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22q11.2 Deletion Syndrome is Associated With Perioperative Outcome in Tetralogy of Fallot

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Abstract

Objectives—We sought to investigate the impact of 22q11.2 deletion on perioperative outcome in tetralogy of Fallot.

Methods—We conducted a retrospective review of patients with tetralogy of Fallot who underwent complete surgical reconstruction at The Children's Hospital of Philadelphia between 1995 and 2006. Inclusion criteria included diagnosis of tetralogy of Fallot and known genotype. Fisher's exact and Mann Whitney tests were used for categorical and continuous variables, respectively. Regression analysis was used to determine whether deletion status predicts outcome.

Results—We studied 208 subjects with tetralogy of Fallot, 164 (79%) without, and 44 (20%) with a 22q11.2 deletion (22q11.2DS). There were no differences in sex, race, gestational age, age at diagnosis, admission weight, and duration of mechanical ventilation. Presenting anatomy, survival, complications and re-operations were also comparable between patients with and without 22q11.2DS. Those with 22q11.2DS had more aortopulmonary shunts preceding complete surgical repair (21% vs. 7%, p= 0.02). This association was present after adjustment for presenting anatomy (stenosis, atresia, or absence of pulmonary valve and common atrioventricular canal) and surgical era. In addition, those with 22q11.2DS had longer cardiopulmonary bypass time (84 vs. 72 minutes, p=0.02), and duration of intensive care (6 days vs. 4 days, p=0.007).

Conclusions—Genotype affects early operative outcomes in tetralogy of Fallot resulting, in particular, in longer duration of intensive care. Future studies are required to determine factors contributing to such differences in this susceptible population.

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Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease, comprising up to 7% of all cardiac defects. [1] It is commonly associated with genetic syndromes, particularly the 22q11.2 deletion syndrome (22q11.2DS), which is present in 15–20% of TOF patients. [2, 3, 4, 5] The presence of a genetic syndrome has been associated with increased morbidity and mortality in TOF; however, the underlying mechanisms remain to be identified and may vary by genotype. [6] For example, increased mortality in the TOF subset with pulmonary atresia and 22q11.2DS is seen irrespective of the degree of pulmonary artery hypoplasia. [7] In addition, non-cardiac abnormalities and malformation syndromes appear to be independent risk factors for prolonged intubation, re-intubation and longer intensive care duration. [8, 9] Therefore, factors related to genotype influence outcomes.

Risk stratification and counseling of patients with 22q11.2DS are of paramount importance in an era of pre-natal diagnosis, advanced peri-natal intensive care, and access to sub-specialized medicine. Understanding how genotype impacts outcomes might guide surgical decisions, perioperative care and pre and postnatal counseling. In addition, this knowledge may allow us to optimize management, consequently leading to shorter hospital stays and improved cardiovascular and neurocognitive outcomes.

We therefore sought to investigate the association of 22q11.2DS and peri-operative outcomes in patients with TOF.

Methods

Study population

The study protocol was approved by the Institutional Review Board for the Protection of Human Subjects at The Children's Hospital of Philadelphia (CHOP). We conducted a retrospective chart review study of patients that underwent surgical repair for TOF at CHOP between 1995 and 2006. We included patients who underwent complete surgical reconstruction for TOF in a single operation, whether or not it was preceded by placement of an aortopulmonary shunt. Patients who underwent multiple stages of operations to reach complete repair and those with genetic syndromes other than 22q11.2DS (such as trisomy 21 and Alagille syndrome) were excluded. The hospital's cardiothoracic surgical database was used for subject ascertainment. Deletion status was confirmed for all patients. All patients with 22q11.2DS were included. All non-deleted subjects with TOF and pulmonary valve atresia, absent pulmonary valve leaflets and associated common atrioventricular canal were included. A subset of non-deleted subjects with TOF and pulmonary valve stenosis were randomly selected for comparative chart review based on a power analysis that determined the sample size of TOF with pulmonary stenosis needed for comparison with the 22q11.2DS group to detect differences in length of hospital stay.. Surgical repair was categorized as: 1) closure of ventricular septal defect (VSD) without need for relief of right ventricular (RV) outflow tract obstruction; 2) VSD closure and relief of RV outflow tract obstruction with placement of a patch without crossing the pulmonary valve annulus (non-transannular patch); 3) VSD closure and relief of RV outflow tract obstruction with placement of a patch crossing the pulmonary valve annulus (transannular patch); 4) VSD closure and placement of an RV to pulmonary artery conduit. Surgical era was divided between early (1995 to 2000) and late (2001 to 2006) time periods.

Data collection

Hospital medical records were reviewed to abstract the demographic and relevant clinical variables from the index hospitalization. Intensive care was defined as the time between

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post-operative admission to the cardiac intensive care unit to the time of discontinuation of mechanical ventilation, removal of chest tubes and intracardiac lines, and discontinuation of vasopressor medications. Subjects were grouped according to deletion status. Anatomy was divided according to the pulmonary valve morphology: stenosis, atresia, absent leaflets, and TOF with complete common atrioventricular canal defect. Major congenital anomalies (e.g. cleft palate, intestinal malrotation, tracheo-esophageal fistula) were recorded. Operative and peri-operative variables were collected, including cardiopulmonary bypass (CPB) duration, cardiac and non-cardiac events, discharge status (feeding method), and number of medications. Examples of non-cardiac events included number of consulting services, infections requiring antibiotic treatment, post-operative seizures confirmed by electroencephalogram, pleural effusions requiring drainage, and tracheostomy. Examples of cardiac events included pericardial effusions requiring pericardiocentesis, arrhythmias requiring treatment, post-operative cardiac catheterizations, re-operations, and cardiac arrest requiring resuscitation.

Statistical Analysis

Continuous variables were described as mean and standard deviation (SD) or as median with inter-quartile ranges (IQR), where appropriate. Frequencies with proportions were reported for categorical variables. The differences between deleted and non-deleted groups were tested with the Wilcoxon Rank Sum test for continuous variables and the Fisher's exact test for categorical variables. Multivariable regression models were used to assess the independent associations between deletion status and length of intensive care, palliative procedure, and cardiopulmonary bypass time, adjusting for potential confounders including birth weight, age at repair, gestational age and pulmonary valve status. Statistical significance was reached if p-values were < 0.05 (2-sided tests). All analyses were performed using SAS statistical software version 9.2 (Cary, NC, USA).

Results

General characteristics

The study included 208 subjects who met eligibility criteria. One hundred sixty -four ND patients were included for comparison with 44 patients that had confirmed 22q11.2DS. Analysis limited to survivors did not affect the comparisons between the two groups, therefore we included survivors and non-survivors in the results. We found a predominance of males (60%) and whites (76%). Most were born full term (79%), and were diagnosed postnatally (71%) (Table 1). Pulmonary valve stenosis was the most common presenting pulmonary valve status (63%). Ten percent of subjects received an aortopulmonary shunt preceding complete repair. Most subjects underwent surgery before six months of age with 30% in the neonatal period. Relief of RV outflow tract obstruction was achieved with a transannular patch in 60% (Table 1).

Comparisons according to genotype

Subjects with and without 22q11.2DS were comparable in terms of gender, race, weight, gestational age, timing of diagnosis, presenting pulmonary valve status, and age at surgical repair. In addition, there was no difference in frequency of neonatal repairs (Table 1). A total of 22 aortopulmonary shunts preceded complete repair, 12 performed in the early surgical era and 10 in the late era ($p=0.37$).

Four patients died (3 ND and 1 22q11.2DS). There was no difference in mortality between the two groups ($p=1.0$). Most patients were discharged directly home, with a minority being transferred to other facilities for continuation of care (Table 2).

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The 22q11.2DS and ND groups were comparable in terms of duration of time in the hospital preceding operation, length of stay after discharge from the intensive care unit, duration of mechanical ventilation, number of cardiac and non-cardiac complications and number of reoperations (Table 2). There was a trend for longer overall length of hospital stay in the 22q11.2DS group (p=0.053). Feeding status at discharge and the number of infections in the hospital were comparable between the two groups (p value 0.11 and 0.21, respectively).

Major congenital anomalies were found in both groups, without significant difference by deletion status. As expected for this patient population, those with 22q11.2DS had more dysmorphic facies and more frequent ear, nose, mouth, palate, hand, and skeletal anomalies. Other organ systems were equally affected in the two subgroups.

There were important differences between the two groups. Patients with 22q11.2DS more commonly received an aortopulmonary shunt preceding complete surgical repair [9/44 (21%) compared to 13/164 (7%) in the ND group, p=0.03)]. This association remained significant after adjusting for pulmonary valve status, gestational age, birth weight, admission weight, age at surgical repair, extracardiac malformations, and era of surgical repair. Moreover, the patients with 22q11.2DS had longer duration of CPB (84 ± 31, compared to 74 ± 30minutes, p=0.02). This association persisted after adjusting for previous shunt placement and presenting pulmonary valve status. Overall length of intensive care was longer for the 22q11.2DS group (6 days [4; 12], compared to 4 days [3; 8] in the ND group, p=0.007) (Table 2). CPB was a confounder of the association of deletion status and length of intensive care, although CPB was not an independent predictor of length of intensive care. While most of the ND group had no consultations by other sub-specialties, 50% of the 22q11.2DS had consultations, of which 25% had more than two consultations during the hospital stay (p=0.001). Finally, the 22q11.2DS population was discharged on more medications compared to the ND [3 (2; 5) vs. 2 (1; 3), p=0.001].

Discussion

Our study identifies important differences in perioperative outcomes between subjects with 22q11.2DS and ND subjects with TOF. Patients with 22q11.2DS were observed to have more palliative procedures, longer CPB, longer duration of intensive care, and more resource utilization in terms of consultations by other sub-specialties. Potential etiologies for increased intensive care in the 22q11.2DS population could be their tendency towards airway difficulties and need for increased respiratory support. [10] However, mechanical ventilation was comparable in the two groups, thus it is unlikely that intensive care was prolonged on account of the duration of mechanical ventilation. Therefore, other factors must have contributed to longer intensive care duration. Importantly, patients with 22q11.2DS did not have more infections than the ND and therefore, infections were not likely to contribute to the increased length of intensive care.

We found that 22q11.2DS patients had longer duration of CPB. Although not substantially different clinically, this difference could in itself be associated with a longer duration of intensive care due to a greater systemic inflammatory response, and resultant post-operative edema and end-organ dysfunction. Allan et al found a positive correlation between interleukin production and duration of CPB, longer intubation times and intensive care stay. [11] However, the reason deletion status is associated with longer CPB is unclear and the retrospective nature of our study did not allow for its determination.

Effect of genotype on surgical outcome, specifically the Renin-Angiotensin-Aldosterone System genotype, has been linked to other groups of congenital heart disease. [12] Thus, 22q11.2DS could likewise contribute to surgical outcome, given that 22q11.2DS can affect

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genes that are not only involved in the septation of the conotruncus, but also involved in RV structure thus perhaps contributing to RV function and adaptation to surgical stress. [13, 14] Alternatively, 22q11.2DS might contribute to postoperative RV restrictive physiology in TOF. [15]

Placement of an aortopulmonary shunt was more commonly performed in patients with the 22q11.2DS, independent of gestational age, pulmonary valve status, age at surgical repair and extracardiac malformations. Once again, the retrospective nature of our study limits our ability to discern specific factors that resulted in this management plan. Moreover, it was not possible to ascertain from chart review whether deletion status was known to the caretakers before the surgical planning. Therefore, the knowledge of deletion status could have impacted the decision to perform a shunt. Additional malformations might influence surgical planning as suggested by Michielon. [16] However, in our study the 22q11.2del population did not have more major anomalies than the ND subset and thus the difference in management strategy cannot be ascribed to the presence of non-cardiac anomalies. Although placement of an aortopulmonary shunt does not appear to impact survival after complete repair for TOF, it may increase the risk for pulmonary artery distortion, which has the potential to prolong the peri-operative recovery and hospitalization. [17] Thus, indirectly, a prior aortopulmonary shunt has the potential to add morbidity and increase costs. [18,19]

A prolonged hospitalization and longer period of intensive care support in patients with 22q11.2DS may have significant clinical implications. As a result of the deletion, children with 22q11.2DS already have developmental delays, hypotonia and speech problems that appear to be independent of the cardiac disease. [20] Evidence also suggests that the length of the post-operative hospitalization for congenital heart disease affects later neurodevelopment outcomes independent of genetic syndromes and other factors such as demographic and socioeconomic status, perioperative complications, and CPB times. [21, 22] Such evidence stresses the need for focused management, especially in patients with genetic syndromes, to accomplish a shorter hospital stay, and thereby optimize neuro-cognitive outcomes.

Major extracardiac anomalies were present in both groups, and significant differences were found in organs that are typically involved with greater frequency in patients with 22q11.2DS: anomalies of the ears, nose, mouth, palate and hand, most of which describe minor facial features rather than major anomalies expected to confer a clinical difference. We also found skeletal anomalies to be more common in the 22q11.2DS (Table 3). Other studies found 22q11.2DS and ND patients to be comparable in terms of major organ system anomalies, such as, airway, gastrointestinal, genital, renal, and central nervous system. [2324] Therefore, although dysmorphisms are common in patients with 22q11.2DS, major extracardiac malformations were not more common in the TOF group with as compared to without 22q11.2DS.

Our study also describes important similarities between TOF patients with and without 22q11.2DS. We found that overall patient characteristics, presenting anatomy, complications, reoperations, major congenital anomalies, and survival were comparable between the two groups. Of note, feeding problems were not more common in the del22q11. 2 group, a pertinent finding in light of the common assumption that patients with 22q11.2DS have more feeding difficulties. All of these findings are important and highlight the fact that 22q11.2DS results in increased morbidity, rather than mortality, in this particular patient population. [8,9, 25] The same may not be true in the more complicated cohort with major aorto-pulmonary collateral arteries requiring staged repairs as suggested by Mahle et al. [7]

Finally, our results suggest that patients with 22q11.2DS require more resource utilization as reflected by the increased number of consulting services. These consultations likely provide

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appropriate routing of the patient with 22q11.2DS to the various specialties needed in their follow-up.

Limitations

The retrospective nature of this study limits our ability to further detail differences between the patients with and without a 22q11.2DS, including the ability to ascertain whether the patient was recognized clinically to have DiGeorge syndrome or whether deletion status was known to the caretakers before surgical planning. Such knowledge might have biased caretakers towards placement of an aortopulmonary shunt preceding a complete repair in the 22q11.2DS group.

We opted not to examine echocardiographic variables (such as the size of the pulmonary arteries) because of the inconsistency associated with retrospective data collection. Nonetheless, we were able to study a large number of patients with TOF operated at a single institution. In addition, since we only included subjects with a complete repair preceded or not by an aorto-pulmonary shunt, we were able to study a relatively homogeneous population in terms of cardiac phenotype and surgery. Therefore, these results apply to TOF patients with anatomy favorable for this type of surgical approach.

Summary

This study examined a large group of TOF patients operated at a single institution, and reports outcomes in the subset undergoing complete surgical repair. We found that, while outcomes are comparable in many respects,, patients with TOF and 22q11.2DS are at risk for longer post-operative recovery, suggesting that post-operative management may need to be tailored to the 22q11.2DS patient. This finding is particularly important given the evidence for worse cognitive outcomes associated with longer hospital stays. Also noteworthy was the encouraging finding that patients with 22q11.2DS had a similar survival as the ND group.

In the era of prenatal diagnosis and tailored patient care, genetic stratification is important and should be considered when counseling parents, planning surgical procedures, and determining post-operative management strategies in patients with TOF. Future studies should target the perioperative period in order to identify modifiable factors to improve outcomes.

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Table 1

Patient characteristics

Variable	ND (N=164)	22q11.2DS (N=44)	P value
Gender			
Female	65 (40)	20 (46)	0.30
Male	99 (60)	24 (54)	
Race			
White	128 (78)	30 (68)	0.18
African American	22 (13)	6 (14)	
Other	14 (9)	8 (18)	
Gestational age *			
Full term	128 (78)	36 (82)	0.29
Premature	33 (20)	6 (14)	
Unknown	3 (2)	2 (4)	
Timing of TOF diagnosis			
Prenatal	41 (25)	13 (30)	0.56
Postnatal	119 (73)	29 (66)	
Unknown	4 (2)	2 (4)	
Age at surgery, months	3 (0.5; 5.3)	3.9 (1.6; 6.8)	0.13
Neonatal repair (<1month)	47 (29)	9 (20)	0.34
Weight on admission (Kg)	5.1 (±1.9)	5.0 (±1.6)	0.91
Pulmonary valve anatomy			
Stenosis	108 (66)	26 (59)	0.70
Atresia	42 (25)	14 (32)	
Absent	13 (8)	4 (9)	
Atrioventricular canal	1 (1)	0 (0)	
Shunt - pre †	13 (7)	9 (21)	0.03
Surgical repair			
VSD closure alone ‡	20 (12)	1 (2)	0.20
Non-transannular patch	13 (8)	5 (11)	
Transannular patch	101 (62)	24 (55)	
RV-PA conduit §	30 (18)	14 (32)	

Data are expressed as mean (±sd), median (interquartile range) or as frequency (percentage).

* Prematurity is defined as gestational age < 37 weeks.

† Shunt-pre refers to placement of aortopulmonary shunt before complete surgical repair.

‡ VSD denotes ventricular septal defect.

§ RV-PA denotes right ventricle to pulmonary artery.

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Table 2

Outcomes according to 22q11.2DS status

Variable	ND (N=164)	22q11.2DS (N=44)	P value
Outcome			
Death	3 (2)	1 (2)	0.9
Discharge home	148 (90)	39 (89)	
Other *	13 (8)	4 (9)	
Length of stay, days †	6 (4; 13)	9 (6; 16)	0.053
Length of stay if discharged home, days	6.0 (4; 11)	9.0 (5; 15)	0.02
Hospital stay > 4 weeks	9 (5)	2 (5)	1.00
Intensive Care, days	4 (3; 7)	6 (4; 12)	0.007
Cardiopulmonary bypass, minutes	74 (± 30)	84 (± 31)	0.02
Deep hypothermic circulatory arrest, minutes	15.3 (±20)	20.8 (± 23)	0.06
Ventilation, hours	25.4 (10; 74)	32 (23; 90)	0.09
Resource Utilization			
Number of consultations			
0	125 (76)	22 (50)	0.001
1	20 (12)	7 (16)	
≥ 2	19 (12)	15 (34)	
Complications			
Infections	11 (7)	6 (14)	0.21
Pericardial effusion	7 (4)	1 (2)	1.00
Junctional ectopic tachycardia	13 (8)	1 (2)	0.31
Catheterizations	31 (19)	13 (30)	0.15
Reoperations	15 (9)	4 (9)	0.85
Extra-corporeal membrane oxygenation	1 (0.6)		1.00
Cardiac arrest	5 (3)	1 (2.3)	1.00
Discharge characteristics ‡	**N= 161**	**N=43**	
Feeding			
Nasogastric + oral	24 (15)	11 (26)	0.11
Oral	137 (85)	32 (74)	
Number of medications	2 (1; 3)	3 (2; 5)	0.0001

Data are expressed as mean (±sd), median (interquartile range) or as number (percentage).

*Discharged to another hospital or chronic care facility.

†Length of stay for the whole cohort

‡Includes survivors only

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Table 3

Extra-cardiac malformations according to 22q11.2DS status

	ND N=164	22q11.2DS N=44	P value
Dysmorphic facies	43 (26)	37 (84)	<0.001
Head	8 (5)	2 (5)	0.95
Eye	6 (x4	4 (9)	0.13
Ear	16 (10)	17 (39)	<0.001
Nose	8 (5)	17 (39)	<0.001
Mouth	6 (4)	10 (23)	0.001
Palate *	8 (5)	12 (27)	<0.001
Airway †	7 (4)	4 (9)	0.23
Abdominal ‡	6 (xx)	2 (4.5)	0.92
Renal §	6 (4)	2 (5)	0.98
Genital ‖	10 (6)	2 (5)	0.61
Skeletal ¶	17 (10)	11 (25)	0.03
Hand	23 (14)	18 (41)	<0.001

Data are expressed as number (percentage).

* Cleft lip/palate, submucous cleft, bifid uvula, high arched palate and velopharyngeal incompetence.

† Laryngo-bronchio-tracheomalacia, tracheal stenosis, subglottic stenosis, choanal stenosis or atresia, tracheal web, tracheoesophageal fistula.

‡ Intestinal malrotation, omphalocele, umbilical/inguinal hernia, pyloric stenosis, polysplenia.

§ Horseshoe, cystic, dysplastic, and single kidney; hydronephrosis; ureteral abnormalities.

‖ Ambiguous genitalia, hypospadias, undescended testes, imperforate anus, anteriorly placed anus.

¶ Hemi and butterfly vertebrae, fused ribs, short limbs, scoliosis, winged scapula, sacral dimple, tethered cord.