Predictors of Health-Related Quality of Life in Adolescents with Tetralogy of Fallot

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Objective To assess health-related quality of life (HRQoL) of adolescents with repaired tetralogy of Fallot (TOF) and whether impairments in HRQoL domains are associated with neurocognitive and medical factors.

Study design Parents of subjects with TOF and healthy referents 13-16 years of age completed the Child Health Questionnaire-Parent Form 50, generating psychosocial (PsS) and physical (PhS) health summary scores. Adolescents completed the Child Health Questionnaire-Child Form 87 and concurrent in-person neurocognitive testing. We analyzed relationships of PsS and PhS scores with neurocognitive performance and medical factors.

Results Compared with referents (n = 85), adolescents with TOF without a genetic diagnosis (n = 66) had lower PsS (50.9 ± 9.4 vs 57.2 ± 4.2, $P < .001$) and PhS scores (49.4 ± 9.5 vs 55.8 ± 4.9; $P < .001$). Compared with a normative sample, these adolescents with TOF had similar PsS scores ($P = .52$) but significantly lower PhS scores ($P = .01$). Within adolescents with TOF without genetic disorders, lower PsS scores were highly associated with worse neurocognitive measures, particularly the parent-reported Behavior Rating Inventory of Executive Function composite ($r = -0.66$, $P < .001$) and Parent Conners' attention deficit-hyperactivity disorder Index T score ($r = -0.54$, $P < .001$), whereas associations of PhS scores with neurocognitive measures were weaker.

Conclusions Psychosocial health status in adolescents with TOF without genetic disorders was worse than in healthy referents without risk factors for brain injury but similar to a normative sample; physical health status was worse in these adolescents than in either comparison group. Within these subjects with TOF, worse psychosocial health status was most highly associated with concurrent executive dysfunction and attention deficit-hyperactivity disorder. Optimizing HRQoL constitutes another indication for attention to neurodevelopment in children with congenital heart disease. *(J Pediatr 2015;166:132-8)*.

Tetralogy of Fallot (TOF) is the most common cause of cyanotic congenital heart disease (CHD), comprising 8%-10% of all congenital cardiac lesions.[1-3] Survival of patients with TOF ranges from 80% to 90% at 30-year follow-up,[4,5] highlighting the importance of their general functioning and health-related quality of life (HRQoL). Furthermore, the population with CHD is at high risk for neurologic and developmental disabilities.[6,7] To our knowledge, no studies have examined the relationship between neurocognitive function and HRQoL in subjects with repaired TOF, particularly those without velocardiofacial syndrome or other genetic disorders.

In the present study, we sought to determine the psychosocial and physical health status of adolescents with repaired TOF and to explore whether impairments in these domains are associated with neurocognitive and medical factors. We also sought to compare HRQoL measures of this cohort with those of locally recruited healthy adolescent referents and a published normative sample. Finally, we compared parent- and adolescent-reported measures of HRQoL within the TOF cohort.

Methods

Subjects were enrolled between June 2004 and September 2007 in a single-center, cross-sectional study of adolescents with TOF who had undergone repair, as previously described.[8] In brief, the study evaluated subjects with respect to academic achievement, cognition, behavior, and brain structure and function assessed by magnetic reso-

ADHD	Attention deficit-hyperactivity disorder	NYHA	New York Heart Association
CHD	Congenital heart disease	PhS	Physical health summary
CHQ	Child Health Questionnaire	PsS	Psychosocial health summary
CHQ-CF87	Child Health Questionnaire-Child Form 87	TOF	Tetralogy of Fallot
CHQ-PF50	Child Health Questionnaire-Parent Form 50	TVPS	Test of Visual-Perceptual Skills
D-KEFS	Delis-Kaplan Executive Function System	WIAT	Wechsler Individual Achievement Test, Second Edition
HRQoL	Health-related quality of life	WISC	Wechsler Intelligence Scale for Children, Fourth Edition

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nance imaging. Eligibility criteria included ages 13 through 16 years at time of enrollment, diagnosis of TOF with or without pulmonary atresia, and most recent cardiac operation at least 3 months before neurocognitive testing. Exclusion criteria included disorders that would prevent successful completion of planned study testing (ie, pacemaker, metal implants), trisomy 21, and primary caregiver with lack of reading fluency in English. Subjects with pre-existing neurologic abnormalities or known 22q11 microdeletion were not excluded. Subjects with TOF were classified as having a genetic diagnosis based on either medical history of a genetic/phenotypic syndrome consisting of multiple anomalies or a finding of a genetic disorder on formal diagnostic testing as previously reported.[8] Subjects with TOF were otherwise assumed to have no known genetic diagnosis.

In addition to a published normative sample,[9] a group of normally developing, local healthy referent subjects ages 13 through 16 years also was recruited.[8] Exclusion criteria for this group are described in the National Institutes of Health study of normal brain development.[10] These subjects had no known risk factors for brain injury and hence reflect optimal neurocognitive performance in a healthy population.[8] The Institutional Review Board approved this protocol. Informed consent was obtained from parents or guardians and assent from all subjects.

The Child Health Questionnaire (CHQ) is a validated, comprehensive tool providing a qualitative assessment of psychosocial and physical functioning across multiple domains in children ages 5-18 years.[11] Both CHQ-Parent Form 50 (CHQ-PF50) and CHQ-Child Form 87 (CHQ-CF87) can be self-administered. The CHQ-PF50 includes 50 questions and generates psychosocial (PsS) and physical (PhS) health summary scores, derived as a weighted average of 10 subscale scores. PsS scores are primarily determined by the mental health, role/social-emotional/behavioral, behavior, and self-esteem subscales. PhS scores are primarily determined by the physical functioning, role/social-physical, bodily pain, and general health perceptions subscales. The parent emotional impact and parent time impact subscales contribute to each summary score. Greater summary scores indicate better psychosocial and physical health status. The CHQ-CF87 includes 87 questions and generates subscale scores corresponding to those of the CHQ-PF50 with the exception of parent impact subscales. Additionally, the role/social-emotional/behavioral subscale of the CHQ-PF50 is separated into role/social-emotional and role/social-behavioral subscales on the CHQ-CF87. The CHQ-CF87 does not generate summary scores.[11]

As previously described,[8] an extensive battery of neurocognitive testing was performed. Administered tests included the Wechsler Intelligence Scale for Children, Fourth Edition (WISC)[12]; Wechsler Individual Achievement Test, Second Edition (WIAT)[13]; Children's Memory Scale[14]; Delis-Kaplan Executive Function System (D-KEFS)[8,15]; parent, child, and teacher versions of the Behavior Rating Inventory of Executive Function[16,17]; the Test of Visual-Perceptual Skills (TVPS; nonmotor, Upper Level), Revised[8,18]; the Autism Spectrum Quotient[19]; and adolescent and parent versions of the Conners' attention deficit-hyperactivity disorder (ADHD)/Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition rating scale.[20]

Statistical Analyses

The study's primary focus was on the relationships of PsS and PhS scores in subjects with TOF with: (1) performance on concurrent neurocognitive measures, analyzed by the use of partial Pearson correlation; and (2) medical factors, analyzed by the use of multivariable linear regression. These analyses were adjusted for concurrent family social status, measured with the Hollingshead Four Factor Index of Social Status.[21] Subjects with TOF were compared with healthy local referents with respect to sociodemographic and medical history characteristics via 2-sample t tests for continuous variables and Fisher exact tests for categorical variables. Using linear regression adjusting for social status, we compared PsS and PhS summary and subscale scores of: (1) subjects with TOF compared with referents; (2) subjects with TOF with vs without a genetic diagnosis; and (3) subjects with TOF with vs without concurrent cardiac symptoms. CHQ-PF50 summary and subscale scores of subjects with TOF were compared with published normative data[11] via 2-sample t tests. For the CHQ-PF50, normative data for the 13- to 15-year age group were used to provide the closest age-matched comparison. Parent and child subscale scores of subjects with TOF were compared via paired-sample t tests.

Univariate analyses identified factors associated with PsS and PhS scores of subjects with TOF without a genetic diagnosis. Sociodemographic characteristics evaluated as predictors were sex, race/ethnicity (non-Hispanic white vs other), and age at assessment. Predictors from operative and medical history were birth weight; gestational age; diagnosis of pulmonary atresia; age at initial operation; first operation being an open heart procedure; deep hypothermic circulatory arrest and total support durations at first operation; number of operative complications at first operation; total number of operations, open operations, operative complications, catheterizations, and catheterization complications; and neurological event occurrence. Neurological events were defined as seizure, stroke, choreoathetosis, or meningitis. Predictors associated with PsS or PhS scores at a level of $P < .15$ were considered for stepwise backward regression in which $P < .05$ served as the significance criterion for independent risk factors while we adjusted for family social status. Robust regression methods (via MM-estimation using PROC ROBUSTREG in SAS [SAS Institute, Cary, North Carolina]) were used to reduce any undue influence of outlying or high leverage observations in identifying these factors.[22] Analyses were generated using SAS (v. 9.3) and STATA (v. 12, StataCorp, College Station, Texas).

Results

Sociodemographic and medical characteristics of subjects with TOF in this cohort (n = 91) have been previously