## Psychiatric Disorders and Function in Adolescents with Tetralogy of Fallot

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### Objectives
To assess psychiatric disorders and function in adolescents with repaired tetralogy of Fallot (TOF) without and with a genetic diagnosis and to evaluate associations of functioning with medical factors, IQ, and demographics.

### Study design
Adolescents with TOF (n = 91) and 87 healthy referents completed a clinician-rated structured psychiatric interview, parent-/self-report measures of psychopathology, and brain magnetic resonance imaging. Twenty-three of the adolescents with TOF had a known genetic diagnosis.

### Results
The prevalence of anxiety disorders did not differ significantly between adolescents with TOF without genetic diagnosis (n = 68) and referents. Adolescents with TOF and a genetic diagnosis showed an increased lifetime prevalence of anxiety disorder (43%) and lower global psychosocial functioning (median, 70; IQR, 63-75) compared with adolescents with TOF without genetic diagnosis (15% and 83; IQR, 79-87, respectively; \( P < .001 \)) and referents (6% and 85; IQR, 76-90, respectively; \( P = .001 \) and \( < .001 \), respectively). Adolescents with TOF without and with a genetic diagnosis had a higher lifetime prevalence of attention deficit-hyperactivity disorder (ADHD) than referents (19% and 39%, respectively, vs 5%; \( P = .04 \) and \( .002 \), respectively) and worse outcomes on parent-/self-report ratings of anxiety and disruptive behavior compared with referents. Risk factors for anxiety, ADHD, and lower psychosocial functioning for adolescents with TOF without a genetic diagnosis included older age, male sex, and low IQ. Medical variables were not predictive of psychiatric outcomes.

### Conclusion
Adolescents with TOF, particularly those with a genetic diagnosis, show increased rates of psychiatric disorder and dysfunction. Continued mental health screening and surveillance into young adulthood is warranted for adolescents with TOF. (*J Pediatr* 2017;■■:■■-■■).

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**With improvements in surgical and catheter therapies, patients with tetralogy of Fallot (TOF), one of the most common forms of critical congenital heart disease (CHD), now experience excellent long-term survival.**¹² As a result, issues of morbidity, particularly neurodevelopmental and psychiatric sequelae thought to undermine quality of life in TOF survivors, have become an important focus.¹³ Youths with TOF reportedly are at elevated risk for neurodevelopmental impairments across cognitive, self-regulatory, and academic domains, as well as abnormal magnetic resonance imaging (MRI) findings.³

In addition, the prevalence of genetic conditions is high in the TOF population (ie, 18%-25%);¹³ the risks for neurodevelopmental impairment, attention deficit-hyperactivity disorder (ADHD), anxiety, and schizophrenia are increased in those with a co-occurring genetic condition, such as 22q11 microdeletion.⁶⁷ Advancements in genetic testing, as well as the increasing worldwide implementation of cardiac neurodevelopmental intervention programs for critical CHD,⁸ underscore the importance of understanding the psychiatric profile of youths with TOF, specifically the extent to which psychiatric functioning is associated with genetic, medical, and neurodevelopmental impairments. To our knowledge, no previous study has examined the prevalence of psychiatric disorders and function among adolescents with TOF, specifically looking at those without and with an identified genetic diagnosis.

### Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tr>
<td>ADHD</td>
<td>Attention deficit-hyperactivity disorder</td>
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<td>BPRS-C</td>
<td>Brief Psychiatric Rating Scale for Children</td>
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<td>CADS</td>
<td>Conners ADHD Rating Scales</td>
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<td>CDI</td>
<td>Children’s Depression Inventory</td>
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<td>CDS</td>
<td>Conduct Disorder Scale</td>
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<td>CGAS</td>
<td>Children's Global Assessment Scale</td>
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<td>CHD</td>
<td>Congenital heart disease</td>
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<td>CSDC</td>
<td>Child Stress Disorders Checklist</td>
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<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 4th Edition</td>
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<tr>
<td>d-TGA</td>
<td>Dextro-transposition of the great arteries</td>
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<tr>
<td>K-SADS-PL</td>
<td>Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>RCMAS</td>
<td>Revised Children's Manifest Anxiety Scale</td>
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<td>TOF</td>
<td>Tetralogy of Fallot</td>
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Knowledge of the psychiatric disorders faced by adolescents with TOF is limited by a reliance on parent-/self-report rating scales rather than on a gold standard structured diagnostic interview.9,10 To date, only 3 studies have reported on interview-derived psychiatric diagnoses in youths with critical CHD. A Portuguese study found that 22% of a mixed CHD cohort had a psychiatric disorder (mostly depression and anxiety),11 whereas DeMaso et al12 reported that 19% of adolescents with repaired dextro-transposition of the great arteries (d-TGA) met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for ADHD. More recently, DeMaso et al13 reported that among adolescents with single-ventricle CHD, a stunning 55% met the DSM-IV lifetime criteria for anxiety disorder and 53% met the criteria for ADHD.

We compared adolescents with repaired TOF, stratified by genetic diagnosis, with a referent group of healthy adolescents with respect to the prevalence of structured interview-derived psychiatric disorders, clinician-rated psychosocial functioning, and informant-rated measures of anxiety, disruptive behavior, and depression symptoms. Given previously reported risks for neurocognitive impairment and MRI abnormalities in this population, we examined associations between psychiatric status and physical illness severity, cognitive functioning, and MRI outcomes. We hypothesized that adolescents with TOF both without or with a genetic diagnosis would have a higher prevalence of psychiatric disorders compared with healthy adolescents. Similar to findings among other critical CHD diagnoses, we hypothesized that anxiety disorders and ADHD would be the most prevalent psychiatric disorders.12,13 We also postulated that adolescents with TOF and a known genetic diagnosis would be at higher risk for psychiatric disorders than those without a genetic diagnosis.

### Methods

Patients were enrolled between 2004 to 2008 at Boston Children’s Hospital in a single-center cross-sectional study looking at brain structure and functioning, as reported previously.7 The TOF cohort included adolescents aged 13-16 years who had a diagnosis of TOF with or without pulmonary atresia. Exclusion criteria included cardiac surgery within 6 months of study enrollment, a disorder preventing successful completion of the planned study (eg, pacemaker, metal implants), trisomy 21, and lack of English reading fluency by the primary caregiver.

A referent group of healthy adolescents was recruited for comparison purposes in accordance with the National Institutes of Health’s MRI Study of Normal Brain Development criteria, which excluded subjects with disorders recognized to affect brain structure and function.14 The study was approved by the hospital’s Committee on Clinical Investigation and conducted in accordance with institutional guidelines. Primary caregivers provided informed consent, and adolescents provided assent.

Mental health data were obtained by clinician-administered semistructured interviews of adolescents and parents, as well as parent- and self-report questionnaires. Patient operative and medical history characteristics (Table 1) were ascertained from medical records and interviews. Genetic classification was assigned for adolescents with TOF who had a known genetic diagnosis at enrollment or a genetic disorder detected on formal testing, as described previously.1 Family social status was measured with the Hollingshead Four Factor Index of Social Status,15 with higher scores indicating higher status. All adolescents (ie, TOF patients and healthy controls) were evaluated for general cognitive ability, as measured by the Wechsler Intelligence Scale for Children, Fourth Edition16 Full-Scale IQ score, during the current study.5

Most participants underwent structural anatomic brain MRI, performed with a 1.5-T MRI scanner (TwinSpeed; GE Healthcare, Chicago, Illinois).3 A neuroradiologist, blinded to participant group, examined the MRI images for the presence of structural brain abnormalities.

### Outcome Measures

**Psychiatric Disorders.** The Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version17 (K-SADS-PL), a semistructured clinician psychiatric interview, was administered to each adolescent and his or her caregiver(s) to assess for lifetime or current DSM-IV diagnoses. Information from caregiver and adolescent interviews was combined using standard procedures to ascertain the presence of psychiatric diagnoses. The interviews were performed by research assistants who underwent extensive instrument training and were reviewed by a board-certified child psychiatrist to determine final diagnoses, if any. The main endpoints were binary: whether or not the adolescent met criteria for a lifetime or current psychiatric diagnosis.

**Global Psychosocial Functioning.** We assessed global psychosocial functioning using 2 clinician-rated scales: the Children’s Global Assessment Scale18 (CGAS) and the Brief Psychiatric Rating Scale for Children19 (BPRS-C). Infirmed by the K-SADS-PL, the CGAS focuses on functioning during the previous 30 days. It provides a continuous score (0–100) used in analysis; normal functioning is indicated by a score >70. The BPRS-C is a 21-item questionnaire providing a brief descriptive profile of psychopathology in the domains of behavioral problems, depression, thinking disturbance, psychomotor excitation, withdrawal, anxiety, and organicity. The total severity score served as the main endpoint. Higher scores indicate greater symptom severity.

**Psychiatric Symptoms.** A battery of parent-/self-report measures was used to assess anxiety, disruptive behavior, and depressive symptoms. The Revised Children’s Manifest Anxiety Scale20 (RCMAS) is a 37-item self-report scale assessing numerous anxiety symptoms. The total anxiety T score served as the main endpoint. A T score >65 indicates clinically significant anxiety symptoms.

The Child Stress Disorders Checklist21 (CSDC) is a 36-item caregiver rating scale that assesses posttraumatic stress symptoms in youths. Caregivers in the TOF group were asked to complete this checklist using their child’s cardiac illness as a traumatic event. Parents of healthy adolescents were asked...
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