article

Anatomic patterns of conotruncal defects associated with deletion 22q11

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Purpose: Patients with cardiovascular malformations (CVMs) and deletion 22q11 from our series were studied in order to (1) analyze the association with dysmorphic features and noncardiac anomalies, (2) identify specific cardiac patterns and the distinctive association with additional CVMs. **Methods:** From 1993 to 2000, 931 patients with CVM (95 with a clinical diagnosis of DiGeorge/velocardiofacial syndrome (DG/VCFS), 208 with different genetic syndromes, 628 without dysmorphic features) underwent accurate cardiac assessment, clinical and phenotypical examination, and screening for deletion 22q11 by fluorescence in situ hybridization (FISH). **Results:** Deletion 22q11 was detected in 88 of the total patients, and in 87 of the 95 patients with a clinical diagnosis of DG/VCFS. Only one patient among the 628 without dysmorphic features had deletion 22q11. Conotruncal heart defects were the most common CVMs, often presenting in association with additional anomalies in four areas of the cardiovascular system: (1) the aortic arch can be right sided, cervical, double, and the subclavian artery can be aberrant, (2) the pulmonary arteries can present discontinuity, diffuse hypoplasia, discrete stenosis, defect of arborization and major aortopulmonary collateral arteries (MAPCA), (3) the infundibular septum can be malaligned, hypoplastic, or absent, (4) the semilunar valves can be bicuspid, severely dysplastic, insufficient, or stenotic. **Conclusion:** In subjects with deletion 22q11 CVM is virtually always associated with one or more noncardiac anomalies. Deletion 22q11 is exceptionally rare in children with nonsyndromic CVMs. Specific patterns of CVMs are observed in patients with deletion 22q11, including (1) anomalies of the aortic arch, (2) anomalies of the pulmonary arteries and of the pulmonary blood supply, (3) defects of the infundibular septum, (4) malformations of the semilunar valves. These additional CVMs may influence the surgical treatment of these patients. ***Genetics in Medicine*, 2001:3(1):45–48.**

Key Words: *congenital heart disease, cardiovascular malformation, deletion 22q11, DiGeorge/velocardiofacial syndrome, conotruncal heart defects, genotype-phenotype correlation*

The impact of cardiac problem is very important in children with DiGeorge/velocardiofacial syndrome (DG/VCFS) and deletion 22q11, since symptomatic cardiovascular malformations (CVMs) affect the 75% of patients.[1] Moreover, the CVM is the cause of death in the great majority of cases accounting for 87% of patients with this syndrome.[1] The increasing rate of diagnosis of asymptomatic aortic arch malformations in patients with deletion 22q11 will further increase the number of CVMs associated with this genetic condition.

The "classic" CVMs occurring in patients with deletion 22q11 are conotruncal defects,[2–10] including tetralogy of Fallot (TF), pulmonary atresia with ventricular septal defect (PA-VSD), truncus arteriosus (TA) and interrupted aortic arch (IAA), but also ventricular septal defect was commonly described. However, in children with this syndrome, other types of CVM were occasionally reported, including atrial septal defect, atrioventricular canal, tricuspid atresia, transposition of the great arteries, hypoplastic left ventricle, heterotaxy, aortic coarctation, vascular rings, and other anomalies of the aortic arch.[1–14]

The accurate study of cardiac phenotype revealed that additional CVMs are common in children with conotruncal defects and deletion 22q11 so that distinctive patterns could be recognized in patients with this syndrome as well as were recognized in patients with other genetic syndromes.[15–18] In this report, we summarize our experience and the cardiac anatomy in children with conotruncal defects and deletion 22q11, describing the association with phenotypical findings.

MATERIALS AND METHODS

From 1993 to 2000, 931 children with CVM were screened for deletion 22q11 in our hospital; 628 patients presented nonsyndromic CVM, 95 children had a clinical diagnosis of DG/VCFS, and 208 cases presented with clinical features of various different genetic syndromes. Nonsyndromic patients were de-

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fined as those without dysmorphic features or noncardiac anomalies. A clinical diagnosis of DG/VCFS was made in the presence of almost three of the classic features, including CVM, facial anomalies, immune defect, palatal anomalies, neonatal hypocalcemia, and mental retardation. All patients underwent accurate cardiac assessment by echocardiography, and in selected patients, cardiac catheterization or magnetic resonance imaging were performed. In the majority of patients, the cardiac diagnoses were confirmed at cardiac surgery. All patients were clinically examined by two clinical geneticists (MCD, AG) and checked for additional major or minor extracardiac malformations. Standard metaphase chromosome analysis was performed in all cases. Slides were also processed for fluorescence in situ hybridization (FISH) using the Sc11.1, Co23, and D22S75 and D22S39 (control ONCOR) probes.

RESULTS

A total of 88 patients were found to have deletion 22q11. There were 52 males and 36 females. Age ranged between 0.1 and 15.9 years (age ± SD 4.82 ± 4.55). Among the 95 children with clinical diagnosis of DG/VCFS, 87 patients had deletion 22q11. Among 628 patients with nonsyndromic CVM, only one patient had deletion 22q11. The types of CVM in patients with deletion 22q11 are reported in Table 1.

Tetralogy of Fallot (23 cases)

Additional CVMs were found in the half of the patients with deletion 22q11.[19–22] These associated defects were (1) right or cervical aortic arch with or without aberrant left subclavian artery, (2) hypoplasia or absence of the infundibular septum (subarterial doubly committed VSD), (3) absence of the pulmonary valve, (4) discontinuity or diffuse hypoplasia of the pulmonary arteries.

Table 1
Types of congenital heart defects in patients ($n = 88$) with deletion 22q11 from our series

Cardiac defect	No. of patients	%
Pulmonary atresia with ventricular septal defect	24	27.3
Tetralogy of Fallot	23	26.1
Ventricular septal defect	15	17.0
Perimembranous	10	
Subarterial	4	
Right malalignment	1	
Truncus arteriosus	10	11.4
Interrupted aortic arch	8	9.1
Type B	7	
Type C	1	
Transposition of the great arteries	3	3.4
Atrial septal defect	2	2.3
Double outlet right ventricle	1	1.1
Tricuspid atresia	1	1.1
Double aortic arch	1	1.1

Pulmonary atresia with ventricular septal defect (24 cases)

Also in this malformation, in presence of deletion 22q11, there was a prevalence of (1) right aortic arch, (2) additional anomalies of the pulmonary arteries, including discontinuity and defects of arborization.[23–27] A particular anatomic subtype was represented by the patients in which the pulmonary artery blood flow was supplied by major aortopulmonary collateral arteries (MAPCA). These patients present significant anatomic differences from those with confluent pulmonary arteries and a single ductus arteriosus so called TF with PA. Also the prevalence of deletion 22q11 is different in two groups: 16% in children with TF and PA (similar to that observed in patients with simple TF) and 41% in patients with PA, VSD, and MAPCA.[28]

Truncus arteriosus (10 cases)

In these patients, in the presence of deletion 22q11, the additional CVMs were very common and consisted of (1) interruption or right aortic arch, (2) discontinuity, stenosis, or crossing of the pulmonary arteries, (3) severe dysplasia (prevalent stenosis) of the truncal valve, (4) origin of the TA from the right ventricle.[29–31] In particular, deletion 22q11 is common in patients with TA with nonconfluent pulmonary arteries (Type A3 of Van Praagh), in which the right pulmonary artery arises from the TA near to the truncal valve, and the left pulmonary artery is supplied by the ductus arteriosus.[31]

Interrupted aortic arch (8 cases)

Deletion 22q11 was common in patients with IAA type B (between left carotid and left subclavian arteries).[32–38] In children with IAA type A (after the left subclavian artery), deletion 22q11 was never observed in our series[32] but was occasionally reported by others.[36] When IAA type B is associated with deletion 22q11, the infundibular septum is commonly hypoplastic or absent and is deviated posteriorly and to the left; the VSD results in a subarterial position doubly committed with the pulmonary and aortic valves.[32,38]

Ventricular septal defect (15 cases)

Additional CVMs were detected also in patients with VSD and deletion 22q11.[3,8,39] In these children, there was a prevalence of (1) subarterial doubly committed type of defect, and (2) right or cervical aortic arch. Muscular VSD was not present in our series of patients with deletion 22q11.[39]

DISCUSSION

Deletion 22q11 is exceptionally rare among children with isolated nonsyndromic conotruncal defects,[24,40–47] and patients with CVM and deletion 22q11 virtually always present one or more noncardiac anomalies of DG/VCFS. On the basis of these data, we suggest that the accurate study of clinical

phenotype (including cardiac phenotype) can select patients at risk for having deletion 22q11. We believe that, in clinical practice, FISH analysis is indicated in all patients with TA, IAA type B, PA with VSD and MAPCA, considering the high rate of occurrence of deletion 22q11 in these CVMs (the 35% in TA,[9,29] the 60–80% in IAA type B,[9,32,36] and the 40% in PA with VSD and MAPCA.[28]) In the other CVMs, including TF with or without PA, VSD, vascular rings etc., the FISH analysis is indicated only in the presence of other clinical or cardiac signs of DG/VCFS.

Differences in cardiac anatomy, occurring in children with isolated or syndromic CVMs, are well recognized in the literature. Patients with Down syndrome,[15] Noonan syndrome,[16] Ellis-van Creveld syndrome,[17] and Holt-Oram syndrome[18] present distinctive type and subtype of CVMs, different from those observed in children without genetic anomalies. Recent contributions show that also in subjects with DG/VCFS and deletion 22q11 there are some anatomic aspects characterizing a specific cardiac phenotype.[3–14] All types of conotruncal defects, when associated with deletion 22q11, commonly present additional anomalies in four areas of the cardiovascular system: (1) *the aortic arch* can be right sided, cervical, double, and the subclavian artery can be aberrant; (2) *the pulmonary arteries* can present discontinuity, diffuse hypoplasia, discrete stenosis, defect of arborization, and major aortopulmonary collateral arteries (MAPCA); (3) *the infundibular septum* can be malaligned, hypoplastic, or absent, (4) *the semilunar valves* can be bicuspid, severely dysplastic ("absent valve"), insufficient, or stenotic.

Interestingly, the infundibular septum is virtually always involved in the CVM of this syndrome, because it is malaligned and/or absent in TF, PA with VSD, and in IAA, and is always absent in TA. VSDs involving the infundibular septum are quite rare in Caucasian children, but are commonly described in oriental population.[38] Moreover, TF with absent infundibular septum is frequently reported in South American patients ("Mexican type of TF" - Dr. Aldo Castaneda, personal communication, Boston, 1985[48]). In subjects with deletion 22q11, the infundibular septum is affected in both, Caucasian and Asian populations.[19,20,32,47]

In consideration of the distinctive anatomic, surgical, and genetic characteristics of TF with PA and PA with VSD and MAPCA, these two groups of malformations should be regarded as separate entities.[49] Interestingly, deletion 22q11 is quite rare in children with PA and complex intracardiac anatomy as single ventricle and complete or corrected transposition of the great arteries.[28]

In conclusion, all these anatomic findings represent specific cardiac patterns characteristic of children with conotruncal defects and deletion 22q11. The knowledge of these aspects should be useful for the clinical recognition (cardiac phenotype) and for the cardiological diagnosis of these patients. However, these additional CVMs can influence the surgical treatment of children with deletion 22q11. In our experience, in patients with TF with or without PA and in those with IAA, the presence of deletion 22q11 and related additional CVMs are not risk factors for heart surgery. On the contrary, additional CVMs observed in patients with PA with VSD and MAPCA and in those with TA can complicate the surgical correction of these CVMs.

Further studies on this argument should be addressed: (1) to define the prevalence of major and minor CVMs in this syndrome, (2) to understand morphogenetic mechanism of the CVMs in relation to the specific expression of the genes, (3) to evaluate the impact and to minimize the effects of deletion 22q11 on surgical results of CVMs.

References

1. Ryan AK, Goodship JA, Wilson DI, Philip N, Levy Seidel H, Shuffenhauer S, Oechsler H, Beloharadsky Prieur M, Aurias A, Raymond FL, Clayton-Smith J, Hatchwell E, McKeown C, Beemer FA, Dallapiccola B, Novelli G, Hurst JA, Ignatius J, Green AJ, Winter RM, Brueton L, Brondum-Nielsen K, Stewart F, Van Essen T, Paterson J, Scambler PJ. Spectrum of clinical features associated with interstitial chromosome22q11 deletions: a European collaborative study. *J Med Genet* 1997;34:798–804.
2. Kinouchi A, Mori K, Ando M, Takao A. Facial appearance with conotruncal anomalies. *Pediatr Jpn* 1976;17:84–89.
3. Young D, Shprintzen RJ, Goldberg RB. Cardiac malformation in the velocardiofacial syndrome. *Am J Cardiol* 1980;46:643–648.
4. Marmon LM, Balsara RK, Chen R, Dunn JM. Congenital cardiac anomalies associated with DiGeorge syndrome: a neonatal experience. *Ann Thorac Surg* 1984;38:146–150.
5. Van Mierop LH, Kutsche LM. Cardiovascular anomalies in DiGeorge syndrome and importance of neural crest as a possible pathogenetic factor. *Am J Cardiol* 1986;58:133–137.
6. Momma K, Kondo C, Matsuoka R, Takao A. Cardiac anomalies associated with a chromosome 22q11 deletion in patients with conotruncal anomaly face syndrome. *Am J Cardiol* 1996;78:591–594.
7. Marino B, Digilio MC, Grazioli S, Borzaga U, Toscano A, Giannotti A, Dallapiccola B. Cardiac defect and del 22q11 deletion. *J Med Genet* 1997;34:20.
8. Matsuoka R, Kimura M, Scambler PJ, Morrow BE, Imamura S, Minoshima S, Shimizu N, Yamagishi H, Joh-O K, Watanabe S, Oyama K, Saji T, Ando M, Takao A, Momma K. Molecular and clinical study of 183 patients with conotruncal anomaly face syndrome. *Hum Genet* 1998;103:70–80.
9. Goldmuntz E, Clark BJ, Mitchell LE, Jawad AF, Cuneo BF, Reed L, McDonald-McGinn D, Chien P, Feuer J, Zackai EH, Emanuel BS, Driscoll DA. Frequency of 22q11 deletions in patients with conotruncal defects. *J Am Coll Cardiol* 1998;32:492–498.
10. Marino B, Digilio MC, Toscano A, Giannotti A, Dallapiccola B. Congenital heart defects in patients with DiGeorge/Velocardiofacial syndrome and del22q11. *Genet Couns* 1999;10:25–33.
11. Marino B, Marcelletti C, Giannotti A, Dallapiccola B. DiGeorge anomaly with atrioventricular canal. *Chest* 1991;99:242–243.
12. Melchionda S, Digilio MC, Mingarelli R, Novelli G, Scambler P, Marino B, Dallapiccola B. Transposition of the great arteries associated with deletion of chromosome 22q11. *Am J Cardiol* 1995;75:95–98.
13. Marino B, Digilio MC, Novelli G, Giannotti A, Dallapiccola B. Tricuspid Atresia and 22q11 deletion. *Am J Med Genet* 1997;72:40–42.
14. Kazuma N, Murakami M, Suzuki Y, Umezu R, Murata M. Cervical aortic arch associated with 22q11.2 deletion. *Pediatr Cardiol* 1997;18:149–151.
15. Marino B, Vairo U, Corno A, Nava S, Guccione P, Calabro R, Marcelletti C. Atrioventricular canal in Down syndrome: prevalence of associated cardiac malformations compared with patients without Down syndrome. *Am J Dis Child* 1990;144:1120–1122.
16. Marino B, Digilio MC, Toscano A, Giannotti A, Dallapiccola B. Congenital heart diseases in children with Noonan syndrome: an expanded cardiac spectrum with high prevalence of atrioventricular canal. *J Pediatr* 1999;136:703–706.
17. Digilio MC, Marino B, Ammirati A, Borzaga U, Giannotti A, Dallapiccola B. Cardiac malformations in patients with oral-facial-skeletal syndrome: clinical similarities with heterotaxia. *Am J Med Genet* 1999;84:350–356.
18. Bennhagen RG, Menahem S. Holt-Oram syndrome and multiple ventricular septal defects: an association suggesting a possible genetic marker? *Cardiol Young* 1998;8:128–130.
19. Marino B, Digilio MC, Grazioli S, Formigari R, Mingarelli R, Giannotti A, Giannotti A, Dallapiccola B. Associated cardiac anomalies in isolated and syndromic patients with tetralogy of Fallot. *Am J Cardiol* 1996;77:505–508.

20. Momma K, Kondo C, Ando M, Matsuoka R, Takao A. Tetralogy of Fallot associated with chromosome 22q11 deletion. *Am J Cardiol* 1995;76:618–621.
21. Johnson MC, Strauss AW, Dowton SB, Spray TL, Huddleston CB, Wodd MK, Slaugh RA, Watson MS. Deletion within chromosome 22 is common in patients with absent pulmonary valve syndrome. *Am J Cardiol* 1995;76:66–69.
22. Saliba Z, Le Bidois J, Sidi D, Kachaner, Bonnet D. Prenatal detection of a tetralogy of Fallot with origin of the left pulmonary artery from the ascending aorta in a familial 22q11 microdeletion. *Prenat Diagn* 1999;19:260–262.
23. Jedele KB, Michels VV, Puga FJ, Feldt RH. Velo-cardio-facial syndrome associated with ventricular septal defect, pulmonary atresia, and hypoplastic pulmonary arteries. *Pediatrics* 1992;89:915–919.
24. 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.
25. 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;77:1375–1376.
26. Chessa M, Butera G, Bonhoeffer P, Iserin L, Kachaner J, Lyonnet S, Munnich A, Sidi D, Bonnet D. Relation of genotype 22q11 deletion to phenotype of pulmonary vessels in tetralogy of Fallot and pulmonary atresia-ventricular septal defect. *Heart* 1998;79:186–190.
27. Hofbeck M, Rauch A, Buheitel G, Leipold G, von der Emde J, Pteiffer R, Singer H. Monosomy 22q11 in patients with pulmonary atresia, ventricular septal defect, and major aortopulmonary collateral arteries. *Heart* 1998;79:180–185.
28. Anaclerio S, Marino B, Digilio MC, Toscano A, Gitto P, Di Donato R, Dallapiccola B. Pulmonary atresia with ventricular septal defect: prevalence of deletion 22q11 in the different anatomic patterns. *Ital Heart J* 2000;1(Suppl 4):11.
29. Momma K, Ando M, Matsuoka R. Truncus arteriosus communis associated with chromosome 22q11 deletion. *J Am Coll Cardiol* 1997;30:1067–1071.
30. Marino B, Digilio MC, Dallapiccola B. Severe truncal valve dysplasia: association with DiGeorge syndrome? *Ann Thorac Surg* 1998;66:980.
31. Toscano A, Marino B, Digilio MC, Giannotti A, Dallapiccola B. Truncus arteriosus with discontinuity of the pulmonary arteries and DiGeorge phenotype. *G It Cardiol* 1998;28(Suppl 3):7.
32. Marino B, Digilio MC, Persiani M, Di Donato R, Toscano A, Giannotti A, Dallapiccola B. Deletion 22q11 in patients with interrupted aortic arch. *Am J Cardiol* 1999; 84:360–361.
33. Moerman P, Dumoulin M, Lauweryns J, Van der Hauwaert LG. Interrupted right aortic arch in DiGeorge syndrome. *Br Heart J* 1987;58:274–278.
34. Moor GW, Hutchins GM. Association of interrupted aortic arch with malformation producing reduced blood flow to the fourth aortic arch. *Am J Cardiol* 1978;42:467–472.
35. Lewin MB, Lindsay EA, Jurecic V, Goytia B, Towbin JA, Baldini A. A genetic etiology for interruption of the aortic arch type B. *Am J Cardiol* 1997;80:493–497.
36. Rauch A, Hofbeck M, Leipold G, Klinge J, Trautmann U, Kirsch M, Singer H, Pfeiffer RA. Incidence and significance of 22q11.2 hemizygosity in patients with interrupted aortic arch. *Am J Med Genet* 1998;78:322–331.
37. Loffredo CA, Ferencz C, Wilson PD, Lurie IW. Interrupted aortic arch: an epidemiologic study. *Teratology* 2000;61:368–375.
38. Momma K, Ando M, Matsuoka R, Joo K. Interruption of the aortic arch associated with deletion of chromosome 22q11 is associated with a subarterial and doubly committed ventricular septal defect in Japanese patients. *Cardiol Young* 1999;9:463–467.
39. Toscano A, Marino B, Digilio MC, Anaclerio S, Fariello G, Giannotti A, Dallapiccola B. Ventricular septal defect and deletion 22q11. *Ital Heart J* 2000;1(Suppl 4):11.
40. Amati F, Mari A, Digilio MC, Mingarelli R, Marino B, Giannotti A, Novelli G, Dallapiccola B. 22q11 deletion in isolated and syndromic patients with tetralogy of Fallot. *Hum Genet* 1995;95:479–482.
41. Fokstuen S, Arbens U, Artan S, Dutly F, Bauerfeld U, Brecevic L, Fasnacht M, Rothlisberger B, Schinzel A. 22q11.2 deletions in a series of patients with nonselective congenital heart defects: incidence, type of defects and parental origin. *Clin Genet* 1998;53:63–69.
42. Mehraein Y, Wippermann CF, Michel-Behnke I, Ngo TKN, Hillig U, Giersberg M, Aulepp U, Berth H, Fritz B, Rehder H. Microdeletion 22q11 in complex cardiovascular malformations. *Hum Genet* 1997;99:433–442.
43. Takahashi K, Kido S, Hoshino K, Ogawa K, Ohashi H, Fukushima Y. Frequency of a 22q11 deletions in patients with conotruncal heart malformations: a prospective study. *Eur J Pediatr* 1995;154:878–881.
44. Webber SA, Hatchwell E, Barber JCK, Daubeney PEF, Crolla JA, Salmon AP, Keeton BR, Temple IK, Dennis NR. Importance of microdeletions of chromosomal region 22q11 as a cause of selected malformations of the ventricular outflow tracts and aortic arch: a three-year prospective study. *J Pediatr* 1996;129:26–32.
45. Digilio MC, Marino B, Giannotti A, Dallapiccola B. Search for 22q11 deletion in non-syndromic conotruncal cardiac defects. *Eur J Pediatr* 1996;155:619–620.
46. Digilio MC, Marino B, Giannotti A, Dallapiccola B. Chromosome 22q11 microdeletion and isolated conotruncal heart defects. *Arch Dis Child* 1997;76:79–81.
47. Digilio MC, Marino B, Giannotti A, Novelli G, Dallapiccola B. Conotruncal heart defects and chromosome 22q11 microdeletion. *J Pediatr* 1997;130:675–677.
48. Vargas FJ, Kreutzer GO, Pedrini M, Capelli H, Coronel AR. Tetralogy of Fallot with subarterial ventricular septal defect. *J Thorac Cardiovasc Surg* 1986;92:908–912.
49. Tchervenkov CI, Roy N. Congenital heart surgery nomenclature and database project: pulmonary atresia-ventricular septal defect. *Ann Thorac Surg* 2000;69:S97–S105.