Surgical Outcomes in Syndromic Tetralogy of Fallot: A Systematic Review and Evidence Quality Assessment

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Abstract

Background: Tetralogy of Fallot (ToF) is one of the most common cyanotic congenital heart defects. We sought to summarize all available data regarding the epidemiology and perioperative outcomes of syndromic ToF patients.

Methods: A PRISMA-compliant systematic literature review of PubMed and Cochrane Library was performed.

Results: Twelve original studies were included. The incidence of syndromic ToF was 15.3% (n=549/3,597). The most prevalent genetic syndromes were 22q.11.2 deletion (47.8%; 95% CI: 43.4-52.2) and trisomy 21 (41.9%; 95% CI: 37.7-46-3). Complete surgical repair was performed in 75.2% of the patients (n=161/214; 95% CI: 69.0-80.1) and staged repair in 24.8% (n=53/214; 95 CI: 19.4-30.9). Relief of RVOT obstruction was performed with transannular patch in 64.7% (n=79/122; 95% CI: 55.9-72.7) of the patients, pulmonary valve-sparing technique in 17.2% (n=21/122; 95% CI: 11.5-24.9), and RV-PA conduit in 18.0% (n=22/122; 95% CI: 12.1-25.9). Pleural effusions were the most common postoperative complications (n=28/549; 5.1%; 95% CI: 3.5-7.3). Reoperations were performed in 4.4% (n=24/549; 95% CI: 2.9-6.4) of the patients. All-cause mortality rate was 9.8% (n=51/521; 95% CI: 7.5-12.7).

Conclusion: Genetic syndromes are seen in approximately 15% of ToF patients. Long-term survival exceeds 90%, suggesting that surgical management should be dictated by anatomy regardless of genetics.

Key words: Tetralogy of Fallot, TOF, cardiac surgery, gene mutation, genetics

Introduction

Tetralogy of Fallot (ToF) has an incidence of one in 3,500 live births and constitutes one of the most common cyanotic congenital heart defects [1]. Classically, ToF is comprised of four components: ventricular septal defect (VSD), obstruction of the right ventricular outflow tract (RVOT), override of the aorta, and right ventricular hypertrophy. A significant number of anatomical variants have been described, most commonly regarding malformations of the RVOT, such as hypertrophied subvalvar muscle, pulmonary annular hypoplasia, pulmonary valve stenosis, supravalvar pulmonary stenosis, and/or branch pulmonary artery (PA) stenosis [2].

Several chromosomal and genetic syndromes have been associated with ToF [3]. DiGeorge syndrome and other disorders within the 22q11.2 deletion spectrum are the genetic aberrations most commonly seen with ToF. Patients with trisomy 21, VACTERL syndrome, and trisomy 18 can also manifest ToF phenotypes. Syndromic patients tend to present with different cardiac anatomy and extracardiac features, which may impact their prognosis [4]. The purpose of this study was to systematically review and summarize all available data regarding the epidemiology and perioperative outcomes of syndromic ToF patients.

Materials and methods

Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines **(Online Resource 1)** and in line with the protocol agreed by all authors. Eligible studies were identified through search of the PubMed bibliographical database and the Cochrane Library (end-of-search date: April 7th, 2018). The literature search was executed by two independent investigators (DIA and KK) using the following algorithm: tetralogy of Fallot AND (gene OR mutation OR variant OR genetics OR genome OR pathway).

Original clinical studies, published in English, reporting on demographics, clinical manifestations, diagnostic interventions, and postoperative outcomes of syndromic patients undergoing surgical repair of ToF were considered eligible for the present systematic review. The reference lists of systematically reviewed articles were hand-searched for potentially eligible, missed studies using snowball methodology.

Excluded studies were: 1) papers published in a language other than English, 2) studies irrelevant to syndromic ToF, 3) in vitro studies, 4) animal studies, 5) reviews and meta-analyses, 6) letters to the editor, comments, errata, and 7) abstracts. Any disagreements were resolved by consensus with another author (KSM). No sample size restriction was applied when screening eligible studies.

Data extraction and tabulation

A standardized, pre-piloted form was used to extract and tabulate data from the included studies for evidence synthesis and assessment of study quality. Two reviewers (DIA and KK) extracted the data independently and any discrepancies were identified and resolved through quality control discussions with another author (KSM) whenever necessary. The following data were extracted for each eligible study: study characteristics (first author, year of publication, study design, number of patients), demographics (sex, age, race, weight), genetic data, extracardiac malformations (craniofacial, ocular, ear, nose, mouth, palate, respiratory, abdominal, renal, genital, skeletal, extremity), pulmonary valve status (stenosis, atresia, absent), PA stenosis, PA hypoplasia, aortic dilatation, valve regurgitation, right aortic arch, aberrant right subclavian artery, major aortopulmonary collateral arteries (MAPCA), aortic override more than 50%, patent ductus arteriosus (PDA), discontinuous PA, multiple ventricular septal defects (VSDs), anomalous coronary artery pattern, anomalous systemic venous connection, choanal septal hypoplasia, surgical approach, operative data, hospitalization (length of stay, length of stay in intensive care unit, mechanical ventilation duration), complications, mortality, and cause of death.

Statistical analysis

Categorical variables were summarized as frequencies and percentages accompanied by 95% confidence intervals (95% CI), while continuous variables were summarized as means and standard deviations (SDs). Data on outcomes of interest were tabulated and analyzed cumulatively. All relative rates were estimated based on available data for each variable of interest. Data analyses were performed in R 3.3.2 (R Core Team, Vienna, Austria).

Assessment of study quality

The quality of included studies was evaluated using the Newcastle-Ottawa Quality scale (NOS); [5] with a score of at least 6 indicating high quality. In the item assessing whether the follow-up period was long enough for outcomes to occur, the cut-off value was *a priori* set at 12 postoperative months, whereas regarding the item about the adequacy of follow-up, a 90% rate was also *a priori* adopted. Two reviewers (DIA and KK) working independently rated the studies and final decision was reached by consensus with another author (KSM).

Results

Article selection

The initial literature search yielded 968 potentially relevant records. After screening titles and abstracts, 287 studies were retrieved for full-text evaluation. Ultimately, 12 studies [3,4,6-15] satisfied the predetermined search criteria and were included in this systematic review **(Figure 1)**. Four studies were conducted in the United States [6,8,11,13], two in Canada [9,14], four in Europe [3,4,7,12], one in Latin America [15], and one in Asia [10].

Quality of evidence assessment

The mean NOS score for the 12 cohort studies that were included in the present systematic review was 5.7 (SD: 1.5), (high quality: six studies; fair quality: six studies). Detailed modified NOS quality assessment for included comparative studies is provided in **Online Resource 2**.

Patient characteristics

Systematically reviewed studies recruited a total of 3,597 patients with ToF. The incidence of syndromic ToF was 15.3% (n=549/3,597). The male to female ratio was 1.5:1 (201 males, 134 females, 214 unreported) and mean patient age at the time of surgery was 7.7 ± 4.7 months [3,7,8,13]. Neonates accounted for 3.6% (n=20/459; 95% CI: 2.8-6.7) of syndromic patients for whom age data were available. Mean weight at the time of surgery was 5.8 ± 1.6 kilograms [8,13]. Clinical manifestations were reported in 55 syndromic patients. Cardiac and extra-cardiac malformations are summarized in **Online Resource 3** and **4**, respectively.

Genetics

Out of 549 patients with genetic syndromes, the specific genetic malformation was stated in 90.7% (n=498/549; 95% CI: 87.9-92.9) while in 9.3% of patients the genetic malformation was not reported. 22q11.2 deletion was found in 47.8% (n=238/498; 95% CI: 43.4-52.2), and Trisomy 21 in 41.9% (n=209/498, 95% CI: 37.7-46.3) of the patients. VACTERL association was described in 2.6% (n=13/498; 95% CI: 1.3-4.1) of syndromic cases. A more detailed overview of genes associated with ToF can be found in **Table 1**.

Perioperative management

Details on surgical approach were available in 46.6% (n=214/459) of syndromic ToF cases [3,6,7,10,11,13]. Complete surgical repair was performed in 75.2% of the patients (n=161/214; 95% CI: 69.0-80.1) and staged repair in 24.8% (n=53/214; 95 CI: 19.4-30.9). Details on palliation were available for eight patients: one central shunt, four Blalock-Taussig shunts (BT shunts), and three catheter-based balloon dilations. VSDs were repaired with patches. Relief of RVOT obstruction was performed with transannular patch in 64.7% (n=79/122; 95% CI: 55.9-72.7) of the patients, while in 17.2% (n=21/122; 95% CI: 11.5-24.9) a pulmonary valve-sparing technique was used. Furthermore, a RV-PA conduit was created in 18.0% (n=22/122; 95% CI: 12.1-25.9). Mean lengths of intensive care unit stay and hospitalization were 6.9 ± 4.9 days and 9.9 ± 6.1 days, respectively [6-8,13]. Moreover, patients requiring mechanical ventilation stayed on the ventilator for a mean of 45.5±72.3 hours [6,7,13]. Mean cardiopulmonary bypass time was 105.6 ± 33.5 min [8,13].

Postoperative complications and reoperations

Postoperative morbidity was described in 5 studies (n=318) [3,7,8,12,13]. A total of 102 complications were reported. The most frequent complications were pleural effusions (5.1%, n=28/549; 95% CI: 3.5-7.3), mostly chylothorax (n=23 of 28). Infections requiring antibiotics developed in 4.7% of the patients (n=26/549; 95% CI: 3.2-6.9). Specifically, half were mild infections, including six surgical site infections and seven cases of pneumonia (n=13/549; 95% CI: 1.3-4.1). Sepsis was recorded in 2.4% of our cohort (n=13/549; 95% CI: 1.3-4.1). Reoperations and cardiac catheterizations were performed in 4.4% (n=24/549; 95% CI: 2.9-6.4) and 2.5%

(n=14/549; 95% CI: 1.5-4.3) of the patients, respectively. Prolonged ventilation for over 48 hours was needed in 2.2% of the patients (n=12/549; 95% CI: 1.2-3.8). Only 1.1% of the patients experienced arrhythmias (n=6/549; 95% CI: 0.4-2.4), of which four were junctional tachycardias, one third-degree atrioventricular block, and one unspecified. Postoperative complications are summarized in **Table 2**.

Long-term outcomes

Survival data were available for 521 (94.8%) patients with syndromic ToF. Specifically, 90.2% of the patients survived (n=470/521; 95% CI: 87.3-92.5) and all-cause mortality was 9.8% (n=51/521; 95% CI: 7.5-12.7). The timeline and cause of death was described in 16 out of 51 fatalities (Table 3). Of note, four patients died in-hospital, but the cause of the death was not further defined. Most common cause of in-hospital and out-of-hospital death were sepsis (n=5/16; 31.2%, 95% CI: 13.91-55.85) and pulmonary over-circulation (n=2/16; 12.5%, 95% CI: 5.8-43.8), respectively.

Discussion

In the present systematic review, we analyzed the clinical and pathological features and surgical outcomes of patients with syndromic Tetralogy of Fallot. Using published literature, we estimated the incidence of syndromic ToF at approximately 15%. Our analysis validates prior work showing 22q11.2 deletion (47.8%) and Down's syndrome (41.9%) to be the most common genetic abnormalities associated with ToF. We found that syndromic ToF is frequently associated with aortic dilatation (92.9%) and MAPCAs (61.5%) and describe in detail other cardiac pathology that can be found in this group of patients. Importantly, our findings suggest that hypoplastic pulmonary arteries (22.3%) may be more prevalent in syndromic compared to non-syndromic ToF (approximately 10%) [3,16].

It is important to emphasize that cardiac phenotype does differ based on underlying genetic profiles. Malformations of the aortic arch are extremely prevalent in ToF/22q11.2 deletion. The incidence of MAPCAs seems to be particularly high (91.0%) in this population. Right (70.0%) and high (43.0%) aortic arch as well as aberrant right or left subclavian artery (35.0%) are also quite common in 22q11.2 deletion [17-19]. Higher frequency of isolated left PA, subaortic VSDs, and persistent left superior vena cava have also been reported in

patients within the 22q11.2 deletion spectrum. The presence of atrioventricular septal defect (AVSD) is more often correlated with Down syndrome and typically makes 22q11.2 deletion less likely. Large genotype-phenotype studies have shown that ToF in the setting of Down syndrome is coupled with AVSDs in 25% of the cases [20-22]. Patients with ToF and mutations in exons 24-28 of the fibrillin-1 (FBN1) gene usually have aortic dilation [10]. In our systematic review, 92.8% of patients with FBN1 gene mutations had aortic dilatation and 28.5% had aortic regurgitation. Additionally, among patients with FBN1 mutations, 85.7% had aortic override more than 50%, 67.8% had MAPCAs, and 46.4% had right aortic arches. In CHARGE association, the prevalence of ToF is around 30% and cardiac pathology typically includes concomitant conotruncal abnormalities [20].

Surgical intervention is usually performed in the first year of life, with the majority of repairs performed electively before age six months. If the RVOT obstruction is not critical, intracardiac repair is typically deferred until after the neonatal period not only to allow pulmonary vascular resistance to drop but also to give time to the infant to gain weight [23]. Neonatal surgical intervention may be needed in the setting of severe RVOT obstruction with or without ductal dependency [24]. Primary intracardiac repair is generally attempted in these patients [25]. Palliative shunts, most frequently BT shunts, are performed when primary surgical repair is not an option (e.g. prematurity, medically refractory tet spells, coronary abnormalities, and hypoplastic PAs) [26,27]. According to our analysis [3,6,7,10,13], nearly 25% of syndromic ToF patients underwent a staged repair, which is more than two times higher compared to the rate of staged repairs in non-syndromic ToF (approximately 10%) [3]. This phenomenon may be at least partly attributed to the very high incidence of hypoplastic pulmonary arteries seen in syndromic patients.

Complete repair includes enlargement of the RVOT and patch closure of the VSD [22]. Most syndromic patients (64.7%) seem to undergo RVOT enlargement through resection of infundibular and subinfundibular muscle bundles followed by placement of a transannular patch to create unobstructed flow from the RV into the PAs [28, 29]. Although the transatrial approach carries a lower risk for late ventricular arrhythmias compared to ventriculotomy, two large population-based analyses demonstrated that ventriculotomy with transannular patch repair remains the most common strategy for repair of ToF [21,30].

Nevertheless, techniques that help maintain pulmonary valve competence are increasingly gaining traction. In our systematic review, a "valve-sparing approach" [3,13] was performed in 17.2% of syndromic ToF patients. However, there is no definite consensus on the size of the pulmonary annulus and the acceptable degree of residual RVOT obstruction that is amenable to a valve-sparing approach [31,32]. Valved conduits from the RV

to the distal main PA were placed in 18.0% of syndromic ToF patients [3,13]. Although stenosis and/or regurgitation of the conduit prosthetic valve and conduit stenosis can occur, none of the eligible studies reported any of these complications [33,34].

In our analysis, the most frequent complications were pleural effusions and infections requiring antibiotics. Of note, large series from Europe have shown that the complication rate of syndromic ToF patients (47.1%) is significantly higher than those without genetic malformations (17.4%). For this reason, longer ICU stay seems to be required in syndromic patients postoperatively (7.4 vs 2.9 days) [3]. No ventricular dysrhythmias or need for implantable cardioverter-defibrillator were reported. All-cause mortality for patients with syndromic ToF was 9.8% and the most common cause of death was in-hospital sepsis. Reports from Europe suggest that genetic defects, other than 22q11.2 deletion and Down syndrome, may negatively impact long-term outcomes of ToF [3]. PA hypoplasia and surgical repair or palliation of extracardiac lesions seem to be independent risk factors for mortality in syndromic patients, possibly due to secondary changes in pulmonary compliance and pulmonary mechanics, as well as an increased incidence of gram-negative infections.

Freedom from reintervention in syndromic ToF has been shown to be significantly lower compared with non-syndromic patients [3]. Residual RVOT obstruction and recurrent VSDs seem to be the dominant indication for redo operations or interventional procedures in the syndromic subgroup. Central PA hypoplasia and more frequent use of palliative procedures can account for a higher incidence of recurrent RVOT obstruction or branch PA stenosis after complete repair of cardiac lesions in syndromic ToF. Recurrent VSDs occur three times more frequently in TOF patients with genetic disorders [3]. Lastly, syndromic patients undergoing ToF repair may have poorer neurologic outcomes in the long-run; presence of 22q11.2 deletion and APOE ε2 allele are independently associated with neurodevelopmental dysfunction one year after surgery [11,35].

To our knowledge, this is the first systematic review looking at surgical outcomes after repair of ToF in syndromic patients. Methodological strengths of the present paper include: 1) comprehensive literature search following rigorous and systematic methodology, 2) detailed data extraction with pre-piloted forms, and 3) standardized quality assessment of eligible studies using the Newcastle-Ottawa Quality scale. This analysis has certain limitations. First, as with any systematic review, certain studies did not report on all outcomes of interest and therefore relative rates were estimated based on available data. Clinical manifestations were only reported in two papers [7,13]. Second, eligible studies did not consistently report whether residual RVOT obstruction, chronic pulmonary regurgitation, and surgical or transcatheter pulmonary valve replacement occurred. Therefore, we

could not estimate the true incidence of these important complications in syndromic patients undergoing surgical repair of ToF. Similarly, we could not assess whether placing a mechanical prosthetic valve in the RVOT at the time of transannular patch affects the postoperative course or severity of pulmonary insufficiency.

Conclusion

Syndromic Tetralogy of Fallot accounts for approximately 15% of all ToF cases. Deletion of 22q11.2 and Down syndrome are the most prevalent genetic abnormalities associated with ToF. Aortic dilatation and MAPCAs constitute the most common forms of comorbid cardiac pathology. Nearly 25% of patients with syndromic ToF undergo some type of palliation prior to complete intracardiac repair, which may be associated with the high rate of hypoplastic pulmonary arteries that is seen in this patient population. Although relief of RVOT obstruction is typically performed with transannular patch placement, pulmonary valve-sparing technique or RV-PA conduits are used in over one third of syndromic patients. Long-term survival exceeds 90%, suggesting that surgical management should be dictated by anatomy regardless of genetics.

Compliance with Ethical Standards

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