n=90) task. ADHD indicates attention-deficit/hyperactivity disorder.

**P* values are determined by Fisher's exact tests.

†Outcomes are based on those Fontan subjects (n=120) aged <17 years.

‡Outcomes are based on those Fontan subjects (n=36) aged ≥17 years.

non-Norwood group (*P*=0.02 for both). Among the Norwood adolescents, 42% scored ≤85 and 18% scored ≤70 on the Reading Composite. On the Mathematics Composite, 47% scored ≤85 and 23% scored ≤70. For nearly one-third (31%) of those who had undergone the Norwood procedure as neonates, the Reading Composite score was significantly lower than would be expected based on the Full-Scale IQ score, while the corresponding figure for the Mathematics Composite score was 39%. One (20%) in 5 adolescents in the non-Norwood group scored ≤85 on the Reading Composite and 8% scored ≤70. The corresponding figures for Mathematics Composite scores were 27% and 17%, respectively. On the Reading Composite, 26% scored significantly lower than expected based on Full-Scale IQ, and 31% scored significantly lower than expected on the Mathematics Composite.

Memory

The overall mean scores of adolescents in the Norwood and non-Norwood groups did not differ significantly, though the mean scores of the Norwood group were ≈0.5 SD lower for both age groups. In the Norwood group on the Children's Memory Scale, ≈2 (41%) in 5 scored ≤85 and 25% scored ≤70, while in the non-Norwood group, 28% scored ≤85 and 12% scored ≤70. On the Wechsler Memory Scale, 64% of the Norwood group scored ≤85 and 27% scored ≤70, while in the Norwood group, 28% scored ≤85 and 8% scored ≤70.

Executive Functions

The mean executive function summary score of the Norwood group was lower than the mean score of the non-Norwood group ($P<0.05$). In the Norwood group, 35% scored ≥3 points below 10 (ie, ≈>1 SD), and 5% scored ≥6 points below 10 (ie, ≈>2 SDs). In the non-Norwood group, 14% scored ≥3 points below the expected mean and 4% scored ≥6 points below the expected mean. On the BRIEF, the mean General Executive Composite scores of the Norwood and non-Norwood groups did not differ significantly for any of the 3 informants, though the scores of the Norwood group tended to be somewhat higher. On the parent BRIEF, 35% of the Norwood group scored ≥65 (ie, "potential clinical significance"), compared with 32% of the non-Norwood group. On the teacher BRIEF, these figures were 44% and 27%, respectively, and on the self-report BRIEF, they were 12% and 10%, respectively.

Visuospatial Skills

The scores of the Norwood and non-Norwood groups did not differ significantly for the Test of Visual-Perceptual Skills summary or the Sense of Direction Scale, but the Norwood group did score lower on all scales of both the copy and immediate recall trials of the Rey–Osterrieth Complex Figure ($P=0.001$ to 0.007).

Attention

Although the mean score of the Norwood group was higher than that of the non-Norwood group, the difference was not significant. Approximately 2 (40%) in 5 of adolescents in the Norwood group and 29% of adolescents in the non-Norwood group scored ≥66, which is considered to be "moderately atypical."

Social Cognition

The scores of the Norwood and non-Norwood groups did not differ significantly on the Toronto Alexithymia Scale (total score), but the Norwood group did score significantly worse on the Reading the Mind in the Eyes Test–Revised ($P=0.02$) and the Autism Spectrum Quotient ($P=0.03$).

MRI Data

MRI data were available for 144 adolescents who underwent the Fontan procedure and 105 referents. The frequency of any abnormality was 11-fold greater among the patients than the referents (66% versus 6%, $P<0.001$; Table 5). The majority of abnormalities were focal or multifocal, with most involving brain mineralization or iron deposits, and 19 (13%) patients had evidence of a stroke. Among these, stroke had been previously diagnosed in only 12 patients (60%). Diffuse

Table 5. Structural Magnetic Resonance Imaging Findings of Fontan and Referent Adolescents

Variable	Fontan				*P* Value, All Fontan Versus Referent	*P* Value, Norwood Versus Non-Norwood
	All (n=144)	Norwood (n=59)	Non-Norwood (n=85)	Referent (n=105)		
	n/Total N (%)					
Any abnormality	69/105 (66)	30/42 (71)	39/63 (62)	6/94 (6)	<0.001	0.40
Focal or multifocal abnormality	64/106 (60)	27/42 (64)	37/64 (58)	1/94 (1)	<0.001	0.55
Focal infarction or atrophy	19/144 (13)	7/59 (12)	12/85 (14)	0/105 (0)	<0.001	0.80
Brain mineralization/iron deposit	57/106 (54)	23/42 (55)	34/64 (53)	1/94 (1)	<0.001	1.0
Diffuse abnormality	12/133 (9)	6/53 (11)	6/80 (8)	2/104 (2)	0.03	0.54
Myelination delay	0/144 (0)	0/59 (0)	0/85 (0)	0/104 (0)	—	—
Ventriculomegaly	3/144 (2)	1/59 (2)	2/85 (2)	0/104 (0)	0.27	1.0
Abnormal T2 hyperintensities	9/133 (7)	5/53 (9)	4/80 (5)	2/105 (2)	0.12	0.48
Generalized abnormality	0/144 (0)	0/59 (0)	0/85 (0)	0/104 (0)	—	—
Developmental abnormality	6/144 (4)	1/59 (2)	5/85 (6)	4/104 (4)	1.0	0.40
Major malformation*	1/144 (1)	0/59 (0)	1/85 (1)	0/104 (0)	1.0	1.0
Minor malformation†	5/144 (3)	1/59 (2)	4/85 (5)	4/104 (4)	1.0	0.65

Values are n/total N (%). *P* values are determined by Fisher's exact tests.

*The major malformation is agenesis of the corpus callosum.

†Minor malformations include arachnoid cyst, absent septal leaflets, pericallosal lipoma, and periventricular cycts in the left and right frontal lobes in the Fontan group and polymicrogyria, Chiari malformation, developmental venous anomaly in the right parietal lobe, and pineal cyst in the referent group.

abnormalities were also more common in the Fontan group (9% versus 2%, P=0.03), with the majority consisting of abnormal T2-weighted hyperintensities. The Norwood and non-Norwood groups did not differ in the frequency of MRI abnormalities.

Predictors of Neuropsychological and MRI Outcomes

Risk factors of selected neuropsychological test scores, after adjustment for concurrent family social status and Norwood status, are presented in Table 6. Longer total support or deep hypothermic circulatory arrest duration at first operation was significantly associated with lower scores on each of the Wechsler Intelligence Scale composites ($P \leq 0.01$ for each). Executive functions, as measured by both parent and teacher BRIEFs, was worse (ie, higher scores) in patients with ≥6 operative complications, compared with those with no complications (P=0.02 and 0.006, respectively). Scores on several end points were worse among patients who were of Hispanic ethnicity, had a possible or definite genetic abnormality, required more operations, experienced more operative complications, required more catheterizations, experienced more catheterization complications, were of younger gestational age, had an open first operation (versus shunt), had occurrence of seizure, and were younger at developmental testing.

Stepwise logistic regression analyses were conducted of 4 MRI end points (any abnormality, focal/infarction or atrophy, brain mineralization/iron deposit, any diffuse abnormality). The odds of any diffuse abnormality were associated with operative complications (P=0.009), with marginally greater odds among patients who had ≥6 operative complications compared with those with no operative complications (odds ratio=7.8, 95% CI 0.8 to 71.9, P=0.07) and significantly greater odds compared with those with 1 to 5 operative complications (odds ratio=7.0, 95% CI 1.9 to 25.9, P=0.004) after adjusting for the presence of a genetic abnormality. We did not find any statistically significant risk factors for the categories of any abnormality, focal/infarction or atrophy, or brain mineralization. The CIs for all odds ratios were wide, however, because of the small number of patients in many categories.

We also explored whether MRI findings added additional predictive ability to the models of neuropsychological test scores presented in Table 6. Focal infarction or atrophy predicted higher (worse) parent BRIEF scores (7.4±2.7, P=0.008), higher (worse) parent Conners' ADHD/Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition ADHD Index scores (8.3±3.1, P=0.008), and higher (worse) Autism Spectrum Quotient scores (2.8±1.3, P=0.03), relative to subjects without these MRI findings, respectively. The presence of brain hemosiderin/iron deposits was not a predictor of worse neurocognitive outcomes. The presence of diffuse abnormalities on anatomic MRI was not associated with any neurocognitive score, with limited power.

Discussion

In our study of adolescents who had undergone the Fontan procedure, we found that about two-thirds (66%) had an abnormality on structural brain MRI, and 13% showed evidence of a stroke. Fontan adolescents scored significantly lower than population norms and a healthy local referent group in all of the neuropsychological domains assessed, and scores of adolescents with HLHS or other single right ventricle abnormalities who underwent the Norwood procedure were generally lower than those of adolescents who did not undergo the Norwood procedure and were significantly lower in the domains of general intelligence, reading and math achievement, and executive function. Some aspects of neuropsychological function in Fontan patients appeared to be more impaired than others. In terms of intelligence, verbal skills appeared to be stronger than perceptual reasoning skills. Processing speed, which is based on the subtests of Coding and Symbol Search, was also a relative weakness. With regard to academic achievement, substantial percentages of adolescents had reading and mathematics skills that were significantly lower than expected based on their Full-Scale IQ scores. Fontan patients performed more poorly than referents in mnemonic function in what appeared to be a development-dependent fashion. In terms of executive functions, parents and teachers perceived greater executive dysfunction in the adolescents than did the adolescents themselves. As many studies of children with CHD have reported, visuospatial skills were particularly weak. The frequency of parent-reported ADHD-related behaviors was high.

Like children with other forms of CHD,[20,21] Fontan patients manifested difficulties in social cognition, scoring worse than the referents in their ability to identify the emotions behind facial expressions (Reading the Mind in the Eyes Test) and a dimensional assessment of the ability to recognize one's own emotions (Toronto Alexithymia Scale). Compared with referents, they showed concrete, "externally-oriented thinking" (eg, endorsing statements such as, "I prefer talking to people about their daily activities rather than their feelings" and "Looking for hidden meanings in movies or plays distracts from their enjoyment").

Abnormalities on MRI were detected at a frequency 11-fold higher in the Fontan patients than in the referents, with focal/multifocal abnormalities being much more common than diffuse abnormalities. Previous studies have

Table 6. Stepwise Linear Regression of Select Neuropsychological Outcomes of Fontan Adolescents (n=156), Adjusting for Concurrent Family Social Status and Norwood Status

Variable	Total Support Duration, min	Total DHCA Duration, min	Other Covariates
	β Estimate±SE (*P* Value)		
Wechsler Intelligence Scales, Combined*			
Full-Scale IQ	−0.09±0.03 (0.002)		Hispanic ethnicity: −7.7±3.7 (0.04) Genetic abnormality: −6.5±2.5 (0.009) Three total operations (vs <3): −8.6±3.6 (0.02) Four or 5 total operations (vs <3): −9.1±4.2 (0.03)
Verbal Comprehension	−0.07±0.03 (0.006)		Hispanic ethnicity: −9.6±3.1 (0.003) One or 2 catheterization complications (vs 0): −1.1±2.2 (0.63) Three or more catheterization complications (vs 0): −8.6±3.5 (0.01)
Perceptual Reasoning	−0.08±0.03 (0.006)		Genetic abnormality: −6.4±2.5 (0.01) Three total operations (vs <3): −10.6±3.6 (0.004) Four or 5 total operations (vs <3): −14.3±4.2 (<0.001)
Working Memory		−0.18±0.07 (0.01)	Gestational age (per week): 1.1±0.6 (0.049)
Processing Speed		−0.19±0.07 (0.01)	Genetic abnormality: −5.9±2.6 (0.02)
Wechsler Individual Achievement Test			
Reading Composite		−0.16±0.08 (0.04)	Seizure: −8.0±3.8 (0.04)
Mathematics Composite			One operative complication at first operation (vs 0): −6.9±4.3 (0.11) Two or more operative complications at first operation (vs 0): −15.5±4.2 (<0.001) Age at developmental testing (per year): −2.1±0.6 (<0.001)
Children's Memory Scale General Memory Index†			Birth weight (per kg): 6.2±2.9 (0.03) One to 5 operative complications (vs 0): 3.4±5.1 (0.51) Six or more operative complications (vs 0): −15.7±6.5 (0.02) One or 2 catheterization complications (vs 0): −9.0±3.8 (0.02) Three or more catheterization complications (vs 0): −8.5±5.7 (0.14) Seizure: −11.8±5.3 (0.03)
Wechsler Memory Scale Composite‡		−0.63±0.21 (0.006)	One operative complication at first operation (vs 0): −16.3±5.3 (0.006) Two or more operative complications at first operation (vs 0): −14.8±5.7 (0.02) One or 2 catheterization complications (vs 0): 7.3±4.5 (0.11) Three or more catheterization complications (vs 0): −27.0±11.9 (0.03)
Executive Function Summary Score	−0.01±0.004 (0.009)		Three total operations (vs <3): −1.1±0.5 (0.03) Four or 5 total operations (vs <3): −2.0±0.6 (0.001)
Behavior Rating Inventory of Executive Function			
Parent			Gestational age (per week): −1.0±0.4 (0.02) Hispanic ethnicity: 8.1±3.0 (0.007) One to 5 operative complications (vs 0): 1.9±2.8 (0.50) Six or more operative complications (vs 0): 8.0±3.5 (0.02)
Teacher			Open first operation (vs shunt): 10.7±5.4 (0.0496) One to 5 operative complications (vs 0): 6.8±5.4 (0.21) Six or more operative complications (vs 0): 18.9±6.7 (0.006)
Test of Visual-Perceptual Skills Composite§			Three to 5 catheterizations (vs <3): −2.5±4.9 (0.62) Six or more catheterizations (vs <3): −18.9±5.8 (0.002) Seizure: −10.0±4.8 (0.04)
Parent Conners' ADHD Index T Score			Hispanic ethnicity: 10.1±3.3 (0.003)
Reading the Mind in the Eyes Test Score	−0.02±0.01 (0.04)		Three to 5 catheterizations (vs <3): −4.9±1.7 (0.006) Six or more catheterizations (vs <3): −7.0±1.9 (<0.001) Age at developmental testing (per year): 0.9±0.2 (<0.001)

Continued

Table 6. Continued

Variable	Total Support Duration, min	Total DHCA Duration, min	Other Covariates
	β Estimate±SE (*P* Value)		
Toronto Alexithymia Scale Total Score			Hispanic ethnicity: 5.4±2.7 (0.04) Neonatal status: 6.5±2.2 (0.004)
Autism Spectrum Quotient		0.06±0.03 (0.02)	Genetic abnormality: 2.3±0.8 (0.007) Three total operations (vs <3): 3.8±1.2 (0.001) Four or 5 total operations (vs <3): 3.2±1.4 (0.02)

All characteristics from Table 1 were considered for inclusion in the regression models except cardiac diagnosis, continuous age at operation, indicator for use of DHCA at first operation, NYHA functional class, and use of special services. Coefficients for intercepts, concurrent family social status, and Norwood status are not reported. Missing <10% of outcomes except for the Behavior Rating Inventory of Executive Function–Teacher (n=90), Test of Visual-Perceptual Skills (n=93), and Reading the Mind in the Eyes (n=140) tasks. ADHD indicates attention-deficit/hyperactivity disorder; DHCA, deep hypothermic circulatory arrest; IQ, intelligence quotient; NYHA, New York Heart Association.

*Outcomes were also adjusted for type of test, either the Wechsler Intelligence Scale for Children or the Wechsler Adult Intelligence Scale.

†Outcomes are based on those Fontan subjects aged <17 years (n=120).

‡Outcomes are based on those Fontan subjects aged ≥17 years (n=36).

§Outcomes are based on those Fontan subjects aged ≥12 years (n=119).

reported that, as fetuses, patients with HLHS show reduced maturation and volumetric growth disturbances[38,39] and diffuse white matter injury.[40] Preoperative brain MRI studies have shown abnormalities of myelination, cortical infolding, involution of glial cell migration bands, and presence of germinal matrix tissue,[41] including periventricular leukomalacia.[38] In one study, nearly three-fourths of patients with HLHS showed new or worsened ischemic lesions (including periventricular leukomalacia) postoperatively.[42] For a substantial minority (40%) of the adolescents in our cohort who showed evidence of a stroke, this finding had not been previously reported, highlighting that its occurrence can be clinically silent.

Among those who underwent genetic evaluation and testing with chromosomal microarray, 7% had a pathogenic finding. There is limited information about the diagnostic yield of chromosomal microarray in CHD. De novo CNVs have been reported in HLHS.[43] Of the previously published loci thought to confer a significant risk for CHD,[44–46] 3 members of our cohort had overlapping CNVs: a 15q11.2 deletion previously reported in 12 cases with CHD,[44] a 2q13 duplication,[47] and a 4q35.1 terminal deletion previously associated with CHD.[48] The remaining 3 CNVs were not previously described, but unaffected parents were tested and all 3 were de novo rare CNVs (3q28 deletion, 7q36.3 deletion, and 9q31.2 duplication). Our 5% (7/134) pathogenic CNV detection rate for loci with significant risk for CHD is at the lower end of published estimates of 5% to 10%.[44,46–50] This is most likely because of the relatively high number of variants of unknown significance for which parent samples were not available to determine de novo status and a more complete assessment for pathogenicity.

Our study should be viewed in light of its limitations. The cross-sectional design required retrospective record review of medical history. Further, some patients did not have their surgeries or catheterizations performed at our institution, limiting the comprehensiveness of medical information available to us. In particular, the total number of hospital admissions or total lengths of stays across admissions as a measure of global morbidity could not be analyzed. Approximately half of potential subjects who were eligible for this study were either followed elsewhere and lost to our follow-up or declined participation; participants may have been biased toward either better or worse outcomes than the general Fontan population. Although all subjects were invited to participate in the genetic arm of the study, only 87% chose to do so. Moreover, known single gene point mutations, an established cause of syndromic and nonsyndromic CHD, would not be detected by array comparative genomic hybridization. We did not adjust for multiple testing and many variables were collinear in this exploratory analysis. In addition, we did not validate our risk factor analysis in an independent sample. Finally, anatomic brain MRI findings in Fontan patients were compared with those in optimal referents without known risk factors for brain injury. Anatomic brain MRI is relatively insensitive for delineating subtle central nervous system injury, and further reports describing abnormalities of brain structure, microstructure, and function in this cohort are in process.

In summary, we found that abnormalities of neuropsychological performance in patients who have undergone the Fontan procedure are common and generally more severe than those of children with 2-ventricle congenital heart defects. Moreover, larger SDs of the scores in Fontan patients, compared with those of the referents, indicate great variability of outcomes within the Fontan population. The neurodevelopmental deficits and high frequency of structural brain and genetic abnormalities in the Fontan cohort highlight the need for continued research on interventions to improve long-term outcomes in this high-risk group.

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Disclosures

None.

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