

# Conotruncal heart defects: impact of genetic syndromes on immediate operative mortality

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Genetics; Heart defects;  
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**Background.** The surgical outcome of conotruncal heart defects in patients with genetic syndromes has been poorly studied. The aim of this prospective 5-year multicenter study was to elucidate the post-surgical death rate of children with conotruncal heart defects in relation to the presence of associated genetic syndromes.

**Methods.** Two institutions enrolled 350 consecutive inpatients with conotruncal heart defects, aged between 1 day and 60 months, who were submitted to surgery; all patients were evaluated by a clinical geneticist and had a standard metaphase chromosome analysis and a fluorescent *in situ* hybridization study searching for deletion of chromosome 22q11 (del22q11).

**Results.** No genetic syndrome was diagnosed in 289 patients; among the other 61 patients, 27 had DiGeorge velocardiofacial syndrome (del22q11), 16 patients had Down syndrome, and 18 presented with other genetic syndromes. The overall post-surgical death rate was higher in syndromic patients (18%) than in non-syndromic ones (10.7%) with a relative risk of 1.9 ( $p = 0.06$ ). However, children with del22q11 showed a higher risk for surgical mortality (25.9 vs 10.7%; relative risk 2.4,  $p = 0.03$ ). Del22q11 was identified as a risk factor for immediate surgical mortality in patients with pulmonary atresia and ventricular septal defect and in patients with interrupted aortic arch.

**Conclusions.** Down syndrome is not a risk factor for surgery in children with conotruncal heart defects. The presence of a del22q11 may influence the surgical results in children with pulmonary atresia and ventricular septal defect and in those with interrupted aortic arch. Patients with genetic syndromes other than del22q11 and Down syndrome have a higher surgical mortality compared to that observed in non-syndromic patients. These data may be useful for preoperative counseling and for the elaboration of specific protocols of perioperative treatment.

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## Introduction

Epidemiological studies have recently pointed out that a significant number of patients with congenital heart defects carry an association with genetic syndromes and/or with extracardiac malformations<sup>1,2</sup>. Genetic syndromes, sometimes related to a specific cardiac phenotype<sup>3</sup>, may influence the clinical course of patients with congenital heart diseases and in many cases may complicate the prognosis<sup>4-8</sup>. Conotruncal heart defects (CTHDs) represent 10-15% of congenital heart diseases<sup>2-4</sup> and are frequently associated with genetic syndromes, in particular with deletion of chromosome 22 (del22q11) in the setting of DiGeorge velocardiofacial syndrome<sup>2,4,9-12</sup>. The "classic" CTHDs share the morphological architecture of the presence of ventricular outflow tract anomalies with normally related great arteries and include tetralogy of Fallot (TF), pul-

monary atresia with ventricular septal defect (PA-VSD), truncus arteriosus (TA) and interrupted aortic arch (IAA)<sup>1-4,11,12</sup>. Transposition of the great arteries and double outlet right ventricle (transposition complex), even though comprising some sort of outflow tract, differ from the "classic" CTHDs since the great arteries are parallel and transposed and because of a low prevalence of associated genetic syndromes and extracardiac malformations<sup>1-4,13</sup>.

Recent studies have pointed out that the "classic" CTHDs may present a specific cardiac pattern if related to genetic syndromes<sup>9-17</sup>, but to date, only a few studies regarding the impact of genetic syndromes on surgical results have been published in the literature<sup>18,19</sup>. The aim of this prospective 5-year multicenter study is to determine the prognostic impact of genetic syndromes on the surgical in-hospital mortality in patients with "classic" CTHDs.

## Methods

From January 1997 to December 2001, 350 patients with CTHDs were enrolled and evaluated in this survey. Two pediatric cardiology institutions participated in this study: the “Bambino Gesù” Pediatric Hospital in Rome (270 patients) and the “S. Orsola” Hospital in Bologna (80 patients).

Two hundred and four patients were males and 146 females; the mean age at the first observation was  $11.1 \pm 13.5$  months (median age 6 months, range 1 day to 60 months). All patients were enrolled at the time of initial clinical presentation and the cardiac diagnosis was made at echocardiography alone in 63.4% and together with cardiac catheterization in 36.6%, and was confirmed at surgical intervention in all instances.

The clinical phenotype of all patients was examined by a clinical geneticist and checked for genetic syndromes and for additional extracardiac anomalies. Standard metaphase chromosome analysis was performed in all cases. Slides were also processed for fluorescent *in situ* hybridization using the Sc11.1, Co23, and D22S75 and D22S39 (control ONCOR) probes searching for del22q11.

The study was approved by the Ethics Committee of both hospitals.

The study was restricted to patients with TF (245 cases), PA-VSD (48 cases), TA (37 cases) and IAA (20 cases). All had situs solitus of the atria, levocardia, D-loop of the ventricles and concordant atrioventricular connections. We have included only these types of cardiac defects because the risk of associated extracardiac anomalies and genetic syndromes is higher<sup>1-4</sup>.

The in-hospital mortality was recorded and was correlated with the presence of genetic syndromes for the entire series and for the specific cardiac malformations.

We divided the patients into two groups: group 1 including 61 patients (17.5%) with genetic syndromes and group 2 including 289 non-syndromic patients (82.5%). Group 1 included three subgroups: 27 patients with del22q11, 16 patients with Down syndrome and 18 patients with other syndromes including 7 patients VACTERL, 1 CHARGE, 1 Williams, 1 Alagylle, 1 Cantrell-Ravich, 2 Rubinstein Taybi, and 5 with various chromosomal anomalies.

Statistical evaluation was performed using SPSS (version 11.5). Specific endpoints included death at surgery or during hospitalization.

Univariate analysis was performed calculating the relative risks (RR), with Cornfield's 95% confidence limits and Fisher's exact test for the p value (a p value < 0.05 was considered statistically significant). Multiple logistic regression analysis was applied for adjustment.

## Results

**Overall mortality.** The overall death rate was 12% (95% confidence interval 8.7-15.8). A patient age < 3 months proved to be a significant risk factor for early postoperative death (RR 3,  $p = 0.0002$ ) whereas the type of surgical procedure (palliative or corrective) was not associated with an increase in surgical mortality (Table I).

There was no significant difference in the overall mortality between syndromic patients (11/61, 18%) and non-syndromic patients (31/289, 10.7%): the difference did not reach statistical significance ( $p = 0.06$ ) but the RR was higher in syndromic patients (1.9, 95% confidence interval 1-3.6) (Table II).

Taking into account the single genetic subgroups (Table I), patients with del22q11 showed a higher risk of surgical mortality than non-syndromic patients (25.9 vs 10.7%, RR 2.4), as well as with respect to the group of patients with all the other genetic syndromes (25.9 vs 11.8%,  $p = 0.2$ , RR 2.2).

Moreover, patients with other syndromes presented an increased risk of surgical mortality (16.7%) if compared with non-syndromic patients (10.7%) with a RR of 1.51.

Down syndrome was not associated with a higher surgical mortality (RR 0.6).

**Specific conotruncal heart defect.** Mortality figures were examined for each heart defect and the impact of genetic syndromes (groups 1 and 2) and for specific syndromic subgroups was evaluated (Table II).

In TF the slight difference in mortality between syndromic (3/42, 7.1%) and non-syndromic patients (14/203, 6.9%) was not significant. No fatality occurred among patients with del22q11 or with Down syndrome.

In children with PA-VSD the mortality between syndromic (3/7, 42.8%) and non-syndromic patients (6/41, 14.6%) was different but this may have been due to chance ( $p = 0.1$ ). However, patients with PA-VSD and del22q11 showed a higher mortality (40%) with respect to non-syndromic patients (14.6%) with a RR of 2.9 (Table II).

The only associated syndrome in patients with TA was del22q11. No significant difference in mortality after surgery for TA was observed between syndromic (0 out of 4 patients) and non-syndromic patients (9/33, 27.3%) (Table II). Also, among patients with IAA the syndromic group included only children with del22q11 who featured a higher mortality (62.5%) than non-syndromic patients (10%), with a marginal statistical significance (RR 3.7,  $p = 0.06$ ) (Table II).

## Discussion

Recent investigations have clearly demonstrated a high prevalence of genetic syndromes in patients with

**Table I.** Postoperative death rate (univariate analysis).

	Total	Dead	RR (95% CI)	p
Age				
> 3 months	228	16 (7%)	1	
< 3 months	122	26 (21.3%)	3.03 (1.7-5.4)	0.0002
Sex				
Males	204	24 (11.8%)	1	
Females	146	18 (12.3%)	1.1 (0.6-2)	NS
Phenotype				
Normal	289	31 (10.7%)	1	
Down	16	1 (6.2%)	0.5 (0.1-3.5)	NS
del22q11	27	7 (25.9%)	2.4 (1.2-4.9)	0.03
Other	18	3 (16.7%)	1.5 (0.5-4.6)	NS
Surgical procedure				
Primary repair	278	31 (11.1%)	1	
Two-stage repair	25	1 (4.1%)	0.4 (0.1-2.5)	NS
Palliative	35	7 (0.2%)	1.8 (0.9-3.8)	NS
Other	12	3 (25%)	2.6 (0.8-6.3)	NS
Conotruncal heart defect				
Tetralogy of Fallot	245	17 (6.9%)	1	
PA-VSD	48	9 (18.8%)	2.7 (1.3-5.7)	0.02
Interrupted aortic arch	20	7 (35%)	5.1 (2.4-10.8)	0.0007
Truncus arteriosus	37	9 (24.3%)	3.5 (1.7-7.3)	0.003
Total	350	42 (12%)		

CI = confidence interval; del22q11 = deletion of chromosome 22; PA = pulmonary atresia; RR = relative risk; VSD = ventricular septal defect.

congenital heart disease<sup>1,2</sup> and in particular in children with CTHDs with del22q11 and Down syndrome as the most frequent associated genetic syndrome<sup>1-4</sup>. In recent years, the increased capabilities of pediatric cardiac surgeons to cope with complex heart malformations deeply changed the outcome of this type of cardiac defect. Nevertheless, the additional presence of a genetic syndrome or of extracardiac malformations still represents a challenge for pediatric cardiologists and cardiac surgeons since these factors may influence the clinical course and the final surgical outcome<sup>3-8</sup>. This prospective 5-year multicenter study was undertaken with the aim of evaluating, in a series of 350 consecutive patients with CTHDs, the impact of genetic syndromes on the in-hospital surgical mortality.

The overall surgical results were not statistically different between syndromic and non-syndromic patients but the subgroup of children with del22q11 carried a higher risk of surgical mortality (Table II). In particular, del22q11 did not prove to be a risk factor for surgery in children with TF and TA, whereas patients with PA-VSD or IAA and associated DiGeorge velocardiofacial syndrome and del22q11, showed a higher surgical mortality with respect to non-syndromic children (Table II). On the contrary, Down syndrome was not a risk factor for surgical mortality in any anatomic subtype.

Since our study did not investigate the specific causes of the in-hospital deaths we cannot explain the relation between del22q11 and the immediate surgical

mortality in some specific types of CTHDs. However, in children with del22q11 and PA-VSD the presence of specific and more severe cardiac phenotypes including discontinuity of the pulmonary arteries, aortopulmonary collaterals<sup>15,20,21</sup> and persistent airway hyperresponsiveness<sup>22,23</sup> may complicate the surgical treatment. Airway obstruction due to vascular ring<sup>11</sup> or laryngeal web<sup>24</sup> and vasomotor instability<sup>25</sup> may further complicate the postoperative period. Moreover, the tendency toward serious infections, in particular fungal infections<sup>19</sup>, may increase the risk of mortality. In our series, just as was previously reported for patients with atrioventricular canal<sup>6</sup>, Down syndrome was not a cardiac surgery risk factor for children with CTHD. Our data are in agreement with those of a recent study reporting Down syndrome as not being associated with an increased risk for TF repair<sup>26</sup>.

On the contrary, the subgroup of children with a genetic syndrome other than del22q11 and trisomy 21 showed a higher surgical mortality compared with non-syndromic patients. This aspect deserves further study including a larger series of patients and specific attention in the future.

Our study has several limitations. The number of cases is relatively small, in particular for the groups of TA<sup>27,28</sup> and IAA<sup>29</sup> so that, for these patients, the statistical power is not strong. We recorded only in-hospital mortality and besides, we did not report the cause of death, the morbidity and the length of hospitalization. Moreover, we did not report the long-term mortality and morbidity of our patients.

**Table II.** Heart defect and outcome by genetic syndrome.

	Tetralogy of Fallot			PA-VSD			Interrupted aortic arch			Truncus arteriosus			Total		
	Total	Dead	RR*	Total	Dead	RR*	Total	Dead	RR*	Total	Dead	RR*	Total	Dead	RR*
del22q11	10	0		5	2 (40%)		8	5 (62.5%)		4	0		27	7 (25.9%)	
Down	15	0		1	1 (100%)		0	0		0	0		16	1 (6.2%)	
Other	17	3 (17.6%)		1	0		0	0		0	0		18	3 (16.7%)	
Total syndromic	42	3 (7.1%)	1**	7	3 (42.8%)	2.9**	8	5 (62.5%)	3.7**	4	0	NA	61	11 (18%)	1.9**
p**			0.9			0.1			0.06			NA			0.06
Non-syndromic	203	14 (6.9%)	1	41	6 (14.6%)	1	12	2 (10%)	1	33	9 (27.3%)	1	289	31 (10.7%)	1

del22q11 = deletion of chromosome 22; NA = not applicable; PA = pulmonary atresia; RR = relative risk; VSD = ventricular septal defect. \* vs non-syndromic patients; \*\* total syndromic vs non-syndromic patients.

However, the main strength of this study is that it has allowed us to identify the impact of the major genetic syndromes on the immediate surgical mortality for each specific subtype of CTHDs. Our results show that del22q11 is not a risk factor for surgery in children with TF and in those with TA. On the contrary, this study confirms that the presence of a del22q11 may influence the surgical outcome in children with PA-VSD<sup>18,19</sup> and in those with IAA<sup>24</sup>. These data may be useful for risk assessment during preoperative counseling to families with children with CTHDs. Moreover, our results should be a stimulus for further studies in order to prepare specific perioperative protocols for the treatment of children with genetic syndromes.

**References**

1. Ferencz C, Rubin JD, Loffredo CA, Magee CA. Epidemiology of congenital heart disease. The Baltimore-Washington Infant Study 1981-1989. Mount Kisco, NY: Futura Publishing Company, 1993.
2. Ferencz C, Loffredo CA, Correa-Villasenor A, Wilson PD. Genetic and environmental risk factors of major cardiovascular malformations. The Baltimore-Washington Infant Study 1981-1989. Mount Kisco, NY: Futura Publishing Company, 1997.
3. Marino B, Digilio MC. Congenital heart disease and genetic syndromes: specific correlation between cardiac phenotype and genotype. Cardiovasc Pathol 2000; 9: 303-15.
4. Lurie IW, Kappetein AP, Loffredo CA, Ferencz C. Non-cardiac malformations in individuals with outflow tract defects of the heart: the Baltimore-Washington Infant Study (1981-1989). Am J Med Genet 1995; 59: 76-84.
5. Karr SS, Brenner JI, Loffredo C, Neill A, Rubin JD. Tetralogy of Fallot. The spectrum of severity in a regional study, 1981-1985. Am J Dis Child 1992; 146: 121-4.
6. di Carlo DC, Marino B. Atrioventricular canal with Down syndrome or normal chromosomes: distinct prognosis with surgical management? J Thorac Cardiovasc Surg 1994; 107: 1368-9.
7. Forbess JM, Visconti KJ, Hancock-Friesen C, Howe RC, Bellinger DC, Jonas RA. Neurodevelopmental outcome after congenital heart surgery: results from an institutional registry. Circulation 2002; 106 (Suppl I): I95-I102.
8. Cleves MA, Ghaffar S, Zhao W, Mosley BS, Hobbs CA. First-year survival of infants born with congenital heart defects in Arkansas (1993-1998): a survival analysis using registry data. Birth Defects Res Part A Clin Mol Teratol 2003; 67: 662-8.
9. Momma K, Kondo C, Ando M, Matsuoka R, Takao A. Tetralogy of Fallot associated with chromosome 22q11 deletion. Am J Cardiol 1995; 76: 618-21.
10. Ryan AK, Goodship JA, Wilson DI, et al. Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. J Med Genet 1997; 34: 798-804.
11. Goldmuntz E, Clark BJ, Mitchell LE, et al. Frequency of 22q11 deletions in patients with conotruncal defects. J Am Coll Cardiol 1998; 32: 492-8.
12. Marino B, Digilio MC, Toscano A, et al. Anatomic patterns of conotruncal defects associated with deletion 22q11. Genet Med 2001; 3: 45-8.
13. Digilio MC, Casey B, Toscano A, et al. Complete transposition of the great arteries. Patterns of congenital heart dis-

- ease in familial precurrence. *Circulation* 2001; 104: 2809-14.
14. Marino B, Digilio MC, Grazioli S, et al. Associated cardiac anomalies in isolated and syndromic patients with tetralogy of Fallot. *Am J Cardiol* 1996; 77: 505-8.
  15. Digilio MC, Marino B, Grazioli S, Agostino D, Giannotti A, Dallapiccola B. Comparison of occurrence of genetic syndromes in ventricular septal defect with pulmonic stenosis (classic tetralogy of Fallot) versus ventricular septal defect with pulmonic atresia. *Am J Cardiol* 1996; 77: 1375-6.
  16. Marino B, Digilio MC, Toscano A. Common arterial trunk, DiGeorge syndrome and microdeletion 22q11. *Prog Pediatr Cardiol* 2002; 15: 9-17.
  17. Marino B, Digilio MC, Persiani M, et al. Deletion 22q11 in patients with interrupted aortic arch. *Am J Cardiol* 1999; 84: 360-1.
  18. Mahle WT, Crisalli J, Coleman K, et al. Deletion of chromosome 22q11.2 and outcome in patients with pulmonary atresia and ventricular septal defect. *Ann Thorac Surg* 2003; 76: 567-71.
  19. Carotti A, Marino B, Di Donato RM. Influence of chromosome 22q11 microdeletion on surgical outcome after treatment of tetralogy of Fallot with pulmonary atresia. *J Thorac Cardiovasc Surg* 2003; 126: 1666-7.
  20. Momma K, Kondo C, Matsuoka R. Tetralogy of Fallot with pulmonary atresia associated with chromosome 22q11 deletion. *J Am Coll Cardiol* 1996; 27: 198-202.
  21. Anaclerio S, Marino B, Carotti A, et al. Pulmonary atresia with ventricular septal defect: prevalence of deletion 22q11 in the different anatomic patterns. *Ital Heart J* 2001; 2: 384-7.
  22. Jedele KB, Michels VV, Puga FJ, Feldt RH. Velocardiofacial syndrome associated with ventricular septal defect, pulmonary atresia and hypoplastic pulmonary arteries. *Pediatrics* 1992; 89: 915-9.
  23. Ackerman MJ, Wylam ME, Feldt RH, et al. Pulmonary atresia with ventricular septal defect and persistent airway hyperresponsiveness. *J Thorac Cardiovasc Surg* 2001; 122: 169-77.
  24. McElhinney DB, Jacobs I, McDonald-McGinn DM, Zackai EH, Goldmuntz E. Chromosomal and cardiovascular anomalies associated with congenital laryngeal web. *Int J Pediatr Otorhinolaryngol* 2002; 66: 23-7.
  25. Sashi V, Berry MN, Hines MH. Vasomotor instability in neonates with chromosome 22q11 deletion syndrome. *Am J Med Genet* 2003; 121A: 231-4.
  26. Mulder TJ, Pyles LA, Stolfi A, Pickoff AS, Moller JH. A multicenter analysis of the choice of initial surgical procedure in tetralogy of Fallot. *Pediatr Cardiol* 2002; 23: 580-6.
  27. Duke C, Sharland GK, Jones AM, Simpson JM. Echocardiographic features and outcome of truncus arteriosus diagnosed during fetal life. *Am J Cardiol* 2001; 88: 1379-84.
  28. Momma K, Ando M, Matsuoka R. Truncus arteriosus communis associated with chromosome 22q11 deletion. *J Am Coll Cardiol* 1997; 30: 1067-71.
  29. Marino B, Digilio MC, Persiani M, et al. Deletion 22q11 in patients with interrupted aortic arch. *Am J Cardiol* 1999; 84: 360-1.