Pulmonary atresia with ventricular septal defect: prevalence of deletion 22q11 in the different anatomic patterns

Silvia Anaclerio, Bruno Marino, Adriano Carotti, Maria Cristina Digilio, Alessandra Toscano, Placidino Gitto, Aldo Giannotti, Roberto Di Donato, Bruno Dallapiccola*

*Pediatric Cardiology, Cardiac Surgery and Genetics, "Bambino Gesù" Hospital, *Human Genetics, "La Sapienza" University of Rome, CSS Mendel, Rome, Italy*

Key words:
Congenital heart disease; Deletion 22q11; Genetics.

Background. **Pulmonary atresia with ventricular septal defect (PA-VSD) is one of the most common cardiac defects associated with DiGeorge syndrome. The pattern of the pulmonary circulation determines the complexity of this type of heart disease. The aim of this study was to establish the prevalence of DiGeorge syndrome with deletion 22q11 in patients with simple and complex PA-VSD.**

Methods. **Since 1993 we have studied 128 consecutive patients affected by PA-VSD. In 90 of our patients the PA-VSD was considered "simple" (group I), because it was not associated with any other cardiac defects. In the other 38 children the PA-VSD was considered "complex" (group II) owing to the presence of heterotaxia, tricuspid atresia, a double-inlet left ventricle, transposition of the great arteries and congenitally corrected transposition of the great arteries.**

Results. **In group I, 38 patients (42%) had genetic syndromes or major extracardiac anomalies; deletion 22q11 was detected in 31% of cases. Major aortopulmonary collateral arteries were present in 50% of group I patients and in 57% of those with deletion 22q11. In group II, 10 patients (26%) had genetic syndromes or major extracardiac anomalies but none had deletion 22q11 ($p < 0.005$); in no case was the presence of major aortopulmonary collateral arteries observed ($p < 0.005$).**

Conclusions. **PA-VSD is an anatomically and morphogenetically heterogeneous disease: in the setting of DiGeorge syndrome or velocardiofacial syndrome, PA-VSD is associated with a peculiar cardiac pattern and is due to deletion 22, whereas in case of nonsyndromic PA-VSD or when this disease is associated with different syndromes or with other types of cardiac defects, it is due to other morphogenetic mechanisms.**

(Ital Heart J 2001; 2 (5): 384-387)

Received November 17, 2000; revision received January 15, 2001; accepted January 24, 2001.

Address:

Dr. Bruno Marino

Divisione di Cardiologia Ospedale Pediatrico "Bambino Gesù" Piazza S. Onofrio, 4 00165 Roma

Introduction

Pulmonary atresia with ventricular septal defect (PA-VSD) is a congenital cardiac defect frequently associated with DiGeorge/velocardiofacial syndrome and with deletion of chromosome 22q11 (del22q11)[1-5].

PA-VSD occurs in 10-26% of children with del22q11[6-9]; on the other hand, among patients with PA-VSD the prevalence of del22q11 ranges between 15 and 48%[2-5]. The prevalence of del22q11 in patients with PA-VSD is higher than that in children with "classic" tetralogy of Fallot[2,4,7].

Considering the pattern of pulmonary blood supply, among children with PA-VSD two major groups of patients have been recognized: 1) children with a single ductus arteriosus that usually presents confluent and well formed pulmonary arteries (also called tetralogy of Fallot with PA), and 2) children with major aortopulmonary collateral arteries frequently associated with discontinuity, hypoplasia or absence of the central pulmonary arteries. Recent studies proved that in children with PA-VSD and del22q11 the pattern of pulmonary blood supply provided by the major aortopulmonary collateral arteries is prevalent[3-5].

PA may also occur in a setting of congenital heart defects with complex ventriculoarterial alignment and/or intracardiac anatomy (i.e. simple or corrected transposition of the great arteries, heterotaxia, double-inlet left ventricle, tricuspid atresia, etc.)[10]. However, there is no information in the literature about the prevalence of DiGeorge/velocardiofacial syndrome and del22q11 in patients with such associations.

The aim of this study was to determine the prevalence of DiGeorge/velocardiofacial syndrome with del22q11 in patients

with "simple" PA-VSD as compared to that in patients with "complex" PA.

Methods

From July 1993 to May 2000 we studied 128 consecutive patients with PA-VSD (66 males and 62 females); the age at the first observation ranged from 1 day to 3 years. The cardiac diagnosis was established by echocardiography and selective angiography in each patient paying particular attention to the intracardiac anatomy and to the blood supply to the lungs[3-5].

In 90 of our patients the intracardiac anatomy was considered "simple" (group I) because these cases presented with situs solitus of the atria, d-loop of the ventricles, normal atrioventricular valves, balanced ventricles, a large perimembranous (malalignment) VSD and aortic overriding with fibrous mitro-aortic continuity[1-5]. This is the usual intracardiac anatomic pattern of PA-VSD.

In the other 38 children (group II) the intracardiac anatomy was diagnosed as "complex"[10] owing to the presence of heterotaxia (8 cases), tricuspid atresia (4 cases), a double-inlet left ventricle (2 cases), transposition of the great arteries (18 cases), and congenitally corrected transposition of the great arteries (6 cases). Major aortopulmonary collateral arteries were diagnosed when systemic arteries originating from the aorta or from its main branches and supplying the blood flow to the lungs either directly or in association with the native pulmonary arteries were detected[3-5].

Phenotypic evaluation included facial dysmorphisms and extracardiac anomalies in all patients. Standard chromosome analysis of peripheral lymphocytes and fluorescent *in situ* hybridization with Sc11.1, co23, and D22S75 and D22S39 (control ONCOR) probes were performed in all 128 children. The prevalence of genetic syndromes and of del22q11 as well as that of major aortopulmonary collateral arteries in children with a "simple" intracardiac anatomy were compared to those in children with a "complex" intracardiac anatomy (Table I). Statistical analysis was performed by the Fisher's exact test, and all p values ≤ 0.05 were considered significant.

Results

In group I, 38 patients (42%) had genetic syndromes or major extracardiac anomalies (Fig. 1) and del22q11 was detected in 28/90 cases (31%). In this group major

Table I. Genetic syndromes and extracardiac anomalies in patients with pulmonary atresia with ventricular septal defect.

	Group I (n=90)	Group II (n=38)
Syndromic patients	38 (42%)	10 (26%)
Deletion 22q11	28 (31%)	0
CHARGE association	4	0
VACTERL association	3	2
Townes syndrome	1	0
Coffin-Siris syndrome	1	0
Cranio-cerebello-cardiac syndrome	1	0
Oro-facio-digital II syndrome	0	1
Major extracardiac anomalies	0	7

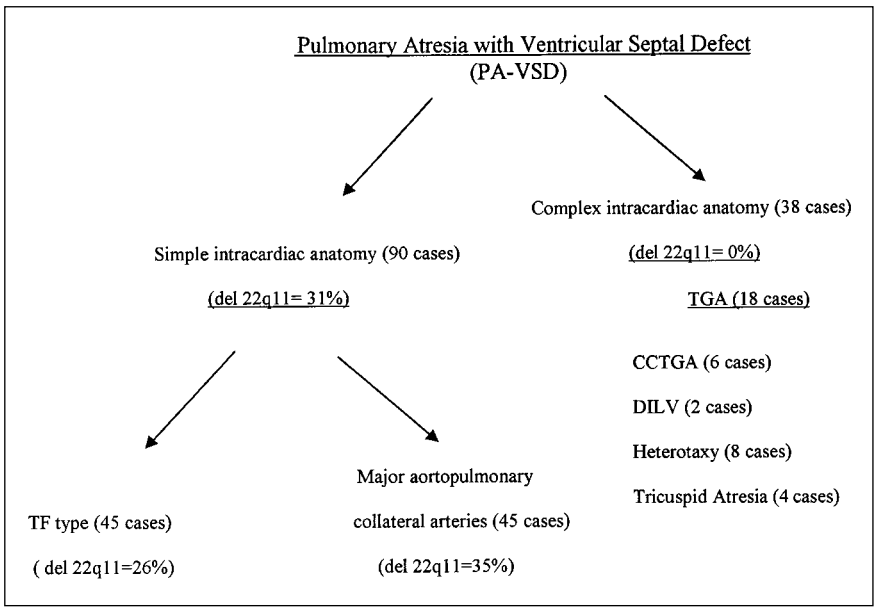

Figure 1. *Pulmonary atresia with ventricular septal defect. CCTGA = congenitally corrected transposition of the great arteries; DILV = double-inlet left ventricle; TF = tetralogy of Fallot; TGA = transposition of the great arteries.*

aortopulmonary collateral arteries occurred in 45 children (50%) and in 16 of 28 patients presenting with del22q11 (57%).

In group II, 10 patients (26%) had genetic syndromes or major extracardiac anomalies (p = NS) but none presented with del22q11 (p < 0.005). In no case was the presence of major aortopulmonary collateral arteries observed (p < 0.005)[10]. Overall, this pattern of pulmonary blood supply was significantly more frequent (16/28, 57%) among patients with del22q11 compared to children with PA but without del22q11 (p = 0.01) (Fig. 1). There were no significant differences in terms of gender or age between the two groups and between patients with and without del22q11. There was complete correspondence between genotype and phenotype: all patients with del22q11 had two or more classic phenotypic signs of DiGeorge/velocardiofacial syndrome and none of the nonsyndromic patients presented with del22q11[11].

Investigation of the familial history revealed recurrent nonsyndromic congenital heart disease in one pedigree, in which two sibs had "simple" PA-VSD without del22q11. No additional familial congenital heart diseases were found in pedigrees of patients with "simple" or "complex" PA-VSD. Consanguinity was noted among the parents of a patient with "simple" PA-VSD without del22q11. Among patients with PA-VSD and del22q11, the deletion segregated from the mother in 2 cases. The affected mothers presented with mental retardation and facial features characteristic of DiGeorge/velocardiofacial syndrome but with no cardiac anomalies.

Discussion

Our study shows that the prevalence of del22q11 is higher among patients with PA-VSD associated with a "simple" intracardiac anatomy (p < 0.005). In these children the pattern of pulmonary blood supply frequently consists of major aortopulmonary collateral arteries[3-5] which, on the other hand, are very rare among patients with PA and a "complex" intracardiac anatomy[10]. Our data suggest that PA-VSD associated with del22q11 increases the risk of the presence of major aortopulmonary collateral arteries (16/28, 57%) compared to PA without del22q11 (29/100, 29%) (p = 0.01). Moreover, the prevalence of del22q11 is significantly higher (16/45, 35%) among patients with PA and major aortopulmonary collateral arteries than in patients with PA and ductus arteriosus (12/83, 14%) (p = 0.01).

Probably these two groups of patients with PA should be considered separate entities with different anatomic, genetic and surgical implications[11]. However, considering only patients with PA-VSD and a "simple" intracardiac anatomy, there is a similar prevalence of del22q11 in children with major aortopulmonary collateral arteries (16/45) and in those with ductus arteriosus "tetralogy of Fallot" type (12/45).

PA, similar to other conotruncal defects[12-15], is an anatomically and morphogenetically heterogeneous disease. In children with DiGeorge/velocardiofacial syndrome, PA is usually associated with a "simple" intracardiac anatomy, frequently presents major aortopulmonary collateral arteries and is caused by del22q11; on the contrary PA in the setting of complex congenital heart disease is not associated with del22q11 and the pulmonary blood supply is usually provided by a patent ductus arteriosus. In the latter cases, PA is due to other morphogenetic mechanisms probably related to the pattern of intracardiac malformations. The heterogeneous morphogenesis of PA is supported by the high number and variety of associated genetic conditions, even different from DiGeorge/velocardiofacial syndrome, present in all anatomic forms (Table I).

The intracardiac and extracardiac anatomic complexity of the heart defects associated with PA continues to stimulate the search for new nomenclature and classifications[16-19]. Patients with PA and major aortopulmonary arteries should be differentiated from those with single ductus arteriosus and confluent pulmonary arteries (tetralogy of Fallot with PA).

We suggest that the genetic aspects are useful for the anatomic comprehension and categorization of these cardiac defects.

References

1. Jedele KB, Michels VV, Puga FJ, et al. Velo-cardio-facial syndrome associated with ventricular septal defect, pulmonary atresia, and hypoplastic pulmonary arteries. Pediatrics 1992; 89: 915-9.
2. Digilio MC, Marino B, Grazioli S, et al. 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.
3. 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.
4. Chessa M, Butera G, Bonhoeffer P, et al. Relation of genotype 22q11 deletion to phenotype of pulmonary vessels in tetralogy of Fallot and pulmonary atresia-ventricular septal defect. Heart 1998; 79: 186-90.
5. Hofbeck M, Rauch A, Buheitell G, et al. Monosomy 22q11 in patients with pulmonary atresia, ventricular septal defect, and major aortopulmonary collateral arteries. Heart 1998; 79: 180-5.
6. Ryan AK, Goodship JA, Wilson DI, et al. Spectrum of clinical features associated with interstitial chromosome 22q11 deletion: a European collaborative study. J Med Genet 1997; 34: 798-804.
7. Matsuoka R, Kimura M, Scambler PJ, et al. Molecular and clinical study of 183 patients with conotruncal anomaly face syndrome. Hum Genet 1998; 103: 70-80.
8. Goldmuntz E, Clarke BJ, Mitchell LE, et al. Frequency of 22q11 deletion in patients with conotruncal defects. J Am Coll Cardiol 1998; 32: 492-8.
9. Marino B, Digilio MC, Toscano A, et al. Congenital heart defects in patients with DiGeorge/velocardiofacial syndrome and del22q11. Genet Couns 1999; 10: 25-33.

10. Marino B, Calabrò R, Gagliardi G, et al. Patterns of pulmonary arterial anatomy and blood supply in complex congenital heart disease with pulmonary atresia. J Thorac Cardiovasc Surg 1987; 94: 518-20.
11. Carotti A, Di Donato R, Squitieri C, et al. Total repair of pulmonary atresia with ventricular septal defect and major aortopulmonary collaterals: an integrated approach. J Thorac Cardiovasc Surg 1998; 116: 914-23.
12. Digilio MC, Marino B, Giannotti A, et al. Conotruncal heart defects and chromosome 22q11 microdeletion. J Pediatr 1997; 130: 675-7.
13. 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.
14. Momma K, Kondo C, Matsuoka R, et al. Cardiac anomalies associated with a chromosome 22q11 deletion in patients with conotruncal anomaly face syndrome. Am J Cardiol 1996; 78: 592-4.
15. Marino B, Digilio MC, Persiani M, et al. Deletion 22q11 in patients with interrupted aortic arch. Am J Cardiol 1999; 84: 360-1.
16. Tchervenkov CI, Roy N. Congenital heart surgery nomenclature and database project: pulmonary atresia-ventricular septal defect. Ann Thorac Surg 2000; 69: S97-S105.
17. Yong DE, Booth P, Baruni J, et al. Chromosome 22q11 microdeletion and congenital heart disease. A survey in a pediatric population. Eur J Pediatr 1999; 158: 566-70.
18. Borgmann S, Luhmer I, Arslan-Kirchner M, et al. A search for chromosome 22q11.2 deletions in a series of 176 consecutively catheterized patients with congenital heart disease: no evidence for deletion in non syndromic patients. Eur J Pediatr 1999; 158: 958-63.
19. Fokstuen S, Arbenz U, Artan S, et al. 22q11.2 deletions in a series of patients with non selective congenital heart defects: incidence, type of defects and parental origin. Clin Genet 1998; 53: 63-9.