Published in final edited form as:
Am J Med Genet A. 2009 May ; 0(5): 939–942. doi:10.1002/ajmg.a.32770.

Aortic Root Dilation in Patients With 22q11.2 Deletion Syndrome

Anitha S. John[1], **Donna M. McDonald-McGinn**[2], **Elaine H. Zackai**[2], and **Elizabeth Goldmuntz**[1,*]

[1]Division of Cardiology, The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

[2]Division of Human Genetics, The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Abstract

The 22q11.2 deletion syndrome is characterized by a highly variable phenotype including a range of cardiac malformations. The most common cardiovascular features include a subset of conotruncal defects, perimembranous ventricular septal defects and aortic arch anomalies. This report describes a series of patients with 22q11.2 deletion syndrome with the novel cardiac finding of mild aortic root dilation. A chart review was performed on 93 patients with documented 22q11.2 deletion without significant congenital heart disease to determine the number of patients with aortic root dilation. Patients ranged in age from 1 to 13 years of age. Of these 93 patients, 10 patients were found to have aortic root dilation on a screening echocardiogram. Seven of these patients did not have any additional risk factors while three patients had a bicuspid aortic valve (BAV). Four of 10 patients had additional minor cardiac anomalies including repaired ventricular septal defect (1), patent ductus arteriosus(1), arch anomalies (1), and left pulmonary artery stenosis (1). Three patients had isolated cases of aortic root dilation. Interestingly, several of these patients did not have aortic root dilation on their initial echocardiograms. The purpose of this study is to draw attention to a novel cardiac finding in patients with 22q11.2 deletion that may be of clinical importance. Further long-term study is warranted to assess the need for echocardiographic screening in the 22q11.2 deleted population for aortic root dilation into adolescence and adulthood.

Keywords

22q11.2 deletion; DiGeorge syndrome; velocardio-facial syndrome; conotruncal anomaly face syndrome; aortic root dilation

INTRODUCTION

Aortic root dilation leading to aortic dissection has been associated with numerous connective tissue disorders such as Marfan syndrome (fibrillin mutations), Ehlers–Danlos

*Correspondence to: Elizabeth Goldmuntz, Associate Professor of Pediatrics, University of Pennsylvania School of Medicine, Abramson Research Center 702A, 3615 Civic Center Boulevard, The Children's Hospital of Philadelphia, Philadelphia, PA 19104. goldmuntz@email.chop.edu.

syndrome (collagen mutations) and Loeys–Dietz syndrome (TGF-β receptor mutation) [Murdoch et al., 1972; Wenstrup et al., 2002; Loeys et al., 2006]. Other patients at risk include those with valvular abnormalities such as bicuspid aortic valve (BAV) and various genetic syndromes such as Turner syndrome, 18q deletion syndrome, and fragile X syndrome [Crabbe et al., 1993; Nistri et al., 1999; Versacci et al., 2005; Carlson and Silberach, 2007]. In addition to valvular abnormalities and genetic syndromes, adult onset diseases, such as hypertension, are additional risk factors for aortic root dilation [Larson and Edwards, 1984]. Identifying patients with aortic root dilation in these at-risk groups of patients is important as progressive dilation can lead to aortic dissection and death if left untreated.

Chromosome 22q11.2 deletion syndrome (DiGeorge, velocardiofacial, and conotruncal anomaly face syndrome) presents with variable phenotypes. Typical features include cardiac and palate anomalies, speech and learning disabilities, hypocalcemia, immunodeficiencies, facial dysmorphisms and many other findings [Goldmuntz 2005]. The cardiac anomalies are also variable but have most commonly comprised a subset of conotruncal defects (tetralogy of Fallot, interrupted aortic arch, and truncus arteriosus), perimembranous and malalignment type ventricular septal defects, and aortic arch anomalies [McDonald-McGinn et al., 1997; Ryan et al., 1997]. Less commonly, patients have been reported to have a variety of other defects including bicuspid aortic valve, pulmonary stenosis and heterotaxy syndrome [Ryan et al., 1997; Goldmuntz, 2005]. Aortic root dilation has not been commonly reported as a cardiac finding in patients with 22q11.2 deletion syndrome.

The purpose of this case series is to document a novel cardiac finding in 22q11.2 patients, namely aortic root dilation. This case series focuses specifically on patients who have been diagnosed with 22q11.2 deletion syndrome who do not have overt conotruncal abnormalities such as tetralogy of Fallot or truncus arteriosus given that the latter diagnoses are associated with aortic root dilation.

METHODS

Patients diagnosed with 22q11.2 deletion were referred for outpatient cardiology evaluation by a single observer. The current case series was derived from review of the clinic records accrued between 1996 and 2008. A total of 93 patients without overt conotruncal defects (tetralogy of Fallot, interrupted aortic arch, truncus arteriosus, transposition of the great arteries, double outlet right ventricle, malalignment type ventricular septal defect) were identified. Although patients with conotruncal anomalies were excluded, patients with less severe cardiac malformations such as perimembranous ventricular septal defects, patent ductus arteriosus, and pulmonary artery stenosis were included in the study cohort (see Table I). All patients underwent an echocardiogram to evaluate for intracardiac and aortic arch anomalies. Aortic root measurements were confirmed by a single observer and were taken in the parasternal long axis view at three sites: the aortic valve annulus, the diameter at the level of the sinuses and the sinotubular junction. The patient charts and echocardiogram reports were reviewed, and those patients with aortic root dilation were identified. Aortic root dilation was defined as a *Z* score greater than 2.5 in children (≤18 years of age) for the

diameter at the level of the sinuses. The actual measurements reported in Table II are from the most recent echocardiograms.

RESULTS

Characteristics of the study cohort (N = 93) are summarized in Table I. Ten of the 93 patients had aortic root dilation as defined in the Methods section. The average age of patients with normal aortic root measurements was 6.9 years (range of 2 months to 27.5 years), which was not significantly different from the 10 patients with aortic root dilation whose average age was 8.1 years (range of 1.4–11.7 years). There was a male preponderance in the patients with aortic root dilation (80%). Arch anomalies were not significantly different between the two groups, and right aortic arch occurred with the same frequency in both groups.

Seven of the 10 patients had aortic root dilation in the absence of identifiable overt factors while three patients had a BAV (see Table II). All three patients in the study population of 93 with a BAV developed aortic root dilation. There was no significant aortic insufficiency observed in the cases with aortic root dilation with the exception of one patient with moderate aortic insufficiency and a BAV (see Table II).

Eight of the 10 patients with aortic root dilation had prior echocardiograms to those reported in Table II. Five of these eight patients had initial studies at an average age of 2.7 years (1 month–9.5 years) that documented normal aortic root size while subsequent studies performed at an older average age of 6.1 years (9 months–13 years) documented aortic root dilation. Once aortic root dilation developed, the only patient with progression in the sinus diameter *Z* score also had a BAV. Patients without a BAV did not demonstrate any appreciable increase in *Z*-scores on serial echocardiograms. However, follow-up studies were limited to six patients and were performed at various time intervals ranging from 1.4 to 5.5 years after the diagnosis of aortic root dilation.

DISCUSSION

This case review highlights a novel cardiac feature in patients with 22q11.2 deletion syndrome. While this syndrome has an extremely variable phenotype, to our knowledge, isolated aortic root dilation has not been described as a cardiac phenotype in patients with 22q11.2 deletion syndrome. The prevalence of isolated aortic root dilation in the general population, especially in the absence of known disorders associated with aortic dissection, is unknown. In our series, seven of 93 patients with documented 22q11.2 deletion and no other risk factors had aortic root dilation. All three patients with BAV also had aortic root dilation for a total of 10 cases. While this study does not accurately estimate the prevalence of aortic root dilation in patients with 22q11.2 deletion syndrome, the data suggest that patients with a 22q11.2 deletion without overt congenital heart disease should nonetheless be evaluated for aortic root dilation, particularly at older ages.

The finding of aortic root dilation in these patients raises several questions. As this is a novel finding, it is unclear (1) at what age dilation may develop; (2) if this dilation can progress over time; and (3) if there is an association with dissection. Of the 10 patients with aortic

root dilation, 5 did not have aortic root dilation on earlier echocardiograms and were diagnosed on subsequent studies performed at older ages. As our study was limited by the fact that patients were referred for evaluation at various ages, there is no uniformity about the ages at which initial or follow up echocardiograms were performed. Our data suggest, however, that an echo-cardiogram performed at a younger age does not preclude the development of aortic root dilation at an older age and raises the question whether aortic root dilation may develop later in this disease and progress in severity over time.

Interestingly, all three patients with a BAV had aortic root dilation. The only patient with an increase in the sinus diameter *Z*-score over time and significant aortic insufficiency also had a BAV. Bicuspid aortic valves are known to be associated with progressive dilation which can lead to dissection [Edwards et al., 1978; Gurvitz et al., 2004]. There are some studies that report 52% of men with BAV eventually develop dilation of the aortic root or the ascending aorta over the course of their lifetime [Nistri et al., 1999]. It is not known if 22q11.2 deletion syndrome adds another risk factor for the progression or development of aortic root dilation in patients with BAV.

Aortic root dilation has been reported in patients with conotruncal anomalies such as tetralogy of Fallot [Tan et al., 2006; Roux et al., 2008]. To date, there have been two published cases of aortic dissection in adult patients with a history of repaired tetralogy of Fallot [Kim et al., 2005; Rathi et al., 2005], and since many patients are lost to follow up when they reach adulthood, the frequency of aortic dissection is not known. Several factors have been associated with progressive aortic root dilation in tetralogy of Fallot including male sex, right aortic arch, and pulmonary atresia [Niwa et al., 2002]. We also observed a male preponderance in our cohort with aortic root dilation, but given the small sample size, a conclusion cannot be made as to whether this represents a risk factor for developing aortic root dilation in this context as well. Arch anomalies, however, did not occur with greater frequency in those patients with aortic root dilation as compared to those with normal aortic root sizes. Patients with overt conotruncal anomalies were excluded in this case series, but this study raises the question as to whether deletion status is a risk factor for developing aortic root dilation in tetralogy of Fallot. 22q11.2 deletion status could serve as an important predictor of disease progression, especially as these patients grow into adulthood.

The exact mechanism of the development of heart disease in 22q11.2 deletion syndrome has not been entirely defined. *TBX1* is likely involved in the cardiac phenotype of 22q11 deletion syndrome, especially aortic arch defects and conotruncal anomalies [Merscher et al., 2001; Xu et al., 2004]. *TBX1*, a gene within the deleted 22q11.2 locus, is involved in cell proliferation in the secondary heart field, which contributes to the cardiac outflow tract [Xu et al. 2004]. Ablation of the secondary heart fields in chick and mouse embryos has been shown to lead to cardiac defects such as overriding aorta and pulmonary atresia [Ward et al., 2005]. The etiology of aortic root dilation in patients with 22q11.2 deletion syndrome is unknown, but may be related to the mechanism that causes aortic root dilation in tetralogy of Fallot patients, which is poorly understood [Tan et al., 2006].

This case series reports aortic root dilation in patients with 22q11.2 deletion in the absence of other significant heart disease, raising several questions about long term cardiac

evaluation in this cohort. Knowing the associated cardiac features of the syndrome, however, allows physicians to properly screen patients, provide adequate treatment, and better predict outcomes. It also provides the impetus to answer further questions regarding the clinical course and the effect of adult onset co-morbidities.

References

Carlson M, Silberach M. Dissection of the aorta in Turner syndrome: Two cases and review of 85 cases in the literature. J Med Genet. 2007; 44:745–749. [PubMed: 17873120]

Crabbe LS, Bensky AS, Hornstein L, Schwartz DC. Cardiovascular abnormalities in children with Fragile X syndrome. Pediatrics. 1993; 91:714–715. [PubMed: 8464655]

Edwards WD, Leaf DS, Edwards JE. Dissection aortic aneurysm associated with congenital bicuspid aortic valve. Circulation. 1978; 57:1022–1025. [PubMed: 639201]

Goldmuntz E. DiGeorge syndrome: New insights. Clin Perinat. 2005; 32:963–978.

Gurvitz M, Chang RK, Drant S, Allada V. Frequency of aortic root dilation in children with a bicuspid aortic valve. Am J Cardiol. 2004; 94:1337–1340. [PubMed: 15541263]

Kim W, Seo J, Kim SJ, Song J, Lee J, Na CY. Aortic dissection late after repair of tetralogy of Fallot. Int J Cardiol. 2005; 101:515–516. [PubMed: 15907429]

Larson E, Edwards W. Risk factors for aortic dissection: A necropsy study of 161 cases. Am J Cardiol. 1984; 53:849–855. [PubMed: 6702637]

Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, De Backer JF, Oswald GL, Symoens S, Manouvrier S, Roberts A, Faravelli F, Greco MA, Pyeritz RE, Milewicz DM, Coucke PJ, Cameron DE, Braverman AC, Byers PH, De Paepe AM, Dietz HC. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med. 2006; 355:788–798. [PubMed: 16928994]

McDonald-McGinn D, LaRossa D, Goldmuntz E, Sullivan K, Eicher P, Gerdes M, Moss E, Wang P, Solot C, Schultz P, Lynch D, Bingham P, Keenan G, Weinzimer S, Ming JE, Driscoll D, Clark BJ, Markowitz R, Cohen A, Moshang T, Pasquariello P, Randall P, Emanuel BS, Zackai EH. The 22q11.2 deletion: Screening, diagnostic workup, and outcome of results; report on 181 patients. Genet Test. 1997; 1:99–108. [PubMed: 10464633]

Merscher S, Funke B, Epstein JA, Heyer J, Puech A, Lu MM, Xavier RJ, Demay MB, Russell RG, Factor S, Tokooya K, Jore BS, Lopez M, Pandita RK, Lia M, Carrion D, Xu H, Schorle H, Kobler JB, Scambler P, Wynshaw-Boris A, Skoultchi AI, Morrow BE, Kucherlapati R. TBX1 is responsible for cardiovascular defects in velo-cardio-facial/DiGeorge syndrome. Cell. 2001; 104:619–629. [PubMed: 11239417]

Murdoch J, Walker BA, Halpern BL, Kuzma JW, McKusick VA. Life expectancy and causes of death in the Marfans Syndrome. N Eng J Med. 1972; 286:804–808.

Nistri S, Sorbo MD, Marin M, Palisi M, Scognamiglio R, Thiene G. Aortic root dilatation in young men with normally functioning bicuspid aortic valves. Heart. 1999; 82:19–22. [PubMed: 10377302]

Niwa K, Siu SC, Webb GD, Gatzoulis MA. Progressive aortic root dilatation in adults late after repair of tetralogy of Fallot. Circulation. 2002; 106:1374–1378. [PubMed: 12221055]

Rathi V, Doyle M, Williams RB, Yamrozik J, Shannon RP, Biederman WW. Massive aortic aneurism and dissection in repaired tetralogy of Fallot; diagnosis by cardiovascular magnetic resonance imaging. Int J Cardiol. 2005; 101:169–170. [PubMed: 15860407]

Roux N, Doguet F, Litzler PY, Tabley A, Adde JM, Fournier JF, Redonnet M, Bizet CN, Bouchart F, Hubscher CH, Bessou JP. Occurrence of an ascending aorta aneurysm 25 years after cure of a tetralogy of Fallot. J Card Surg. 2008; 23:163–164. [PubMed: 18304134]

Ryan A, Goodship J, Ryan AK, Goodship JA, Wilson DI, Philip N, Levy A, Seidel H, Schuffenhauer S, Oechsler H, Belohradsky B, 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, Scambler PJ. Spectrum of clinical features associated with interstititial chromosome 22q11 deletions. J Med Genet. 1997; 34:798–804. [PubMed: 9350810]

Tan J, Gatzoulis M, Ho SY. Aortic root disease in tetralogy of Fallot. Curr Opin Cardiol. 2006; 21:569–572. [PubMed: 17053405]

Versacci P, Digilio MC, Sauer U, Dallapiccola B, Marino B. Absent pulmonary valve with intact ventricular septum and patent ductus arteriosus. Am J Med Genet. 2005; 138A:185–186. [PubMed: 16100728]

Ward C, Stadt H, Hutson M, Kirby ML. Ablation of the secondary heart fields leads to tetralogy of Fallot and pulmonary atresia. Dev Biol. 2005; 284:72–83. [PubMed: 15950213]

Wenstrup R, Meyer RA, Lyle JS, Hoechstetter L, Rose PS, Levy HP, Francomano CA. Prevalence of aortic root dilation in Ehlers-Danlos Syndrome. Genet Med. 2002; 4:112–117. [PubMed: 12180144]

Xu H, Morishima M, Wylie JN, Schwawrtz RJ, Bruneau BG, Lindsay EA, Baldini A. Tbx1 has a dual role in morphogenesis of the cardiac outflow tract. Development. 2004; 131:3217–3227. [PubMed: 15175244]

TABLE I

Study Cohort

	No aortic root dilation (n = 83)	Dilated aortic root (n = 10)
Male sex	46 (55%)	8 (80%)
Arch anomalies[a]	27 (32.5%)	3 (30%)
Right aortic arch	15 (18%)	2 (20%)
Average age	6.9 years	8.1 years
Other cardiac defects[b]	16 (19%)	3 (30%)
Bicuspid aortic valve	0 (0%)	3 (30%)

Sample group: patients with aortic root dilation as documented in Table II.

[a]Includes RAA along with other arch anomalies.

[b]Other defects include atrial or ventricular septal defects, pulmonary artery stenosis, patent ductus arteriosis.

TABLE II

Aortic Root Sizes and Characteristics of Cases

Age at most recent echo, years	Sex	Other cardiac defects	AA size[a] (*Z*-score)	SD[a] (*Z*-score)	STJ size[a] (*Z*-score)	Age at initial echo	Age at diagnosis of ARD	Time from diagnosis of ARD to most recent echo	Progression of ARD after diagnosis of ARD	Degree of AR
8.4	M	RAA/ALSA	1.95 (3.25)	2.64 (3.2)	1.94 (1.6)	7 years	7 years	1.4 years	No	None
6.8	M	None	1.9 (3.35)	2.5 (3.0)	2.2 (3.47)	16 months	16 months	5.5 years	No	None
11.3	M	BAV	1.8 (0.94)	3.18 (4.5)	2.26 (2.3)	7 years	7 years	4.3 years	No	Trivial
11.2	F	LPA stenosis	1.92 (2.2)	2.65 (2.5)	2.08 (1.6)	2 years	6 years	5.2 years	No	None
5.4	M	PDA, s/p coil	1.4 (0.96)	2.4 (3.87)	1.71 (1.77)	1 day	4 years	1.4 years	No	None
2.4	M	BAV	1.2 (0.71)	2.1 (3.75)	1.5 (1.86)	1.5 months	9 months	1.7 years	Yes[c]	None
13	M	RAA/ALS	2.0 (2.15)	3 (3.19)	1.8 (30.33)	2 years	13 years	n/a	Unknown	None
6.5	M	None	1.6 (1.7)	2.4 (3.03)	1.8 (1.64)	5 years	6.5 years	n/a	Unknown	None
5	F	VSD repair[b]	1.7 (3.86)	2.2 (3.38)		No prior study	5 years	n/a	Unknown	Trivial
11.7	M	AS/PS/BAV, AAA	2.36 (5.17)	2.8 (3.13)		No prior study	11.7 years	n/a	Unknown	Moderate

VSD, ventricular septal defect; BAV, bicuspid aortic valve; PDA, patent ductus arteriosus; AS, aortic stenosis; PS, pulmonary stenosis; RAA, right aortic arch; ALSA, aberrant left subclavian artery: AI, aortic insufficiency; AA, aortic annulus; SD, sinus diameter; STJ, sinotubular junction; AAA, aortic arch anomaly; ARD, aortic root dilation; LPA, left pulmonary artery.

[a] From most recent study.

[b] Perimembranous VSD.

[c] Increase in sinus diameter Z-score of 0.82.