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22q11.2 Deletion Status and Perioperative Outcomes for Tetralogy of Fallot with Pulmonary Atresia and Multiple Aorto-Pulmonary Collateral Vessels

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Abstract

Objectives—Deletion of 22q11.2 (del22q11) is associated with adverse outcomes in patients with tetralogy of Fallot (TOF). We sought to investigate its contribution to perioperative outcome in patients with a severe form of TOF characterized by pulmonary atresia (PA) or severe pulmonary stenosis (PS) and major aortopulmonary collateral arteries (MAPCAS).

Methods—We conducted a retrospective review of patients with TOF/MAPCAS who underwent staged surgical reconstruction between 1995 and 2006. Groups were compared according to 22q11.2 deletion status using *t*-tests or the Wilcoxon Rank sum test.

Results—We included 26 subjects, 24 of whom survived the initial operation. Of those, 21 subjects had known deletion status and constitute the group for this analysis [15 with no deletion present (ND) and 6 del22q11subjects]. There was no difference with respect to occurrence of palliative procedure prior to initial operation, or to timing of closure of the ventricular septal defect (VSD). Other than higher prevalence of prematurity (50%) in the del22q11 group vs. no prematurity in the ND, the groups were comparable in terms of pre-operative characteristics. The intra and post-operative course outcomes (length of cardiopulmonary bypass, use of vasopressors, duration of intensive care and length of hospital stay, tube-feeding) were also comparable. Although the del22q11 had longer mechanical ventilation than the ND this difference was not significant (68 hours (range 4–251) vs. 45 hours (range 3–1005), p=0.81.

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Conclusions—In this detailed comparison of a small patient cohort, 22q11.2 deletion syndrome was not associated with adverse perioperative outcomes in patients with TOF, PA and MAPCAS when compared to those without 22q11.2 deletion syndrome. These results are relevant to pre-natal and neonatal pre-operative counseling and planning.

Introduction

The 22q11.2 deletion (del22q11) (DiGeorge syndrome) is present in about 13% of tetralogy of Fallot (TOF) cases and in greater than 30% of subjects when there is TOF with pulmonary atresia (PA) and major aorto-pulmonary collateral vessels (MAPCAS).[1, 2, 3–7] The presence of a genetic syndrome alone has been thought to increase morbidity and mortality in TOF.[8] In addition, non-cardiac abnormalities and malformation syndromes appear to be independent risk factors for prolonged intubation, re-intubation and longer intensive care duration.[9, 10] We have previously demonstrated that del22q11 is associated with worse perioperative outcome in the TOF subset with pulmonary stenosis (PS) or PA that underwent surgical repair with closure of the ventricular septal defect (VSD) as either a single stage operation or one preceded by an aortopulmonary shunt.[11] In the more complex TOF subset associated with MAPCAS, del22q11 is associated with increased mortality in one report irrespective of the degree of pulmonary artery hypoplasia.[8] Risk stratification and counseling of families of patients with del22q11 is therefore of paramount importance. Understanding how genotype impacts outcomes might guide surgical decisions, perioperative care and pre and post-natal counseling. We sought to investigate the association of del22q11 and perioperative outcomes in patients with TOF/MAPCAS that survived the initial surgical procedure.

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 of patients that underwent surgical repair for complex TOF at CHOP between 1995 and 2006. We defined the study population as complex TOF if the diagnosis was TOF with severe PS or PA with MAPCAS. Surgical repair was categorized as: 1) pulmonary artery unifocalization with relief of right ventricular (RV) outflow tract obstruction and no VSD closure, and 2) pulmonary artery unifocalization with relief of RV outflow tract obstruction as a first stage and VSD closure in a subsequent stage. We included patients that had an aorto-pulmonary shut or other palliative procedures prior to the first operation. Those with PA/severe PS without MAPCAS that received a complete intracardiac repair in a single stage were excluded. Only subjects with known del22q11 status (confirmed via chart review) were included in the analysis. The hospital's cardiothoracic surgical database was used for subject ascertainment.

Data collection

Hospital medical records were reviewed to abstract the demographic and relevant clinical variables from the surgical hospitalizations. For those with more than one surgical

admission, cumulative data are presented. Subjects were grouped according to del22q11 status. Major congenital anomalies (e.g. cleft palate, intestinal malrotation, tracheo-esophageal fistula) were recorded. Intensive care was defined as the time between postoperative 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 vasoactive medications. Operative and peri-operative variables included cardiopulmonary bypass (CPB) duration, cardiac and non-cardiac events, discharge feeding status, and number of medications. Examples of non-cardiac events recorded 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 recorded included pericardial effusions requiring pericardiocentesis, arrhythmias requiring treatment, post-operative cardiac catheterizations, re-operations, and cardiac arrest requiring resuscitation, and mechanical circulatory support.

Statistical Analysis

Subjects were divided into two groups according to del22q11 status. Demographic, anatomic, pre-operative and post-operative characteristics were compared. Continuous variables were described as mean and standard deviation (SD) or as median with ranges (minimum-maximum), where appropriate. Categorical variables were described as frequencies and percentages. The differences between subjects with a del22q11 and those without a del22q11 (ND) were compared using Student's *t*-test or Wilcoxon rank-sum test as appropriate for continuous variables and Fisher's exact test for categorical variables. The significance level for two-sided hypothesis testing was set at 0.05. All analyses were performed using Stata 13.1 (StataCorp, College Station, TX).

Results

The study included 26 subjects, 24 of whom survived the initial operation. Two deaths occurred after the first operation (both ND patients, received unifocalization, RV to pulmonary artery conduit and had the VSD left open). Of the 24 survivors, deletion status was confirmed in 21, of which 15 (71.4%) were ND and six (28.6%) had del22q11. There were 16 males and 8 females. Most subjects (80%) were born full term (> 37 weeks gestation) in the ND group, as compared to 50% in the del22q11 group (p=0.025). Most subjects were diagnosed post-natally, and were fed orally upon admission. The ND group had a trend towards a greater number of admissions prior to the initial operation, as compared to the del22q11 group (p=0.05). Otherwise, there were no significant differences in demographic, anatomic, or other pre-operative characteristics between the groups (Table 1).

Both groups reached VSD closure with equal frequency. The del22q11 and ND subjects were comparable in terms of length of cardiopulmonary bypass and deep hypothermic circulatory arrest. The post-operative intensive care course was similar between the two groups. There was no statistically significant difference in the duration of mechanical ventilation, number of vasoactive medications used, or number of days of intensive care.

Finally, the length of hospital stay and the total number of medications upon hospital discharge were similar (Table 2).

Discussion

In this small but detailed comparison of perioperative outcomes in surgical survivors with TOF/MAPCAS, contrary to our expectation, we found that del22q11 status had no significant adverse impact on perioperative outcomes. Other than a higher prevalence of prematurity and fewer pre-operative admissions in the del22q11 group, there were no significant predictors of perioperative outcome or resource utilization measured in this study.

We have found that the del22q11 group had a higher prevalence of prematurity. Other studies have not reported an association of del22q11 and prematurity.[12,13] In our prior study of patients with TOF that underwent a single stage complete repair, we did not find prematurity to be more prevalent in the del22q11 group, or for prematurity to be associated with perioperative outcomes.[11] Because of the potential impact of prematurity on cardiac surgical outcome and its known association with neurological outcomes in del22q11 syndrome, this finding warrants future investigation.

The ability to reach VSD closure was comparable in the 22q11 and ND groups, similarly to prior reports.[1, 14] In the present study we found no difference in the length of mechanical ventilation between the 22q11 and ND groups, a finding similar prior studies.[15, 16] Likewise, despite the fact that the del22q11 group received vasoactive medications for two additional days as compared to the ND, we found that this difference was not statistically significant. For comparison, a study examining the influence of del22q11 on the post-operative course of patients with conotruncal defects demonstrated that patients with TOF and del22q11 had longer intensive care and overall hospital stay as compared to those without a del22q11. However, that study did not report results separately for patients with TOF/MAPCAS.[15] We have previously shown that after surgical repair for truncus arteriosus and interrupted aortic arch, patients with del22q11 have worse post-operative outcome with longer duration of intensive care and length of hospital stay, and a trend towards longer duration of mechanical ventilation.[17] These differences between the ND and the del22q11 groups suggest that the del22q11 could have a different effect on outcome depending on the complexity of the heart defect. Interestingly, all of these reports, including the present study, did not find a difference in feeding status upon discharge, even though clinicians may expect those with del22q11 to have more feeding difficulties and be discharged more commonly on gastric feeds.

In the present analysis, the number of medications at discharge was comparable between the groups. This lack of difference is an additional indication that the postoperative course of this group of complex TOF patients is not influenced by 22q11 deletion status. This finding is in contrast to what was observed in older patients with TOF and 22q11 deletion who were found to have greater number of hospitalizations, consultation with specialists, and use more medications as compared to those without a 22q11 deletion. [18] It is possible, therefore, that the potentially greater morbidity seen in del22q11 patients could become more pronounced over time. To this extent, a study examining the long-term outcome of a similar population

demonstrated that over a follow up time of 14 years, patients with del22q11 had a hazard of death eight times that of those without a del22q11, with greater mortality observed in the first 50 months of life.[1] The association of del22q11 with adverse long-term outcome could be in part secondary to worse aorto-pulmonary arterial morphology, even though there is evidence to suggest that del22q11 is a risk factor for death in TOF/MAPCAS independent of major aortopulmonary collaterals.[8, 19]

In summary, we had hypothesized that differences found in our previous studies of the influence of del22q11 on outcome in TOF would be more pronounced in patients with TOF/MAPCAS, who are known to have a less favorable phenotype. However, our findings demonstrate that the overall perioperative course amongst survivors was comparable between the groups, either because our study was underpowered to detect differences, or because TOF with the presence of MAPCAS may have a greater impact on outcome than 22q11.2 deletion status. It is also possible that the impact of del22q11 will have greater effect on the long-term outcome in TOF. This supposition warrants future investigation.

Limitations

Our study has several potential limitations. First, this was a retrospective analysis at a single center, such that our results might not be generalizable other than to tertiary care institutions. Second, we were limited by a small sample size because we only included subjects with confirmed deletion status. Therefore, some of the comparisons could have resulted in significant findings with a larger sample size.

Conclusions

In a small population of TOF/MAPCAS, perioperative outcomes were comparable in those with and without a del22q11. These results can be used towards family counseling and surgical planning. Future larger studies will help understand whether outcomes will differ in larger study cohorts and in the long-term.

Summary

This study examined a small group of TOF patients with complex TOF and suggests that 22q11.2 deletion status may not influence perioperative course in this particular subset of patients Furthermore, it is possible that the presence of a 22q11 deletion does not add additional morbidity in TOF/MAPCAS given that this is the most complex form of TOF.

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Table 1

Patient characteristics

	Total (N=21)	del22q11 (N=6)	ND (N=15)	P-value
Male	14 (67)	6 (100)	8 (53)	0.061
Female	7 (33)	0	7 (47)	
Gestational Age				
Full term (> 37 weeks)	15 (83.3)	3 (50)	12 (100)	0.025
Premature (< 37 weeks)	3 (16.7)	3 (50)		
Time of diagnosis				
Prenatal	2 (10)	0 (0)	2 (14.3)	0.999
Postnatal	18 (90)	6 (100)	12 (85.7)	
Birth weight, kg	3.3 (1.7 – 4.4)	3.3 (1.8 – 4.4)	2.3 (1.7 – 3.5)	0.286
Admission weight, kg	6.0 (3.0 – 12.5)	6.0 (3.0 – 12.5)	5.5 (4.0 – 8.3)	0.480
Dysmorphic facial features	11 (52.4)	4 (66.7)	7 (46.7)	0.41
Head anomalies	3 (14.2)	0	3 (20)	0.20
Palate malformations	1 (4.7)	0	1 (6.7)	0.63
Renal anomalies	2 (9.5)	0	2 (13.3)	0.33
Neurologic problems (hypertonia, seizure)	2 (9.5)	0	2 (13.3)	0.38
Prior hospitalizations	13 (68.4)	2 (33.3)	11 (84.6)	0.046
Prior palliation procedure with AP shunt				
Yes	5 (23.8)	1 (16.7)	4 (26.7)	0.999
No	16 (76.2)	5 (83.3)	11 (73.3)	

Data are presented as counts (percentage) or as median (range)

Extracardiac malformations were not available by chart review for some patients.

Table 2

Outcomes by deletion status

	Total (N=21)	del22q11 (N=6)	ND (N=15)	P-value
Hypothermic circulatory arrest (hours)	0.52 (0 – 1.3)	0.45 (0 – 1.3)	0.72 (0 – 1.3)	0.75
Hospitalization characteristics				
Medications on discharge, n (%)	4.0 (2.0 – 10.0)	4.0 (2.0 – 10.0)	4.0 (2.0 – 7.0)	0.49
Medication count/day	4.6 (2.9 – 7.7)	4.4 (2.9 – 6.9)	6.2 (3.7 – 7.7)	0.061
Hospital stay, days	10.0 (4.0 – 86.0)	11.0 (4.0 – 86.0)	9.0 (7.0 – 21.0)	0.41
Total days of intensive care	8.0 (4.0 – 86.0)	8.0 (4.0 – 86.0)	7.5 (5.0 – 16.0)	0.72
Length of NPO	3.0 (0 – 21.0)	2.0 (0 – 21.0)	3.5 (1.0 – 7.0)	0.81
Length of tube feeds	0 (0 – 62.0)	0 (0 – 62.0)	0 (0 – 4.0)	0.47
Length of tube +oral feeds	0 (0 – 17.0)	0 (0 – 17.0)	0 (0 – 2.0)	0.38
Length of oral feeds	6.0 (1.0 – 16.0)	4.0 (1.0 – 16.0)	6.0 (4.0 – 11.0)	0.39
Number of hours intubated	51.7 (3.4 – 1005.5)	44.7 (3.4 – 1005.5)	67.8 (3.6 – 251.1)	0.81
Days of vasoactive medication use	4.0 (0 – 19.0)	3.0 (0 – 19.0)	4.0 (2.0 – 8.0)	0.48

Data are presented as counts (percentage) or as median (range)