Adolescents with Tetralogy of Fallot: Neuropsychological Assessment and Structural Brain Imaging

David C. Bellinger[*,†], **Michael J. Rivkin**[*,‡], **David DeMaso**[†,§], **Richard L. Robertson**[‡], **Christian Stopp**[§], **Carolyn Dunbar-Masterson**[§], **David Wypij**[§,||], and **Jane W. Newburger**[§,¶]

[*]Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

[†]Department of Psychiatry, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

[‡]Department of Radiology, Boston Children's Hospital, Boston, MA, USA

[§]Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

[||]Department of Biostatistics, Harvard School of Public Health, Boston, MA, USA

[¶]Department of Pediatrics, Harvard Medical School, Boston, MA, USA

Abstract

Background—Few data are available on the neuropsychological, behavioral, or structural brain imaging outcomes in adolescents who underwent corrective surgery in infancy for tetralogy of Fallot.

Methods—In this single-center cross-sectional study, we enrolled 91 adolescents (13–16 years old) with tetralogy of Fallot and 87 referent subjects. Assessments included tests of academic achievement, memory, executive functions, visual-spatial skills, attention, and social cognition, as well as brain magnetic resonance imaging.

Results—Genetic abnormalities or syndromes were present in 25% of tetralogy of Fallow subjects, who had markedly greater neuropsychological morbidities than did patients without a syndrome. However, even patients without a syndrome performed significantly worse than the referent group or population norms in all of the neuropsychological domains assessed. In multivariable regression in those without a genetlc/phenotypicsyndrome, the strongest predictors of adverse late neurodevelopmental outcomes included a greater number of complications at the first operation, more total surgical complications across all operations, and occurrence of post-operative seizures. The presence of at least one abnormality on structural magnetic resonance imaging was more frequent in tetralogy of Fallot patients than the referent group (42% vs. 8%).

Conclusions—Adolescents with tetralogy of Fallot are at increased neurodevelopmental risk and would benefit from ongoing surveillance and educational supports even after childhood.

Address for correspondence: D.C.B., Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115; david.bellinger@childrens.harvard.edu; (617)355-6565; fax: (617)730-0618.

Keywords

tetralogy of Fallot; neuropsychology; magnetic resonance imaging

INTRODUCTION

A dramatic increase in the number of survivors of pediatric cardiac surgery has been accompanied by recognition of their neurodevelopmental morbidities and the associated personal and societal costs (1). The majority of patients with tetralogy of Fallot, which accounts for 8–10% of all congenital heart lesions (2), survive to adulthood but limited data are available on their long-term neurocognitive outcomes. They manifest deficits as early as infancy (3,4), with poorer outcomes associated with a genetic/phenotypic diagnosis, pulmonary atresia (PA), and the apolipoprotein epsilon allele (5). At 4 years of age, 20% of children with repaired tetralogy of Fallot have a significant impairment in at least one neurodevelopmental domain (6), and at school-age many have difficulties with motor skills, expressive language, speech, executive control, memory, attention, and visual-motor skills (6–10). In adulthood, patients showed reduced IQ scores (11) and deficits in executive functions (12). Patients with the 22q11 microdeletion are at substantial risk of low IQ and psychiatric disorders (12).

We report here on neuropsychological and structural neuroimaging evaluations of 91 adolescents who underwent surgery in infancy for tetralogy of Fallot, comparing their outcomes to those of the general population and a local referent group.

METHODS

Subjects

We enrolled subjects from 2004–2008 at Boston Children's Hospital. Admission criteria included age 13–16 years, diagnosis of tetralogy of Fallot with or without pulmonary atresia, and cardiac surgery for repair at least 6 months before testing. We excluded patients with disorders that would prevent completion of the study assessments (i.e., metal implants), trisomy 21, or lack of reading fluency by the primary caregiver. We recruited a group of 13–16 year old, normally-developing, referents to whom patients were compared with regard to brain magnetic resonance imaging and psychometric tests lacking national norms. Exclusion criteria for the referent group were similar to those used in the National Institutes of Health's magnetic resonance imaging study of normal brain development (13). The study was approved by the hospital Institutional Review Board; informed consent was obtained from parents/guardians, and assent was obtained from adolescents.

Among the 91 tetralogy of Fallot patients, 62 were enrolled in a genetics registry. Assignment to the genetic/phenotypic syndrome group was based on 1) medical history of a genetic/phenotypic syndrome of multiple anomalies or 2) a finding of a genetic disorder, such as 22q11 microdeletion, through testing as part of the registry. Three patients in the syndrome group reported to have the 22q11 deletion were not enrolled in the registry.

Neuropsychological Assessment

Intelligence—The endpoints were the five composite scores of the Wechsler Intelligence Scale for Children-Fourth Edition (14): Full-Scale IQ, Verbal Comprehension, Perceptual Reasoning, Working Memory, Processing Speed.

Academic Achievement—The endpoints were the Reading Composite and Math Composite scores of the Wechsler Individual Achievement Test-Second Edition (15). Tables in the Wechsler Intelligence Scale for Children-Fourth Edition Technical and Interpretive Manual (16) were used to identify scores that differ significantly from the score predicted based on an individual's Full-Scale IQ score.

Memory—The primary endpoint was the General Memory Index of the Children's Memory Scale (17).

Executive Functions—A summary score was calculated by averaging scores on five subtests of the Delis-Kaplan Executive Function System (18): 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). Adolescents, parents, and teachers completed the Behavior Rating Inventory of Executive Function (19–20). The General Executive Composite score was analyzed.

Visual-Spatial Skills—A Visual-Spatial summary score was calculated by averaging scores on the seven subscales of the Test of Visual-Perceptual Skills (non-motor) (Upper Level)-Revised (21). The copy, immediate recall, and delayed recall trials of the Rey-Osterrieth Complex Figure were scored for Organization, Structural Elements, and Incident Elements (22). Adolescents completed the Sense of Directions scale (23).

Attention—The primary score was the ADHD Index score (Attention Deficit Hyperactivity Disorder) on a parent-completed questionnaire (24).

Social Cognition—On the Reading the Mind in the Eyes Test-Revised (25), an adolescent judged the emotions expressed in photographs of the eye region. The Autism Spectrum Quotient (26), a self-report questionnaire, assesses autistic traits in the general population. The Toronto Alexithymia Scale (27), a self-report questionnaire assessing emotional deficits, generates three scores: Difficulty Identifying Feelings, Difficulty Describing Feelings, and Externally-Oriented Thinking.

Magnetic Resonance Imaging

Magnatic resonance imaging was performed on a 1.5 Tesla General Electric Twinspeed magnetic resonance scanner at the 13.0 hardware/software configuration (General Electric Medical Systems, Milwaukee WI). Adolescents were imaged with 3D-volumetric and dual echo MRI during the same scanning session. Following acquisition of the 3D volumetric T1-weighted high-resolution 3D Fourier Transform Spoiled Gradient data, high-resolution proton density and T2-weighted images were obtained. The spoiled gradient neuroanatomic

data were obtained (field of view, 24 cm; contiguous slice thickness, 1.5 mm; slices, 120; repetition time/echo time, 40/4 seconds; matrix, 256×192; flip angle, 20°) in 10 minutes 20 seconds. The T2-weighted and proton density data were acquired using a dual-echo fast-spin echo pulse sequence (echo train length, 8; 3-mm skip, 3-mm interleaved; 2 acquisitions; repetition time/echo time/second echo time, 4000/14/84 seconds; 256×192; field of view, 20 cm; number of excitations, 1) in 6 minutes, 25 seconds. Whole brain susceptibility-weighted imaging data were acquired in 2 minutes, 20 seconds.

Magnetic resonance imaging scans were evaluated by a neuroradiologist (R.L.R.) blinded to the participant group. Images were assessed by visual inspection to rate the quality of data and to identify abnormalities. Abnormalities were classified by origin (i.e., acquired, developmental), type (i.e., infarction, mineralization, iron deposition, myelination delay, ventriculomegaly, abnormal T2W signal hyperintensity), extent (i.e., focal or diffuse), and anatomic location.

Statistical Methods

Comparisons of operative and medical risk factors, special services, cardiac symptomatology, and MRI variables were made using Fisher's exact tests for categorical measures and either 2-sample t-tests for continuous measures when normally distributed or Kruskal-Wallis tests when non-normal. Comparisons with respect to NYHA class utilized Cochran-Armitage trend tests. Neuropsychological outcomes of each syndrome group were compared to expected population means when available using 1-sample t-tests. Linear regression with adjustment for concurrent family social class was used to compare neuropsychological outcomes of the syndrome groups to those of the referent group when a population mean was not available (i.e. Rey-Osterrieth Complex Figure, Sense of Direction Scale, Reading the Mind in the Eyes Test-Revised, Autism Spectrum Quotient) and for such comparisons between the syndrome groups.

Linear regression analyses were used to identify predictors of neuropsychological outcomes of adolescents with tetralogy of Fallot without a genetic/phenotypic syndrome, using the variables listed in Table 1 (except NYHA classification and any neurological event). Predictors were screened to identify associations with the outcomes having a $P<0.20$, adjusting for family class. Predictors meeting this criterion were included in stepwise backward analysis with a $P<0.05$ retention criterion. Similar procedures were used to identify factors predicting MRI outcomes using logistic regression. Surgical complications included cardiac arrest, choreoathetosis, need for extracorporeal membrane oxygenation, junctional ectopic tachycardia, necrotizing enterocolitis, prolonged intensive care unit course (>1 week), renal failure (serum creatinine >1.5 mg/dL), reoperation/exploration, respiratory arrest, seizures, stroke, ventricular fibrillation, ventricular tachycardia, re-intubation, pneumonia, bleeding/hemorrhage, open chest, sepsis, ventricular premature beats, supraventricular tachycardia, "TET spells" during surgery, and tamponade.

RESULTS

Cardiac Status and History

Of 184 patients with tetralogy of Fallot seen at our institution and who met study eligibility criteria, 39 (21%) were followed elsewhere or lost to follow-up, and 54 (29%) declined study participation. Our study cohort included the remaining 91 patients, as well as 87 referent adolescents. Table 1 presents selected aspects of the medical histories of the patients. Most (76%) were older than 30 days at their first operation, slightly fewer than half experienced ≥1 complications during the first surgery, and more than half had undergone ≥2 surgeries (median number 2, range 1–7). Three-quarters (74%) had undergone ≥1 cardiac catheterization (median 2, range 0–14), and 32% experienced ≥1 complications during a catheterization. One-quarter (25%) had a genetic/phenotypic syndrome, including 22q11 (n=11), VATER/VACTERL (n=8), fetal alcohol syndrome (n=2), Alagille's syndrome (n=1), and Turner's syndrome (n=1). Twenty-six (29%) patients had PA. The syndrome and non-syndrome groups were comparable in operative measures and other medical risk factors. Those with pulmonary atresia, compared to those with pulmonary stenosis, were more likely to be neonates at the first operation (P<0.001) and to have had a first operation that was closed, i.e., performed off bypass (P=0.01). They also had more total operations and catheterizations (P<0.001 each), as well as more surgical and catheterization complications (P=0.03 and P<0.001, respectively).

Among patients, medical history was significant for stroke (n=4), seizures (n=11), choreoathetosis (n=4), and meningitis (n=2). Parents reported that 19% (n=17) had been diagnosed with Attention Deficit Hyperactivity Disorder (16% of those without a genetic/ phenotypic syndrome, 26% of those with a syndrome) and 35% (n=32) with a learning disability, which was more common in those with a syndrome (13/23, 56%) than those without a syndrome (19/68, 28%; P=0.02).

Compared to referent subjects, adolescents with tetralogy of Fallot were more likely to have received any special services (82% vs. 49%, P<0.001), including tutoring (52% vs. 26%, P<0.001), early intervention (40% vs. 1%, P<0.001), occupational therapy (44% vs. 0%, P<0.001), special education (42% vs. 1%, P<0.001), psychotherapy or counseling (36% vs. 15%, P=0.002) and physical therapy (35% vs. 19%, P=0.02). Approximately 1 in 4 (24%) patients, compared to 2% of referents, had been retained in grade (P<0.001). Receipt of neurodevelopmental services was more frequent in the group with a syndrome than in the group without a syndrome: early intervention (70% vs. 29%, P=0.001), occupational therapy (65% vs. 37%, P=0.03), and physical therapy (61% vs. 26%, P=0.005). Reports of special services were comparable between patients with and without pulmonary atresia.

Most adolescents with tetralogy of Fallot were in NYHA class I (68%), while 29% were in class II, and 3% in class III, whereas nearly all referent subjects were in class I (97%), with the remaining 3% in class II (P<0.001). NYHA class was not associated with the presence of a genetic/phenotypic syndrome, but was significantly worse for the group with pulmonary atresia compared with those with pulmonary stenosis (P=0.01). With regard to cardiac symptoms, patients were more likely than referents to report exercise intolerance (24% vs. 2%, P<0.001), shortness of breath with exercise (32% vs. 16%, P=0.02), palpitations (20%

vs. 1%, P<0.001), chest pain (22% vs. 3%, P<0.001), and general fatigue (24% vs. 1%, P<0.001). Reports of cardiac symptoms were similar between syndrome groups. Patients with pulmonary atresia were more likely than patients without pulmonary atresia to report shortness of breath with exercise (54% vs. 23%, P=0.006). Three patients (3%) had a pacemaker. Medications included angiotensin-converting-enzyme inhibitors (n=4), beta blockers (n=5), digoxin (n=8), diuretics (n=4), medication for Attention Deficit Hyperactivity Disorder (n=10), and psychotropic medications (n=5). Two adolescents with tetralogy of Fallot reported use of both Attention Deficit Hyperactivity Disorder and psychotropic medications.

Neuropsychological Assessment

The mean age (SD) of the patients was 14.6 (1.2) years. Table 2 summarizes the test scores of all patients and scores stratified by the presence of a genetic/phenotypic syndrome.

General Intelligence

Scores of patients without a genetic/phenotype diagnosis were lower than the expected population means for each index from the Wechsler Intelligence Scale for Children-Fourth Edition except Verbal Comprehension, with differences of 6–10 points (0.4–0.7 SD). Almost a third of patients (31%) had a Full-Scale IQ score of 85 (compared to an expected frequency of 16%) and 16% had a score 70 (compared to an expected 2%).

Scores of adolescents with a syndrome were significantly lower than those of adolescents without a syndrome on all composites, with differences approaching, and in some cases, exceeding 1 SD. Half of these adolescents had a Full-Scale IQ score 85, and 36% a score 70.

Academic Achievement

The Reading and Math Composite scores of adolescents without a genetic/phenotypic diagnosis were slightly lower, though not significantly, than the expected population means. On the Reading Composite, 21% scored 85 and 6% scored 70. On the Math Composite, 29% scored 85 and 19% scored 70. The frequencies of scores significantly lower than expected based on Full-Scale IQ score were 23% for Reading Composite and 29% for Math Composite.

Reading Composite and Mathematics Composite scores of adolescents with a syndrome were significantly lower than scores of adolescents without a syndrome, with the deficit being substantially greater on mathematics than reading. Compared to the expected population, the average deficit on the Mathematics Composite score for those with a syndrome was 27 points (1.8 SD). Half (52%) scored 85 on the Reading Composite and 26% scored 70. The corresponding figures for the Math Composite were 57% and 48%, respectively. On the Reading Composite, 18% scored significantly lower than would be expected based on Full-Scale IQ, and 55% scored significantly lower on the Math Composite.

Memory

The mean General Memory Index score of adolescents without a genetic/phenotypic diagnosis was approximately 0.8 SD lower than the expected population mean. Almost half (47%) scored 85, and 20% scored 70.

The scores of adolescents with a genetic/phenotypic syndrome tended to be lower than those without a syndrome, with a mean difference of approximately two-thirds of a SD. The mean score was approximately 1.4 SDs lower than the expected population mean; 57% of adolescents scored 85 and 38% scored 70.

Executive Functions

The Executive Function Summary scores of adolescents without a genetic/phenotypic syndrome were significantly lower than the expected population mean of 10; 22% scored 1 SD (i.e., 3 points) below the expected mean, and 7% scored 2 SDs or below the expected mean. The mean score of adolescents with a syndrome was significantly lower than that of adolescents without a syndrome; 48% scored 1 one SD below the expected mean, and 29% scored 2 SDs or more below.

On the Behavior Rating Inventory of Executive Function, both parent- and teacher-reported General Executive Composite scores were higher (i.e., more problematic) than the expected population mean. For adolescents without a genetic/phenotypic syndrome, teachers tended to report more problems than parents. On the parent questionnaire, 27% of adolescents without a genetic/phenotypic syndrome had a score 65 ("of potential clinical significance"), compared to 48% of adolescents with a syndrome. On the teacher-questionnaire, these figures were 36% and 50%, respectively. On the adolescent self-report questionnaire, those without and with a syndrome scored similarly (12% and 11% of scores, respectively, were in the range of potential clinical significance). Remarkably, neither group differed significantly from the expected population mean.

Visual-Spatial Skills

Patients scored significantly lower than the expected population mean on the Visual-Spatial Summary score, with the difference corresponding to 1 SD for adolescents without a genetic/phenotypic diagnosis and 2 SD for adolescents with a genetic/phenotypic syndrome. On the Rey-Osterrieth Complex Figure, adolescents with a syndrome scored significantly lower than those without a syndrome on all 3 endpoints for each condition (i.e., Copy, Immediate Recall, Delayed Recall).

On the Sense of Direction scale, scores of adolescents in the two syndrome groups did not differ significantly, nor did the scores of either group differ significantly from those of the referent group.

Attention

ADHD Index scores of the adolescents without a genetic/phenotypic syndrome were approximately 0.75 SD higher (i.e. less optimal) than the expected population mean.

Approximately one in five (21%) scored 66, which is considered to be "moderately atypical" (24).

ADHD Index scores of the adolescents with a syndrome were significantly higher than those of adolescents without a syndrome, with the difference in means being 0.8 SD, and approximately 1.5 SD higher than the expected population mean. Almost half (48%) scored 66.

Social Cognition

On the Reading the Mind in the Eyes Test-Revised, scores of the syndrome groups did not differ significantly, but both groups scored significantly lower (worse) than the referent group. This pattern was also evident for scores on the Autism Spectrum Quotient, with adolescents with tetralogy of Fallot scoring significantly higher (worse) than referents. Scores on the Toronto Alexithymia Scale were similar in the two syndrome groups, but the adolescents with a syndrome scored significantly higher (worse) than referents on the Difficulty Identifying Feelings and Difficulty Describing Feelings subscales (P=0.01 and P=0.04, respectively).

Comparison of tetraology of Fallot subgroups with and without pulmonary atresia

Patients with pulmonary atresia consistently performed worse than those without pulmonary atresia, with many of the relative deficits approaching, and in some cases exceeding, 0.5 SD in magnitude (data not shown). For most endpoints, however, the difference was not statistically significant, presumably due to the small size of the pulmonary atresia subgroup.

Magnetic Resonance Imaging

Complete data were available for 66 adolescents with tetralogy of Fallot and 75 referents. The frequency of "any abnormality" was 5-fold greater among the patients than the referents (42% vs. 8%, P<0.001; Table 3). The great majority of abnormalities were focal or multifocal, with most involving brain mineralization or iron deposits. Developmental abnormalities were almost twice as common among patients as referents (9% vs. 5%, respectively), but the difference did not reach statistical significance, with limited statistical power.

The patients with and without a genetic/phenotypic syndrome did not differ in the frequency of abnormalities. The frequency of any abnormality was greater (P<0.001) among patients with pulmonary atresia (13/16, 81%) than those without pulmonary atresia (15/50, 30%).

Predictors of Neuropsychological and MRI Outcomes

Table 4 lists potential predictors that were retained in stepwise linear regression analyses of selected neuropsychological outcomes of adolescents without a genetic/phenotypic syndrome. The number of complications at first operation was associated with the greatest number of scores. For many scores, a "dose-related" increase in the deficit was observed. Compared to adolescents with no complications, those with 2 complications scored an average of 17 points lower in Verbal Comprehension, and adolescents with one complication averaged 7 points lower. Similarly, adolescents with 2 complications scored

29 points lower on the Mathematics Composite and 25 points lower on the Visual-Spatial Summary score whereas those with one complication scored 11 and 13 points lower, respectively. Other covariates associated with multiple endpoints were the total number of surgical complications, gestational age, and seizures.

In analyses of three magnetic resonance imaging endpoints (i.e., any abnormality, focal/ multifocal abnormality, brain mineralization/iron deposit), patients with pulmonary atresia had greater odds of any abnormality (Odds Ratio=10.1, 95% confidence interval: 2.5–40.7) or a brain mineralization deposit (Odds Ratio=4.1, 95% confidence interval: 1.2–13.3) (Table 5). Reduced odds of focal/multifocal abnormality were significantly associated with higher birth weight (Odds Ratio=0.11, 95% confidence interval: 0.01–0.87). The confidence intervals for all of these odds ratios are wide due to small cell counts, however.

DISCUSSION

We found that a substantial proportion of adolescents with tetralogy of Fallot were experiencing difficulty meeting neurodevelopmental expectations, with many receiving remedial services, having been retained in grade, and manifesting deficits, compared to normative populations. Areas of diminished performance included general intelligence, academic achievement, memory, executive functions, visual-spatial skills, attention, and social cognition. These findings suggest that the deficits observed in patients at younger ages (3–9) persist into adolescence. Because adolescent neurocognitive and behavioral function strongly predicts adult functioning, our data suggest the need to develop strategies to optimize outcomes of the growing population of adults with repaired tetralogy of Fallot.

Among patients without known genetic/phenotypic diagnoses, medical factors that with the strongest association with neurodevelopmental outcomes included a greater number of complications at the first surgery, more total surgical complications across all operations, and occurrence of post-operative seizures. The number of complications at the first operation was "dose-related" with many endpoints, as adolescents with 2 or more complications scored almost 2 standard deviations lower on some tests than patients with no complications. Adolescents who experienced postoperative seizures were more likely to be rated as having difficulties with executive functions and attention. For magnetic resonance imaging outcomes, the diagnosis of pulmonary atresia was associated with a greater likelihood of at least one structural abnormality.

In most respects, patients with a genetic/phenotypic diagnosis performed significantly worse than patients without such a diagnosis, confirming the findings of Zeltser et al. (4) and others, though due to small numbers, we were not able to discern diagnosis-specific associations. In addition to the well-known relationship of tetralogy of Fallot to velo-cardio-facial syndrome, most often related to 22q11 microdeletion, tetralogy of Fallot is also associated with gene mutation or deletion (e.g., NKX2.5, JAG1, TBX5, TBX1, and FOXC2). Indeed, molecular genetic analyses have defined a genetic etiology in greater than 20% of patients (single gene defects and/or cytogenetic abnormalities), and unidentified monogenic mutations may account for an even greater proportion of cases. We hypothesize that as-yet unknown genetic factors involved in the etiology of tetralogy of Fallot may also

impact brain development and could explain, in part, the observation that even patients without known syndromes exhibited significant deficits.

With regard to executive functions, adolescents rated their skills as being average, but both parents and teachers identified many weaknesses, and the frequencies of scores of clinical concern were several-fold greater for these informants than for the adolescents themselves. Similar findings have been reported in adolescents with d-transposition of the great arteries (28), suggesting that relying solely on self-reports of patients with congenital heart disease might underestimate the severity of their challenges, at least in the domain of executive functions.

Our study should be interpreted in light of its limitations. The most important is potential selection bias. Outcomes of patients whose families agreed to participate might not be representative of outcomes among all adolescents with tetralogy of Fallot. In the absence of data on outcomes of non-participants, however, the direction of a bias introduced by selective enrollment is uncertain. Genetic testing was performed in most, but not in every patient. The patients' surgeries occurred more than a decade ago, and more recent cohorts of patients with tetralogy of Fallot might have benefited from recent improvements in surgical and medical management.

In summary, although many adolescents with tetralogy of Fallot have neurodevelopmental outcomes within the average range, a sizeable minority do not, even among patients without a known genetic/phenotypic diagnosis. Our results support recent guidelines recommending enhanced neurodevelopmental surveillance of a child with congenital heart disease (29) so that appropriate, timely interventions can be tailored to assist the patient in achieving his or her fullest potential.

Acknowledgments

References

1. Majnemer A, Limperopoulos C. Developmental progress of children with congenital heart defects requiring open heart surgery. Sem Pediatr Neurol. 1999; 6:12–9.

2. Loffredo CA. Epidemiology of cardiovascular malformations: prevalence and risk factors. Am J Med Genet. 2000; 97:319–25. [PubMed: 11376444]

3. Bellinger DC, Wypij D, duPlessis AJ, et al. Developmental and neurologic effects of alpha-stat versus pH-stat strategies for deep hypothermic circulatory arrest in infants. J Thorac Cardiovasc Surg. 2001; 121:374–83. [PubMed: 11174744]

4. Zeltser I, Jarvik GP, Bernbaum J, et al. Genetic/Phenotypic factors are important determinants of neurodevelopmental outcome after repair of tetralogy of Fallot. J Thorac Cardiovasc Surg. 2008; 135:91–7. [PubMed: 18179924]

5. Gaynor JW, Gerdes M, Nord AS, et al. Is cardiac diagnosis a predictor of neurodevelopmental outcome after cardiac surgery in infancy? J Thorac Cardiovasc Surg. 2010; 140:1230–37. [PubMed: 20951391]

6. Hovels-Gurich HH, Konrad K, Skorzenski D, et al. Long-term neurodevelopmental outcome and exercise capacity after corrective surgery for tetralogy of Fallot or ventricular septal defect in infancy. Ann Thorac Surg. 2006; 81:958–66. [PubMed: 16488701]

7. Hovels-Gurich HH, Konrad K, Skorzenski D, Herpertz-Dahlmann B, Messmer BJ, Seghaye MC. Attentional dysfunction in children after corrective cardiac surgery in infancy. Ann Thorac Surg. 2007; 83:1425–30. [PubMed: 17383351]

8. Hovels-Gurich HH, Bauer SB, Schnitker R, et al. Long-term outcome of speech and language in children after corrective surgery for cyanotic or acyanotic cardiac defects in infancy. Europ J Paediatr Neurol. 2008; 12:378–86.

9. Miatton M, De Wolf D, François K, Thiery E, Vingerhoets G. Intellectual, neuropsychological, and behavioral functioning in children with tetralogy of Fallot. J Thorac Cardiovasc Surg. 2007; 133:449–55. [PubMed: 17258582]

10. Shampaine EL, Nadelman L, Rosenthal A, Behrendt D, Sloan H. Longitudinal psychological assessment in tetralogy of Fallot. Pediatr Cardiol. 1990; 10:135–50. [PubMed: 2798188]

11. Daliento I, Mapelli D, Russo G, et al. Health related quality of life in adults with repaired tetralogy of Fallot: psychosocial and cognitive outcomes. Heart. 2005; 91:213–8. [PubMed: 15657236]

13. Evans AC. Brain Development Cooperative Group. The NIH MRI study of normal brain development. NeuroImage. 2006; 30:184–202. [PubMed: 16376577]

14. Wechsler, D. WISC-IV. Administration and Scoring Manual. San Antonio: The Psychological Corporation; 2003.

15. The Psychological Corporation. Wechsler Individual Achievement Test. 2. San Antonio: The Psychological Corporation; 2002.

16. Wechsler, D. WISC-IV Integrated Technical and Interpretive Manual. San Antonio: Harcourt Assessment, Inc; 2004.

17. Cohen, MJ. Children's Memory Scale. San Antonio: The Psychological Corporation; 1997.

18. Delis, DC.; Kaplan, E.; Kramer, JH. Delis-Kaplan Executive Function System. San Antonio: The Psychological Corporation; 2001.

19. Gioia, GA.; Isquith, PK.; Guy, SC.; Kenworthy, L. The Behavior Rating Inventory of Executive Function. Odessa, FL: Psychological Assessment Resources; 2000.

20. Guy, SC.; Isquith, PK.; Gioia, GA. Behavior Rating Inventory of Executive Function-Self-Report Version. Lutz, FL: Psychological Assessment Resources, Inc; 2004.

21. Gardner, MF. Test of Visual-Perceptual Skills (non-motor) (Upper Level) Revised. Hydeville, CA: Psychological and Educational Publications, Inc; 1997.

22. Bernstein, JH.; Waber, DP. Developmental scoring system for the Rey-Osterrieth Complex Figure: Professional manual. Lutz, FL: Psychological Assessment Resources, Inc; 1996.

23. Hegarty M, Richardson AE, Montello DR, Lovelace K, Subbiah I. Development of a self-report measure of environmental spatial ability. Intelligence. 2002; 30:425–47.

23. Garson A Jr, Williams RB, Reckless J. Long-term follow-up of patients with tetralogy of Fallot: physical health and psychopathology. J Pediatr. 1974; 85:429–433. [PubMed: 4853035]

24. Connors, CK. Connors' Rating Scales-Revised. North Tonawanda, NY: Multi-Health Systems, Inc; 1997.

25. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J Child Psychol Psychiatry. 2001; 42:241–51. [PubMed: 11280420]

26. Wheelwright S, Auyeung B, Allison C, Baron-Cohen S. Defining the broader, medium and narrow autism phenotype among parents using the Autism Spectrum Quotient (AQ). Molec Autism. 2010; 1:1–10. [PubMed: 20678244]

27. Bagby RM, Parker JDA, Taylor GJ. The twenty-item Toronto Alexithymia Scale-I. Item selection and cross-validation of the factor structure. J Psychosom Res. 1994; 38:23–32. [PubMed: 8126686]

28. Bellinger DC, Wypij D, Rivkin MJ, et al. Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure. Circulation. 2011; 124:1361–9. [PubMed: 21875911]

29. Marino BS, Lipkin PH, Newburger JW, et al. American Heart Association Congenital Heart Defects Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012; 126:1143–72. [PubMed: 22851541]

Table 1

Characteristics of Adolescents with Tetralogy of Fallot (N=91).

Variable	%, Mean ± SD, or Median (Range)
Pre-operative characteristics	
Birth weight (kg)	3.1 ± 0.7
Gestational age (wk)	39.2 ± 2.3
Male	55
Race/ethnicity (Caucasian)	87
Genetic diagnosis present	25
Pulmonary atresia	29
Status at first surgery	
Age (d)	112 (2–1378)
Age > 30 d	76
Open procedure	88
Duration of DHCA (min), if open	30 (0–69)
Total support time (min), if open	97 (21–220)
Number of surgical complications	
None	53
One	26
Two or more	21
Medical history	
Total number of surgeries	
One	48
Two	24
Three or more	27
Total number of open surgeries	
One	54
Two	30
Three or more	16
Total number of surgical complications	
None	48
One	21
Two or more	31
Total number of catheterizations	
None	26
One or two	30
Three or more	44
Total number of catheterization complications	
None	68
One or two	13
Three or more	19

Variable	
	%, Mean ± SD, or Median (Range)
Seizures	12
Any neurological event[*]	20
New York Heart Association class	
Class I	68
Class II	29
Class III	3
Family social status[†]	49 ± 12
Age at developmental testing (yr)	14.6 ± 1.2

DHCA = deep hypothermic circulatory arrest.

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

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

Table 2

Neuropsychological Outcomes of Adolescents with Tetralogy of Fallot According to Genetic Diagnosis.

Variable	Tetralogy of Fallot			P value comparing those with genetic diagnosis to those without [*]	P value comparing those without genetic diagnosis to expected population mean [†]	P value comparing those with genetic diagnosis to expected population mean [†]
	All (N=91)	Genetic Diagnosis Absent or No Evaluation (N=68)	Genetic Diagnosis Present (N=23)			
	Mean ± SD					
Wechsler Intelligence Scale						
Verbal Comprehension	95.6 ± 21.5	98.7 ± 20.4	86.4 ± 22.5	0.01	0.62	0.009
Perceptual Reasoning	89.1 ± 21.2	93.7 ± 20.2	75.4 ± 18.2	<0.001	0.01	<0.001
Working Memory	88.9 ± 21.0	91.4 ± 20.2	81.7 ± 22.1	0.046	<0.001	<0.001
Processing Speed	87.0 ± 19.3	90.0 ± 18.4	77.8 ± 19.5	0.008	<0.001	<0.001
Full-Scale IQ	89.0 ± 22.8	93.0 ± 21.4	77.0 ± 23.1	0.002	0.009	<0.001
Wechsler Individual Achievement Test						
Reading Composite	92.6 ± 20.3	96.1 ± 17.8	82.5 ± 24.1	0.003	0.07	0.002
Mathematics Composite	89.5 ± 27.6	95.1 ± 25.6	73.1 ± 27.1	<0.001	0.12	<0.001
General Memory Index	86.3 ± 21.7	88.5 ± 20.5	79.3 ± 24.3	0.09	<0.001	<0.001
Executive Function Summary Score	8.2 ± 2.9	8.7 ± 2.8	6.4 ± 2.7	<0.001	<0.001	<0.001
Behavior Rating Inventory of Executive Function						
Self-Report	50.3 ± 10.8	49.8 ± 10.8	51.9 ± 10.9	0.43	0.89	0.45
Parent	58.0 ± 13.1	55.8 ± 12.8	64.4 ± 12.1	0.004	<0.001	<0.001
Teacher	63.0 ± 19.7	62.3 ± 19.8	65.4 ± 20.1	0.49	<0.001	0.01
Visual-Spatial Summary Score	82.6 ± 19.7	86.4 ± 19.6	70.9 ± 15.2	<0.001	<0.001	<0.001
Rey-Osterrieth Complex Figure [††]						
Copy: Organization	7.8 ± 3.8	8.7 ± 3.7	5.1 ± 3.0	<0.001	0.001	<0.001
Structural Element	23.2 ± 3.8	23.7 ± 3.2	21.6 ± 4.9	0.02	0.004	<0.001
Incidental Element	36.3 ± 6.0	37.3 ± 4.0	33.2 ± 9.3	0.006	0.003	<0.001
Immediate Recall: Organization	6.2 ± 4.1	6.8 ± 4.1	3.9 ± 3.5	0.006	0.008	<0.001
Structural Element	19.8 ± 6.0	21.0 ± 4.8	15.7 ± 7.8	<0.001	0.03	<0.001
Incidental Element	26.4 ± 9.1	27.7 ± 8.1	21.8 ± 11.0	0.01	0.46	<0.001
Delayed Recall: Organization	6.4 ± 4.0	7.0 ± 3.8	4.2 ± 3.7	0.005	0.048	<0.001
Structural Element	19.6 ± 6.5	21.0 ± 5.3	15.2 ± 8.0	<0.001	0.004	<0.001

Variable	Tetralogy of Fallot			P value comparing those with genetic diagnosis to those without *	P value comparing those without genetic diagnosis to expected population mean †	P value comparing those with genetic diagnosis to expected population mean †
	All (N=91)	Genetic Diagnosis Absent or No Evaluation (N=68)	Genetic Diagnosis Present (N=23)			
Incidental Element	25.5 ± 9.2	27.1 ± 8.1	20.1 ± 10.8	0.003	0.30	<0.001
Sense of Direction Scale ††	46.2 ± 9.0	46.1 ± 8.5	46.3 ± 10.8	0.97	0.09	0.29
Parent Conner's ADHD Index T Score	59.3 ± 13.6	57.2 ± 12.8	65.5 ± 14.3	0.007	<0.001	<0.001
Reading the Mind in the Eyes ††	18.8 ± 5.9	19.2 ± 6.0	17.0 ± 5.0	0.38	<0.001	<0.001
Toronto Alexithymia Scale ††						
Difficulty Identifying Feelings	17.3 ± 6.0	16.7 ± 6.0	19.2 ± 6.1	0.42	0.049	0.01
Difficulty Describing Feelings	13.7 ± 4.8	12.9 ± 4.3	16.8 ± 5.5	0.09	0.88	0.04
Externally-Oriented Thinking	20.6 ± 4.7	20.2 ± 4.3	22.0 ± 5.8	0.40	0.93	0.41
Autism Spectrum Quotient ††	17.9 ± 5.6	17.6 ± 5.9	18.9 ± 4.2	0.31	0.03	0.01

*
Determined by linear regression with adjustment for concurrent family social status.

†
Determined by one-sample *t*-tests comparing the TOF group (with or without genetic diagnosis) with expected population means of 100, 10, or 50, as appropriate.

††
Expected population means are not available; P value is determined by linear regression comparing the TOF group (with or without genetic diagnosis) with a group of 87 referents, with adjustment for concurrent family social status.

Missing < 10% of outcomes except for Behavior Rating Inventory of Executive Function - Teacher (n=58), Reading the Mind in the Eyes (n=66) and the Toronto Alexithymia Scale (n=27) tasks.

Table 3

Structural magnetic resonance imaging findings of adolescents with tetralogy of Fallot and referents.

Variable	TOF (n = 66)	Referent (n=75)	P value[*]
	n (%)		
Any abnormality	28 (42)	6 (8)	<0.001
Focal or multifocal abnormality	24 (36)	1 (1)	<0.001
Focal infarction or atrophy	4 (6)	0	0.046
Brain mineralization/iron deposit	21 (32)	1 (1)	<0.001
Diffuse abnormality	2 (3)	1 (1)	0.60
Myelination delay	0	0	-
Ventriculogealy	1 (2)	0	0.47
Abnormal T2 hyperintensities	1 (2)	1 (1)	1.0
Generalized abnormality	1 (2)	0	0.47
Developmental abnormality	6 (9)	4 (5)	0.52
Major malformation[†]	1 (2)	0	0.47
Minor malformation[‡]	5 (8)	4 (5)	0.73

TOF = tetralogy of Fallot.

[*] Determined by Fisher's exact tests.

[†] The major malformation is hypoplasia in the right cerebellar hemisphere and Dandy-Walker spectrum anomaly.

[‡] Minor malformations include agenesis of the corpus and partial anterior absence of corpus callosum (no other findings of holoprosencephaly), arachnoid cyst, subependymal nodular heteropia (right parietal white matter), absent splenium of corpus callosum (not agenesis), and mildly dysmorphic ventricles in TOF group; and Chiari malformation and developmental venous anomaly in right parietal lobe in referent group.

Table 4

Stepwise linear regression of select neuropsychological outcomes of adolescents with tetralogy of Fallot without genetic anomalies (n=68), adjusting for concurrent family social status

Variable	Number of Complications at First Surgery (vs. None)		Other Covariates
	One	Two or More	
	$\beta \pm SE$ (P value)		
Wechsler Intelligence Scale			
Verbal Comprehension	−6.9 ± 5.2 (0.19)	−17.0 ± 5.9 (0.006)	-
Perceptual Reasoning	-	-	One surgical complication (vs. None): −14.8 ± 5.3 (0.007); Two or more surgical complications (vs. None): −24.0 ± 4.8 (<0.001); Three or more open surgeries (vs. < 3): 17.1 ± 5.5 (0.003)
Working Memory	-	-	One surgical complication (vs. None): −9.9 ± 5.7 (0.09); Two or more surgical complications (vs. None): −15.6 ± 5.0 (0.003)
Processing Speed	-	-	-
Full-Scale IQ	−9.9 ± 5.4 (0.07)	−20.1 ± 6.1 (0.002)	-
Wechsler Individual Achievement Test			
Reading Composite	-	-	Seizures (vs. None): −18.4 ± 6.9 (0.01)
Mathematics Composite	−10.8 ± 6.0 (0.07)	−29.1 ± 6.8 (<0.001)	-
General Memory Index	-	-	Male: 13.7 ± 4.8 (0.006); One surgical complication (vs. None): −7.2 ± 6.3 (0.26); Two or more surgical complications (vs. None): −16.0 ± 5.3 (0.004); Gestational age (wk): 2.0 ± 0.9 (0.04)
Executive Function Summary Score	−0.8 ± 0.7 (0.29)	−2.5 ± 0.8 (0.003)	-
Behavior Rating Inventory of Executive Function			
Parent	-	-	Non-Hispanic Caucasian: −10.5 ± 4.2 (0.02)
Teacher	-	-	-
Visual-Spatial Summary Score	−13.3 ± 4.8 (0.008)	−25.0 ± 5.5 (<0.001)	-
Parent Conner's ADHD Index T Score	-	-	Seizures (vs. None): 25.7 ± 6.1 (<0.001); Birth weight (kg): −3.8 ± 1.9 (0.0498)
Reading the Mind in the Eyes	-	-	Gestational age (wk): 0.7 ± 0.3 (0.01); Seizures (vs. None): −6.6 ± 2.7 (0.02); Age at developmental testing: 1.4 ± 0.6 (0.03); One or two catheterizations (vs. None): −3.6 ± 1.7 (0.04); Three or more catheterizations (vs. None): 0.8 ± 1.8 (0.66)
Autism Spectrum Quotient	-	-	DHCA duration: 0.08 ± 0.03 (0.01)

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

All characteristics from Table 1 were considered for inclusion in the regression models except NYHA classification and any neurological event. Coefficients for intercepts and family social status are not reported.

Table 5

Stepwise logistic regression of select magnetic resonance imaging outcomes of adolescents with tetralogy of Fallot (n=66).

Variable	Have Pulmonary Atresia (vs. Do Not Have)	Birth Weight (kg)
	Odds ratio (95% CI), P value	
Any Abnormality	10.1 (2.5, 40.7), 0.001	-
Focal or multifocal abnormality	-	0.11 (0.01, 0.87), 0.04
Brain mineralization deposit	4.1 (1.2, 13.3), 0.02	-

Values are estimated odds ratios, 95% confidence intervals (CI), and P values.

All characteristics from Table 1 were considered for inclusion in the regression models except NYHA classification and any neurological event.