Psychiatric Disorders in Adolescents With Single Ventricle Congenital Heart Disease

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abstract

BACKGROUND AND OBJECTIVES: Mental health outcomes for survivors of critical congenital heart disease (CHD) remain under-investigated. We sought to examine psychiatric disorders and psychosocial functioning in adolescents with single ventricle CHD and to explore whether patient-related risk factors predict dysfunction.

METHODS: This cohort study recruited 156 adolescents with single ventricle CHD who underwent the Fontan procedure and 111 healthy referents. Participants underwent comprehensive psychiatric evaluation including a clinician-rated psychiatric interview and parent- and self-report ratings of anxiety, disruptive behavior, including attention-deficit/hyperactivity disorder (ADHD), and depressive symptoms. Risk factors for dysfunction included IQ, medical characteristics, and concurrent brain abnormalities.

RESULTS: Adolescents with single ventricle CHD had higher rates of lifetime psychiatric diagnosis compared with referents (CHD: 65%, referent: 22%; $P < .001$). Specifically, they had higher rates of lifetime anxiety disorder and ADHD ($P < .001$ each). The CHD group scored lower on the primary psychosocial functioning measure, the Children's Global Assessment Scale, than referents (CHD median [interquartile range]: 62 [54–66], referent: 85 [73–90]; $P < .001$). The CHD group scored worse on measures of anxiety, disruptive behavior, and depressive symptoms. Genetic comorbidity did not impact most psychiatric outcomes. Risk factors for anxiety disorder, ADHD, and lower psychosocial functioning included lower birth weight, longer duration of deep hypothermic circulatory arrest, lower intellectual functioning, and male gender.

CONCLUSIONS: Adolescents with single ventricle CHD display a high risk of psychiatric morbidity, particularly anxiety disorders and ADHD. Early identification of psychiatric symptoms is critical to the management of patients with CHD.

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WHAT'S KNOWN ON THIS SUBJECT: Adolescents with congenital heart disease (CHD) are at high risk for neurodevelopmental morbidities and are particularly vulnerable to adverse outcomes. Their mental health status, including clinician-determined psychiatric disorder diagnosis and psychosocial functioning, remain under-investigated.

WHAT THIS STUDY ADDS: Adolescents with single ventricle CHD after the Fontan procedure have a threefold increased risk of receiving a lifetime psychiatric diagnosis compared with referent adolescents. Frequent psychiatric diagnoses include anxiety disorders and attention-deficit/hyperactivity disorder.

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Congenital heart disease (CHD) occurs in ~1% of live births.[1] Of these, one-third present with critical CHD, defined as lesions requiring infant cardiac surgery or catheter-based intervention. Single ventricle physiology, the highest risk CHD group, typically require 3 reconstructive open-heart surgeries in the first years of life, with the third stage being the Fontan procedure.[2] Advances in medical care have reduced surgical mortality and morbidity for children with critical CHD, but their survival has exposed neurodevelopmental and psychiatric morbidities.[3–12] These children display deficits in visual-perceptive skills[4,5,13] and executive function,[4,5,9–11] attention-deficit/hyperactivity disorder (ADHD) symptoms,[8,14] and reduced quality of life.[15,16] Few data are available on mental health outcomes of critical CHD survivors in adolescence.[17,18]

Studies conducted with heterogeneous CHD populations have reported increased risk and undertreatment of psychiatric symptoms including anxiety and depression.[18,19] However, the prevalence of psychiatric disorders in adolescents with critical CHD, particularly those with single ventricle physiology, remains underinvestigated. Although studies suggest that adolescents with critical CHD display higher incidence of ADHD,[5,8,14] this literature is limited by reliance on parent- and self-report measures. Although the prevalence of clinician-diagnosed psychiatric disorders, such as anxiety and depression, have been investigated in other CHD populations,[17,20] few studies focus on patients with single ventricle CHD. Patients with single ventricle CHD may have associated genetic abnormalities that adversely influence not only neurodevelopmental outcomes[3,5] but also psychiatric functioning.

Our study is the first to report clinician-derived psychiatric outcomes in adolescents with single ventricle CHD who underwent the Fontan procedure. Clinician rates of structured interview-derived psychiatric disorders and global psychosocial functioning were compared between adolescents with single ventricle CHD and a referent group. We hypothesized that adolescents with single ventricle CHD, compared with referent adolescents, would have a higher incidence of psychiatric disorders. In line with findings on adolescents with d-transposition of the great arteries (d-TGA),[17] we predicted that anxiety disorder and ADHD would be among the most prevalent diagnoses in our cohort. We further expected that patients without genetic abnormalities would have less psychiatric morbidity than those with genetic abnormalities.

METHODS

Participants

In this single-center cross-sectional study, we assessed neurodevelopmental, psychiatric, and brain MRI outcomes in adolescents with single ventricle CHD who underwent the Fontan procedure. This study presents the psychiatric data from a larger study where methods are more fully described.[5] Inclusion criteria were age 10 to 19 years at enrollment, single ventricle physiology, and history of Fontan procedure. Exclusion criteria were disorders preventing successful study completion (eg, pacemaker, metal implants preventing MRI), lack of English reading fluency by the primary caregiver, foreign residence, cardiac transplantation, and cardiac surgery within 6 months of testing.[5]

Referent adolescents were recruited based on the National Institutes of Health MRI Study of Normal Brain Development criteria, which excluded subjects with medical conditions that affect brain structure and function.[21] Referents were recruited from the same geographic location as patients (ie, local pediatric practices, our institutional adolescent clinic, and posted notices). This study was approved by the hospital's institutional review board.

Procedures

Data on adolescents' mental health were obtained by clinician-administered semistructured interviews of adolescents and parents reviewed by a board-certified child psychiatrist (D.R.D.) as well as parent- and self-report questionnaires. Patients underwent genetic evaluation involving physical examination and DNA microarray.[5] Adolescents were classified as having possible or definite genetic abnormalities if they met ≥1 of the following criteria: known genetic diagnosis at enrollment, a pathogenic variant or variant of unknown significance on microarray, or syndromic presentation.

Patient characteristics (Table 1) were extracted from medical records and/or interviews. The Hollingshead Four Factor Index of Social Status was used to assess family social status with higher scores indicating higher status.[22] Race/ethnicity options were based on National Institutes of Health–defined standard categories. Characteristics of the first cardiac operation and medical history characteristics are included in Table 2. Associated noncardiac congenital anomalies are presented in Supplemental Table 6.

Adolescents underwent neuropsychological evaluation,[5] using the Wechsler Intelligence Scale for Children—Fourth Edition[23] if <17 years of age and the Wechsler Adult Intelligence Scale—Fourth Edition[24] if aged ≥17 years.

Most adolescents underwent structural anatomic brain MRI. Subjects were scanned at Beth Israel Deaconness Medical Center using either a 3-T General Electric

TABLE 1 Participant Characteristics of Adolescents With Single Ventricle CHD and Referents

Variable	Single Ventricle CHD, Mean (SD) or %			Referents (n = 111), Mean (SD) or %	P, All CHD vs Referents	P, Genetic vs No Genetic Abnormalities
	All (n = 156)	No Genetic Abnormalities (n = 91)	Genetic Abnormalities (n = 65)			
Birth wt, kg	3.3 (0.6)	3.4 (0.6)	3.1 (0.7)	3.5 (0.6)	.005	.008
Gestational age, wk	38.9 (2.2)	39.3 (1.7)	38.4 (2.8)	39.6 (1.3)	.002	.003
Demographic characteristics						
Male	61	65	55	53	.25	.23
White race	93	93	92	83	.01	.79
Hispanic ethnicity	12	12	12	5	.07	.97
Family social status[a]	50 (13)	50 (12)	49 (14)	53 (10)	.02	.33
Age at assessment, y	14.5 (3.0)	14.0 (2.9)	15.2 (3.0)	15.3 (1.8)	.02	.004
Full-scale IQ, combined	91.6 (16.8)	94.8 (14.9)	87.3 (18.4)	108.3 (11.4)	<.001	.002
Structural MRI findings[b]						
Any abnormality	66	62	73	6	<.001	.29
Focal infarction or atrophy	13	8	20	0	<.001	.049
Brain mineralization/iron deposit	54	55	53	1	<.001	.84
Any diffuse abnormality	9	8	11	2	.03	.56

P values were determined by linear regression for continuous variables and logistic regression for binary demographic variables with group (CHD without genetic abnormalities, CHD with genetic abnormalities, and referents) as a categorical predictor. Full-scale IQ comparisons were adjusted for type of assessment. Fisher's exact test was used for structural MRI findings.

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

[b] MRI findings were available for 144 adolescents with CHD and 105 referents.

TABLE 2 Operative and Medical History Characteristics of Adolescents With Single Ventricle CHD

Variable	All (n = 156)	No Genetic Abnormalities (n = 91)	Genetic Abnormalities (n = 65)	P
	Median (Range) or %			
Operative characteristics				
Age at operation ≤30 d	78	82	72	.17
Status at first operation				
Open procedure	59	65	51	.10
Duration of DHCA, if open, min	42 (0–107)	45.5 (0–107)	35 (0–70)	.54
Duration of total support, if open, min	121 (43–325)	124 (43–325)	112 (45–160)	.01
Medical history				
Norwood procedure	40	48	29	.02
Total number of operations				.07
1 or 2	18	15	22	
3	64	71	54	
4 or 5	18	13	25	
Total number of operative complications				.67
0	15	18	12	
1–5	67	65	71	
≥6	17	18	17	
Total number of catheterizations				.57
1 or 2	11	11	11	
3–5	69	71	65	
≥6	21	18	25	
Total number of catheterization complications				.17
0	49	46	54	
1 or 2	40	46	32	
≥3	10	8	14	
Seizure	15	12	18	.36
Any neurologic event[a]	25	19	34	.04
Current ADHD treatment medication	10	10	9	>.99
Current other psychotropic medication	8	5	12	.15
History of any psychotropic medication	24	20	31	.13

P values were determined by the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.

[a] Includes stroke, seizure, choreoathetosis, and meningitis.

(GE) Siemens Trio system or, for participants with a implanted cardiovascular device or coils, a 1.5-T GE Twinspeed system (General Electric Medical Systems, Milwaukee, WI). MRIs were examined for the presence of structural abnormalities by a neuroradiologist blinded to participant group.

Outcome Measures

Psychiatric Disorders

The Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version[25] (K-SADS-PL) is a semistructured clinician psychiatric interview that assesses lifetime and current history of psychiatric diagnosis using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for adolescents. Participants and 1 or both parent(s) were interviewed, and the combined information was scored using standard K-SADS-PL procedures. Interviews were performed by research assistants with bachelor's degrees who underwent extensive instrument training and were reviewed with the child psychiatrist. The main end points were binary, that is, whether the subject met lifetime or current criteria for a psychiatric diagnosis.

Global Psychosocial Functioning

The Children's Global Assessment Scale[26] (CGAS) is a clinician-rated tool for evaluation of global psychosocial functioning (ie, adaptive behavior at home, in school, and with peers) over the previous 30 days. Information from interviews, questionnaires, and clinical observation is transformed into a score on a 100-point scale with lower scores indicating greater impairment. A cutoff value of 70 distinguishes normal from pathologic functioning. Scores were assigned by the child psychiatrist.

Psychiatric Symptoms

The Brief Psychiatric Rating Scale for Children[27] is a clinician-rated tool assessing several dimensions of psychopathology. The total severity score was the main end point, with a higher score indicating greater symptom severity.

The Revised Children's Manifest Anxiety Scale[28] is a self-report measure assessing anxiety symptoms. Scores from 4 domains (social desirability, social concerns/concentration, physiologic anxiety, and worry/oversensitivity) contribute to a total anxiety T score used as the main end point.

The Child Stress Disorders Checklist[29] is a parent-completed measure for acute and traumatic stress symptoms in their child. Scores from 5 domains (reexperiencing, avoidance, numbing and dissociation, increased arousal, and impairment in functioning) contribute to a total posttraumatic symptom score used as the main endpoint.

The Conners' ADHD Rating Scales[30] (CADS; parent and adolescent versions) includes an ADHD Index consisting of those CADS items that most effectively differentiate children with ADHD from nonclinical children. The ADHD Index T score served as the main endpoint.

The Children's Depression Inventory[31] is a self-report questionnaire measuring depressive symptomatology over the previous 2 weeks. Scores on five scales (negative mood, ineffectiveness, negative self-esteem, interpersonal problems, and anhedonia) contribute to a total T score used as the main end point.

Statistical Methods

The presence of lifetime anxiety and ADHD disorders identified by the K-SADS-PL assessment and global psychosocial functioning (CGAS score) served as our primary outcome measures. Other psychiatric measures served as secondary endpoints. Comparisons of subject characteristics among CHD groups with and without genetic abnormalities and the referent group used linear regression for continuous variables and logistic regression for binary demographic variables with group as a categorical predictor and IQ comparisons adjusted for assessment instrument (Wechsler Intelligence Scale for Children or Wechsler Adult Intelligence Scale). Comparisons of structural MRI findings among CHD and referent groups used Fisher's exact test. Comparisons of operative characteristics and medical history measures among CHD groups used Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. Comparisons of lifetime and current K-SADS-PL psychiatric disorders for which ≥1 group (CHD with or without genetic abnormalities or referent) had >3 associated patient diagnoses were made using exact logistic regression with adjustment for family social status. Group comparisons of psychosocial measures, after log transformation of all measures except CGAS, were made using linear regression adjusting for family social status. *P* values of group comparisons of K-SADS-PL psychiatric disorders and psychosocial measures were adjusted for false discovery rate due to the number of comparisons evaluated.[32]

Logistic and linear forward stepwise regression was used to identify risk factors of K-SADS-PL lifetime anxiety disorder and ADHD diagnoses as well as CGAS score in adolescents with CHD. The 18 predictors examined were patient characteristics, IQ, and operative and medical history characteristics except history and current use of psychotropic medication. For closed procedures, values of deep hypothermic circulatory arrest (DHCA) and total support duration were set to 0. Predictors associated with outcomes

at $P < .20$, adjusting for family social status and genetic abnormalities, were included in forward stepwise logistic or linear regression analysis with a $P < .05$ retention criterion. All tests were 2-sided.

RESULTS

Participants

A total of 362 adolescents with single ventricle CHD met eligibility criteria. Of these, 116 (32%) were followed elsewhere or lost to follow-up. Among the remaining 246 families, 90 (35%) declined participation. Eligible patients who consented versus declined did not differ in most demographic or medical characteristics including sex, race, or single ventricle diagnosis. A total of 156 adolescents with single ventricle CHD who underwent the Fontan procedure, including 65 (42%) with possible or definite genetic abnormalities, and 111 referents met eligibility criteria and completed testing. Compared with referents, patients had lower birth weight, gestational age, family social status, and IQ scores (Table 1). They were younger in age and more likely to be white and have abnormal structural MRI findings than referents.

In the CHD cohort, adolescents with genetic abnormalities had lower birth weight, lower gestational age, older age at assessment, and lower IQ scores than those without abnormalities. They had shorter total support durations among those with an open first operation, were less likely to undergo the Norwood procedure, and were more likely to have had a neurologic event (Table 2).

Psychiatric Functioning

Psychiatric Disorders and Global Psychosocial Functioning

Patients were more likely than referents to meet K-SADS-PL criteria of a lifetime psychiatric diagnosis (CHD: 65%, referent: 22%; $P < .001$; Table 3). They showed a fivefold increase in the rate of lifetime anxiety diagnoses relative to referents (CHD: 35%, referent: 7%, $P < .001$), for example, separation anxiety and social phobia/avoidant disorders. Patients were more likely than referents to be diagnosed with lifetime disruptive behavior disorders, specifically ADHD (CHD: 34%, referent: 6%, $P < .001$). The likelihood of meeting criteria for any psychiatric diagnosis at the time of assessment was greater in the CHD cohort (CHD: 46%, referents: 11%, $P < .001$); specifically, rates of current anxiety disorder and ADHD diagnoses were higher in patients.

Results on the K-SADS-PL for psychiatric diagnoses, lifetime or current, did not differ by genetic status of patients. Among 102 adolescents with CHD who met criteria for a lifetime psychiatric diagnosis, 37 (36%) had received pharmacological treatment (ADHD or other psychotropic medication). Criteria for at least 1 current psychiatric diagnosis were met by 71 adolescents, of whom 21 (30%) were currently receiving pharmacological treatment.

CGAS scores were significantly lower in adolescents with CHD compared with referents (CHD median: 62, referent 85, $P < .001$, Table 4). CGAS scores were comparable between the CHD groups with and without genetic abnormalities. Median CGAS scores in both CHD groups were in the pathologic functioning range (ie, <70). Total Brief Psychiatric Rating Scale for Children severity scores were greater for patients than referents, indicating a higher degree of psychiatric symptom severity.

Psychiatric Symptoms

Patients differed significantly from referents regarding parent- and self-reported measures of anxiety, disruptive behavior, and depressive symptoms (Table 4). Scores of adolescents with CHD on these measures did not differ significantly between those with versus without genetic abnormalities. Adolescents with CHD had significantly higher anxiety and depression scores as well as more reported symptoms of posttraumatic stress than did referents. They scored higher (ie, worse) than referents on both versions of CADS.

Risk Factors of Psychiatric Functioning

Higher risk of lifetime anxiety disorder was associated with lower birth weight and longer DHCA duration (Table 5). Higher risk of lifetime ADHD diagnosis was associated with lower IQ scores and male gender. Lower global psychosocial functioning, as represented by CGAS scores, was significantly associated with lower IQ scores, younger age at assessment, and younger age at first operation, adjusting for family social status and genetic abnormalities. Genetic abnormalities were not significantly associated with higher risk of lifetime anxiety or ADHD diagnoses, but were significantly associated with lower CGAS scores in the risk factor model.

Secondary analyses were conducted using the 144 adolescents with CHD with MRI data. The presence of brain abnormalities was not significantly associated with lifetime anxiety diagnosis, lifetime ADHD diagnosis, or CGAS scores in bivariate models or when added to risk factor models.

DISCUSSION

Regardless of genetic comorbidities, adolescents with single ventricle CHD who underwent the Fontan procedure had strikingly high rates of clinician-diagnosed psychiatric disorder, with almost two-thirds presenting with a lifetime diagnosis and nearly half with a current diagnosis. We identified anxiety and ADHD as the most prevalent

TABLE 3 K-SADS-PL Psychiatric Diagnoses of Adolescents With Single Ventricle CHD and Healthy Referents

Psychiatric Diagnosis	Single Ventricle CHD, *n* (%)						Referents (*n* = 111), *n* (%)	
	All (*n* = 156)		No Genetic Abnormalities (*n* = 91)		Genetic Abnormalities (*n* = 65)			
	Lifetime	Current	Lifetime	Current	Lifetime	Current	Lifetime	Current
Any psychiatric disorder[a]	102 (65)**	71 (46)**	56 (62)	40 (44)	46 (71)	31 (48)	24 (22)	12 (11)
Anxiety disorders	55 (35)**	35 (22)*	30 (33)	19 (21)	25 (38)	16 (25)	8 (7)	7 (6)
Separation anxiety disorder	18 (12)*	11 (7)	12 (13)	9 (10)	6 (9)	2 (3)	1 (1)	1 (1)
Simple phobia	11 (7)	6 (4)	7 (8)	4 (4)	4 (6)	2 (3)	5 (5)	4 (4)
Social phobia/avoidant disorder	26 (17)**	13 (8)*	15 (16)	7 (8)	11 (17)	6 (9)	1 (1)	0
Generalized anxiety disorder	10 (6)	10 (6)	2 (2)	2 (2)	8 (12)	8 (12)	1 (1)	1 (1)
Panic disorder[b]	2 (1)	2 (1)	0	0	2 (3)	2 (3)	1 (1)	1 (1)
Obsessive-compulsive disorder[b]	5 (3)	2 (1)	3 (3)	1 (1)	2 (3)	1 (2)	1 (1)	1 (1)
Posttraumatic stress disorder[b]	1 (1)	0	1 (1)	0	0	0	1 (1)	1 (1)
Adjustment disorder with anxious mood[b]	2 (1)	1 (1)	1 (1)	1 (1)	1 (2)	0	1 (1)	1 (1)
Disruptive behavior disorders	60 (38)**	52 (33)**	31 (34)	29 (32)	29 (45)	23 (35)	8 (7)	5 (5)
ADHD	53 (34)**	51 (33)**	30 (33)	29 (32)	23 (35)	22 (34)	7 (6)	4 (4)
Oppositional defiant disorder	15 (10)	7 (4)	5 (5)	3 (3)	10 (15)	4 (6)	2 (2)	2 (2)
Adjustment disorder with disturbance of conduct[b]	1 (1)	0	1 (1)	0	0	0	0	0
Mood disorders	20 (13)	6 (4)	9 (10)	2 (2)	11 (17)	4 (6)	10 (9)	0
Major depressive disorder	8 (5)	2 (1)	4 (4)	1 (1)	4 (6)	1 (2)	6 (5)	0
Adjustment disorder with depressed mood	8 (5)	0	4 (4)	0	4 (6)	0	3 (3)	0
Dysthymia[b]	4 (3)	3 (2)	1 (1)	0	3 (5)	3 (5)	0	0
Depressive disorder NOS[b]	1 (1)	1 (1)	1 (1)	1 (1)	0	0	1 (1)	0
Other disorders[b]	4 (3)	0	3 (3)	0	1 (2)	0	2 (2)	0
Chronic motor or vocal tic disorder[b]	2 (1)	0	1 (1)	0	1 (2)	0	1 (1)	0
Transient tic disorder[b,c]	3 (2)	0	2 (2)	0	1 (2)	0	0	0
Anorexia nervosa[b]	0	0	0	0	0	0	1 (1)	0

P values were determined by exact logistic regression adjusting for family social status and with false discovery rate adjustment. Comparisons were all CHD versus referents and CHD without genetic abnormalities versus CHD with genetic abnormalities. NOS, not otherwise specified.

[a] Includes *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* Axis I mood, anxiety, disruptive behavior, and other disorders referenced in table but excludes elimination disorders and mental retardation.

[b] Comparisons were not included due to the sparse available data (ie, all group cells have ≤3 associated patient diagnosis).

[c] Includes Tourette syndrome.

* $P < .01$.

** $P < .001$.

disorders. Clinician ratings of psychosocial dysfunction and psychiatric symptom severity were higher in the CHD cohort than in referents. Furthermore, 85% of patients scored in the pathologic range on the CGAS, indicating substantial functioning difficulties in different environments (eg, at home, at school, with peers).

Similar to previous studies in which parents report greater frequencies of somatic, social, attention, and internalizing difficulties,[33–35] our cohort reported more anxiety and ADHD symptoms compared with referents. Compared with previous d-TGA[17] and mixed types of CHD[20] studies, the proportion of adolescents with at least 1 lifetime psychiatric diagnosis was higher in our cohort (35% d-TGA[17] and 22% mixed CHD[20] vs 65% single ventricle CHD). In adults with mixed CHD lesions, nearly 50% met diagnostic criteria for a least 1 lifetime mood or anxiety disorder, of whom 40% had never received any psychiatric treatment.[19] Compared with other CHD types, patients with single ventricle CHD may be exposed to increased neurologic risks, which may affect their long-term mental health status. Their limited physical competence relative to other CHD cohorts could further contribute to this heightened vulnerability by increasing the risk of social isolation.

Adolescence is a key developmental period for neuropsychiatric changes[36] and, for physically ill youth, is an opportunity for intervention before they transition to adult health care.[3,37] The higher prevalence of psychiatric disorders in our cohort has the potential to negatively influence their ability to assume responsibility for their medical care, with potential life-threating consequences.[37] Whereas neurodevelopmental outcomes are generally better for CHD cohorts without genetic comorbidities,[3] the risk of psychiatric dysfunction appears equally elevated in our cohort regardless of genetic abnormalities. Our findings suggest

TABLE 4 Dimensional Measures of Psychosocial Functioning in Adolescents With Single Ventricle CHD and Healthy Referents

Psychosocial Measures	Type of Report	Single Ventricle CHD			Referents (n = 111)	P, All CHD vs Referents	P, Genetic vs No Genetic Abnormalities
		All (n = 156)	No Genetic Abnormalities (n = 91)	Genetic Abnormalities (n = 65)			
		Median (Interquartile Range) or %					
Global psychosocial functioning							
CGAS score	Clinician	62 (54–66)	64 (56–67)	58 (53–64)	85 (73–90)	<.001	.07
Score ≤70		85	82	89	18		
BPRS-C total severity score	Clinician	12 (7–18.5)	12 (7–20)	13 (8–18)	2 (0–5)	<.001	.78
Anxiety symptoms							
RCMAS total anxiety T score	Adolescent	45 (38–54)	43 (38–53)	48 (38–55)	38 (33–46)	<.001	.23
Score >65		6	4	9	0		
CSDC total posttraumatic symptom score	Parent	7 (3–13)	6 (3–12)	7 (4–14.5)	2 (0–4)[a]	<.001	.45
Disruptive behavior symptoms							
CADS ADHD Index T score	Parent	58 (48–70)[a]	58 (48–66)	60 (47.5–72.5)	44 (42–48)	<.001	.23
Score >65		33	26	44	4		
CADS ADHD Index T score	Adolescent	48 (41–56)	46 (39–54)	48 (43–59)	44 (39–51)	.02	.16
Score >65		9	3	16	1		
Depressive symptoms							
CDI total T score	Adolescent	42 (39–47)	41 (38–46)	44 (39–48)	40 (37–44)	.001	.09
Score > 65		2	0	5	0		

P values were determined by linear regression with group (CHD without genetic abnormalities, CHD with genetic abnormalities, and referents) as a categorical predictor, adjusting for family social status, and with false discovery rate adjustment. All outcomes except CGAS were log-transformed before analysis. BPRS-C, Brief Psychiatric Rating Scale for Children; CSDC, Child Stress Disorders Checklist; RCMAS, Revised Children's Manifest Anxiety Scale.

[a] For referents, 31 CSDC symptom scores are available; for adolescents with CHD, 118 completed the CADS ADHD self-report measure.

that, given the high risk of psychiatric dysfunction, all patients with single ventricle CHD should be screened for psychiatric vulnerabilities in childhood, and those at risk should be referred for treatment. Special attention to adolescent risk-taking behaviors (eg, substance abuse) that might compromise their long-term cardiac prognosis is highly recommended.[37]

Regarding patient-related risk factors, our findings were in accordance with previous evidence suggesting that few operative variables are correlated with long-term CHD outcomes.[34] Patient-specific demographic, perinatal, medical, and global composite measures of neurologic risk, such as number of open-heart surgeries or age at the first cardiac surgery, are better predictors of global psychosocial outcomes than are intraoperative factors.[35] Several mechanisms for psychiatric morbidity may interact in critical CHD. These patients are exposed to early physiologic risk factors including in utero brain immaturity[38] as well as perioperative hemodynamic alterations and systemic inflammation.[39] These experiences may adversely affect their neurobiological developmental trajectory and consequently modify their long-term response to stress-related factors, increasing the risk of psychiatric morbidities. Supporting this hypothesis, findings from individuals born preterm showed that brain immaturity translates into long-lasting psychiatric vulnerability for many survivors.[40] Psychiatric disorders in critical CHD may be related to their reduced neurocognitive abilities, particularly impairments in self-control processes.[5]

TABLE 5 Risk Factors of K-SADS-PL Lifetime Anxiety Disorder Diagnosis, ADHD Diagnosis, and CGAS Score in Adolescents With Single Ventricle CHD (n = 156)

Outcome	Risk Factor	OR (95% CI)	P
K-SADS-PL lifetime diagnosis			
Anxiety disorder	Genetic abnormalities	1.2 (0.6 to 2.6)	.64
	Birth wt, per kg	0.45 (0.24 to 0.84)	.01
	Duration of DHCA, per min	1.01 (1.00 to 1.03)	.04
ADHD	Genetic abnormalities	1.0 (0.5 to 2.2)	.90
	Male	2.3 (1.1 to 4.8)	.03
	Full-scale IQ, combined[a]	0.97 (0.95 to 0.99)	.01
		β (95% CI)	
CGAS score	Genetic abnormalities	−3.3 (−6.0 to −0.5)	.02
	Age at assessment, per y	1.10 (0.42 to 1.79)	.002
	Full-scale IQ, combined[a]	0.19 (0.11 to 0.27)	<.001
	Age at operation ≤30 d	−3.6 (−6.8 to −0.4)	.03

P values were determined by logistic regression for K-SADS-PL diagnoses and linear regression for CGAS scores. All models were adjusted for family social status and genetic abnormalities. Coefficients for the intercept and family social status are not shown. CI, confidence interval; OR, odds ratio.

[a] Models also included adjustment for type of full-scale IQ assessment.

Critical CHDs are chronic conditions that require close

medical surveillance. Parent-child interactions may be challenged by repeated exposure to high-risk medical conditions, inducing chronic stress and less adaptive coping mechanisms. Interestingly, when compared with other pediatric chronic disease populations, our cohort displayed higher frequencies of lifetime psychiatric disorders (ie, 65% vs 56% in childhood cancer survivors).[41] Other populations with chronic disease, such as those with acute liver failure, do not seem to differ from the general population with regard to mental health functioning.[42] In our cohort, 35% had a lifetime diagnosis of anxiety disorders, particularly separation and social anxiety. The impact of psychosocial variables, such as parental stress levels, on the prevalence of psychiatric disorders in adolescents with critical CHD remains to be investigated. Parental anxiety in critical CHD may potentially contribute to children's separation stress and restricted social competence.

The study's major strength is the use of structured interview–derived psychiatric diagnosis combined with parent- and self-report measures. Most CHD mental health studies have relied on only parent- or self-reports.[19,20] The use of these interviews is more rigorous and helps avoid bias of misrepresentation of vulnerability. This is the first study reporting clinician-based rates of psychiatric disorders in adolescents with single ventricle CHD. Our results underscore the importance of identifying psychiatric morbidities in this population as early as possible to allow earlier interventions (eg, psychotherapy and/or pharmacologic treatment), thereby bolstering their effectiveness. Only 36% of adolescents in our cohort who met lifetime psychiatric diagnosis criteria had a history of psychotropic medication use, suggesting that future research should address whether patients with critical CHD experience any barriers to accessing treatment.

Our study should be interpreted in light of several limitations. Medical history was obtained retrospectively. As a single-center study focusing on patients with single ventricle CHD, our results may not be generalizable to other types of CHD. Our referent group was restricted to healthy individuals without risk factors for brain abnormalities. Our rates of psychiatric disorders were much higher than those reported in the US population (ie, 6.8% for ADHD, 3% for anxiety, and 2% for depression),[43] suggesting future replication of our findings is warranted. Our genetic testing used microarray technology rather than whole exome sequencing; it is possible that as yet undetected genetic variants might be present in patients classified as without genetic abnormalities.

CONCLUSIONS

Adolescents with single ventricle who underwent the Fontan procedure were found to be at increased risk for psychiatric dysfunction, specifically for anxiety disorders and ADHD. The presence of a genetic comorbidity did not significantly affect psychiatric outcomes. Psychiatric disorders and lower psychosocial functioning are associated with patient and medical factors, such as low birth weight, male sex, and longer DHCA duration. Early identification of psychiatric symptoms is an important component of the long-term management of these patients.

ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
CADS: Conners' ADHD Rating Scales
CGAS: Children's Global Assessment Scale
CHD: congenital heart disease
d-TGA: d-transposition of the great arteries
DHCA: deep hypothermic circulatory arrest
K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version

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