Original Article

New Findings concerning Cardiovascular Manifestations emerging from Long-term Follow-up of 150 patients with the Williams-Beuren-Beuren syndrome

Alessia Del Pasqua,[2] Gabriele Rinelli,[1] Alessandra Toscano,[1] Roberta Iacobelli,[1] Cristina Digilio,[3] Bruno Marino,[4] Claudia Saffirio,[4] Sergio Mondillo,[2] Luciano Pasquini,[1] Stephen Pruett Sanders,[1] Andrea de Zorzi[1]

[1]*Dipartimento Medico Chirurgico di Cardiologia Pediatrica, Ospedale Pediatrico Bambino Gesù, Rome, Italy;* [2]*Dipartimento di Cardiologia, Università degli Studi di Siena, Siena, Italy;* [3]*Servizio di Genetica Medica, Ospedale Pediatrico Bambino Gesù, Rome, Italy;* [4]*Dipartimento di Pediatria, Università La Sapienza, Rome, Italy*

Abstract *Aims:* We investigated the prevalence, type, and course of congenital cardiac defects and systemic hypertension in our patients with Williams-Beuren-Beuren syndrome. *Methods and results:* We reviewed the clinical records of all patients with Williams-Beuren syndrome examined between 1981 and 2006. We identified 150 patients, aged from 7 months to 45 years, with a follow-up from 6 months to 25 years, the mean being 6.4 years. A cardiac anomaly was present in 113 of the 150 patients (75%). Defects were typical in over four-fifths of the group. We found supravalvar aortic stenosis in 73 of 113 patients (64.6%), isolated in 43. Pulmonary stenosis, isolated in 18 cases, was found in 51 of 113 (45.1%), while aortic coarctation and mitral valvar prolapse were each found in 7 (6.2%), 3 of the lesions is isolation. Atypical defects were found in 19 patients, tetralogy of Fallot in 2, atrial septal defects in 4, aortic and mitral valvar insufficiencies in 1 each, bicuspid aortic valves in 2, and ventricular septal defects in 9, 4 of the last being isolated. Systemic hypertension, observed in 33 patients (22%), was poorly controlled in 10. Diagnostic and/or interventional cardiac catheterization was undertaken in 24 patients, with 30 surgical procedures performed in 26 patients. Of the group, 3 patients died. *Conclusion:* Cardiac defects were present in three-quarters of our patients. Pulmonary arterial lesions generally improved, while supravalvar aortic stenosis often progressed. Atypical cardiac malformations, particularly ventricular septal defects, occurred frequently. Systemic hypertension was found in one-fifth, even in the absence of structural cardiac defects. The short-term mortality was low.

Keywords: Congenital heart disease; supravalvar aortic stenosis; hypertension; ventricular septal defect; pulmonary stenosis

WILLIAMS-BEUREN SYNDROME IS A RARE DEVELopmental disorder, occurring in between 1 in every (20.000 to 50.000 live births, and which usually occurs sporadically. It has striking physical and behavioral features.[1,2] Patients affected by the syndrome have a characteristic dysmorphic face, short stature, deficient visuo-spatial abilities,[3] overfriendly personalities, mild mental retardation, endocrine and renal anomalies, and typical cardiovascular findings. The complex disease is now known to be due to hemizygous deletion or disruption at the locus 7q11.23,[2] including the elastin gene. Cardiovascular anomalies are present in about four-fifths of patients, most frequently supravalvar aortic stenosis and pulmonary arterial stenosis.[4–7] In this study, we assessed retrospectively the incidence and outcome of cardiac anomalies in a cohort of 150 patients referred to our Institution from the Genetic Service, the diagnosis being confirmed by.

Correspondence to: Dr Andrea de Zorzi, Ospedale Pediatrico Bambino Gesù, DMCCP Cardiologia, Piazza Sant'Onofrio 1, 00165 Rome, Italy. Tel: +390668592333; Fax: +390668592257; E-mail: dez@fastwebnet.it

Materials and methods

We retrospectively reviewed the files of all patients with the diagnosis of Williams-Beuren syndrome confirmed by fluorescent in situ hybridization referred to our echocardiographic laboratory from 1981 to March, 2006, and followed-up in our Institution. We reviewed the reports of clinical visits, blood pressure monitoring, electrocardiogram, echocardiogram, cardiac catheterizations and cardiac operations. Patients were considered lost to the follow-up if there was no evaluation within the 12 months prior to collection of data. We classified the cardiac defects as typical in the presence of supravalvar aortic stenosis, pulmonary valvar and/or arterial stenosis, aortic coarctation and mitral valve prolapse, or atypical when we found ventricular septal defects, tetralogy of Fallot, atrial septal defects, aortic or mitral valvar insufficiency, and bicuspid aortic valves, according to the data previously reported in the literature.[4–13] Systemic hypertension was diagnosed when the measurements of blood pressure were above the 95th percentile for reported normal values[4] in children, and if above 130/90 mmHg for adults. Supravalvar aortic stenosis was graded mild if the peak Doppler gradient was lower than 30 mmHg, moderate between 30 and 50 mmHg, and severe above 50 mmHg.[4,10] The severity of pulmonary arterial stenosis was based on angiographic measurements of the vessels. Mitral valvar prolapse was diagnosed by echocardiography in the parasternal long-axis view if either leaflet of the valve had greater than 2 millimetres systolic displacement above the annulus into the left atrium.

Results

We identified 150 patients with the syndrome, 83 being male (55.3%), who had been referred for echocardiography between 1981 and 2006. The mean age at this review was 13.9 years, with a range from 7 months to 45 years. All patients had positive fluorescent in situ hybridization for deletion at locus 7q11.23, and characteristic clinical findings.[1,3] The mean age at diagnosis of the cardiac anomaly was 4.2 years, while the mean age at diagnosis of the syndrome itself was 6.2 years. The average follow-up was 6.4 years, with a range from 6 months to 25 years.

Cardiovascular anomalies (see Table 1)

A cardiac anomaly was present in 113 of the 150 patients (75%), of which 98 are still followed in our Institution. The remaining 15 patients (13%) were lost to follow-up.

Table 1. Description of the cardiac defects in the 113 patients with Williams-Beuren syndrome.

|	
Supravalvar aortic stenosis	73 (64.6%); isolated in 43 (38%)
Pulmonary stenosis	51 (45.1%); isolated in 18 (15.9%)
Aortic coarctation	7 (6.2%); isolated in 3 (2.6%)
Mitral valvar prolapse	7 (6.2%); isolated in 3 (2.6%)
Ventricular septal defect	9 (7.9%); isolated in 4 (3.5%)
Tetralogy of Fallot	2 (1.8%); both isolated
Atrial septal defect	4 (3.5%); isolated in 1 (0.9%)
Aortic insufficiency	1 (0.9%); associated with supravlavar aortic stenosis
Mitral insufficiency	1 (0.9%); associated with pulmonary stenosis
Bicuspid aortic valve	2 (1.8%); associated with mitral valvar prolapse and pulmonary stenosis
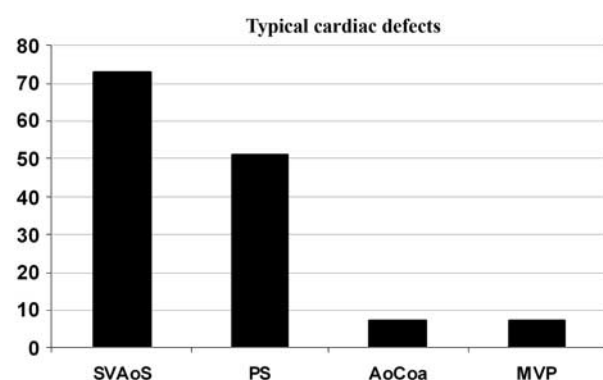
Figure 1.
The graph shows the number of patients with Williams-Beuren syndrome affected by each typical cardiac defect. SVAoS = supravalvar aortic stenosis; PS = pulmonary stenosis; AoCoa = aortic coartaction; MVP = mitral valve prolapse.

Typical cardiac defects were present in 94 of the 113 patients (83%) (see Fig. 1). Supravalvar aortic stenosis was found in 73 (64.6%), being isolated in 43 cases. Pulmonary valvar and/or arterial stenosis was found in 51 patients (45.1%), isolated in 18 cases. Aortic coartation was found on 7 instances, isolated in 3 cases, as was mitral valvar prolapse, both accounting for 6.2% of the cohort. Atypical defects were present in 19 patients (17% – see Fig. 2). These included tetralogy of Fallot in 2 patients, atrial septal defect in 4, isolated in 1, aortic valvar insufficiency in another associated with supravalvar aortic stenosis, mitral valvar insufficiency in yet another, associated with pulmonary arterial stenosis bicuspid aortic valves in 2 patients, associated with mitral valvar prolapse or stenosis of the pulmonary arteries, and ventricular septal defects in 9 patients (7.9%), these being isolated in 4 cases. Of these 9 defects, 4 were sub-aortic and associated with pulmonary stenosis, 2 of these patients requiring surgical closure, and 5 were muscular,
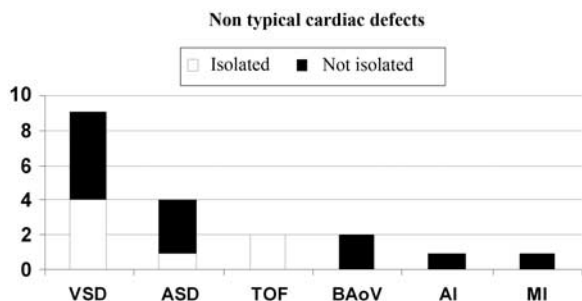
Figure 2.

The graph shows the number of patients with Williams-Beuren syndrome affected by non typical cardiac defects, either isolated or associated with typical or atypical cardiac defects. VSD = ventricular septal defects; ASD = atrial septal defect; TOF = Tetralogy of Fallot; BAoV = bicuspid aortic valve; AI = aortic insufficiency; MI = mitral insufficiency.

3 found in isolation and 2 associated with pulmonary valvar stenosis.

Systemic hypertension was observed in 33 patients (22%), of whom 25 were receiving therapy such as inhibitors of angiotensin converting enzyme and/or blockers of the calcium channels. The blood pressure was poorly controlled in 10 of these 25 patients.

Electrocardiographic abnormalities were seen in 22 patients, with incomplete right bundle branch block noted in 11, left ventricular hypertrophy in 6, right ventricular hypertrophy in 2, and isolated short PR intervals in 3.

Cardiac catheterization

This procedure was undertaken in 24 patients to provide better definition of the anatomy, and/or for interventional procedures, 6 procedures being performed in 5 patients. Percutaneous transluminal angioplasty was attempted for supravalvar aortic stenosis in 2 patients, with failure in 1 necessitating referral for surgery, in 3 patients with peripheral pulmonary arterial stenosis, failure in 1 case again necessitating surgery, and relief of residual aortic coartation after surgical repair. This procedure also failed, and the patient was referred for repeated surgery. In 1 of the patients with peripheral pulmonary arterial stenosis, a stent was placed in the left upper pulmonary artery.

Surgical intervention

It proved necessary to undertake 30 surgical procedures in 26 patients. Surgical relief of supravalvar aortic stenosis was attempted in 17 patients, 3 requiring reinterventions, pulmonary valvotomy with or without plasty of peripheral pulmonary stenosis was performed in 4, repair of aortic coartation in 5 with 1 reintervention, repair

of tetralogy of Fallot in 2, and closure of ventricular septal defects in 2.

Outcomes

Of the overall cohort, 3 patients died. A two week-old neonate with severe obstruction of both outflow tracts, renal arterial stenosis, and coarctation died of renal failure after repair of the coarctation. An 8 month-old, again with severe obstruction of both ventricular outflow tracts, died during induction of anaesthesia for a diagnostic catheterization. A 1 month-old died after repeat aortoplasty for severe, residual supravalvar aortic stenosis. Moderate aortic insufficiency was found in 1 patient, while 2 others had residual obstruction after aortoplasty for supravalvar aortic stenosis.

All the survivors were in good clinical condition, asymptomatic, and with no signs of cardiac failure. We found that most patients with mild supravalvar aortic stenosis, lower than 30 mm Hg gradient, remained stable. About half of those with moderate stenosis tended to progress, and those with severe stenosis generally underwent surgery on diagnosis. A muscular ventricular septal defect in 1 patient closed spontaneously, while the remaining 5 muscular defects, and 1 subaortic defect, remain open, albeit with haemodynamically insignificant shunting.

Discussion

Deletion of the elastin gene on chromosome 7q11.23, leading to deficiency or abnormal deposition of elastin throughout cardiovascular development, appears to be the cause for the widespread cardiovascular abnormalities seen in Williams-Beuren syndrome. The abnormal deposition of elastin in arterial walls leads to proliferation of arterial smooth muscle cells, with the subsequent intimal hyperplasia.[11,12] Some authors[11] have suggested that an altered ratio between metalloproteinases and their specific inhibitors favours degradation of the matrix, leading to migration of smooth muscle cells and neointimal hyperplasia. These features could explain the development of the typical cardiac lesions, as well as the high prevalence of hypertension and the rather poor response to therapy. The more extensive phenotype seen in Williams-Beuren syndrome compared with isolated supravalvar aortic stenosis is likely due to deletion of a variable number of contiguous genes along with the elastin gene.[2,12]

In our series, three-quarters of the patients had cardiac malformations, a figure very similar to other studies.[4–8,13] The distribution of typical defects was also similar to prior reports,[6,7,13,14] with the most common being supravalvar aortic stenosis and valvar and peripheral pulmonary stenosis. When

found in our patients, supravalvar aortic stenosis tended to progress, especially when the Doppler gradient was above 30 mmHg, while the peripheral pulmonary stenosis tended to improve spontaneously with time.[10] We have abandoned percutaneous angioplasty for supravalvar aortic stenosis since our initial attempts in the early 80s.[15,16] This procedure is ineffective, and can be dangerous. Surgery is our treatment of choice for gradients over 50 mmHg, although almost one-fifth of our cohort developed the recurrences. On the other hand, balloon angioplasty can be effective, with or without the placement of stents, for those patients with peripheral pulmonary stenosis, particularly distal stenosis, for whom treatment is indicated. Such patients accounted for less than one-tenth of our series.

Cardiac catheterization with coronary angiography is often recommended[16,17] prior to surgery because of the frequent coexistence of coronary arterial anomalies and decreased coronary flow, with myocardial ischaemia from either anatomical obstruction because of distortion of the aortic leaflets, or intimal fibrosis and muscular hypertrophy from the high pre-stenotic pressure transmitted to the coronary arteries. We failed to identify any coronary arterial abnormalities in our patients, and no patient died from a structural coronary arterial anomaly. Catheterization is not without risk, especially for those with severe obstructions ot both ventricular outflow tracts. Other risks associated with anaesthesia[17] include craniofacial features causing difficult ventilation and tracheal intubation, variable reaction to neuromuscular block-ade, and endocrine and metabolic disorders, which can lead to impaired hepatic drug metabolism and poor temperature regulation.

The new information from our series is the high prevalence of atypical cardiac defects, found in almost one-fifth, and particularly the frequency of ventricular septal defects, present in just over one-twentieth of our total population. This prevalence is higher than in the general population, and could be explained by better detection in syndromic patients undergoing a detailed cardiac evaluation. Further, our findings differ from those of the Baltimore-Washington Infant Study,[18] which did not find a significant association between isolated ventricular septal defect and Williams-Beuren syndrome.

While the obstructive arterial lesions are surely related to the elastin deficiency, it remains unclear if the atypical defects, such as septal defects, occur sporadically, or if they have a common origin with the typical abnormalities. The role of contiguous genes within the critical region has not been defined, and could contribute to development of these atypical defects. Further investigation of the association between Williams-Beuren syndrome and

ventricular septal defect, for example, could further elucidate the genotypic-phenotypic correlation.[2,12]

We also found a high prevalence of systemic hypertension, present in over one-fifth of our patients, even in the absence of aortic coarctation. Only a single hypertensive patient had renal arterial stenosis. The mechanism underlying primary hypertension[19,20] in Williams-Beuren syndrome has not been established, but is likely related to the alterations in the distensibility of the aorta and large systemic arteries. Increased vascular stiffness leads to higher pulse pressure, and ultimately higher mean blood pressure. It has been suggested[21] that impaired fetal synthesis of elastin in low birth weight individuals is the mechanism underlying the higher mean blood pressure and increased risk for hypertension in these individuals. Other investigators[22] suggest that hypertension is more likely to develop in low birth weight individuals because they are born with smaller kidneys and fewer nephrons. Since only patients with cardiac abnormalities are followed in our department, we cannot provide information on the prevalence of hypertension in the population of patients without cardiac defects.

In conclusion, in our large population of patients with Williams-Beuren syndrome we found a high prevalence of typical cardiac defects. Supravalvar aortic stenosis tended to progress, while peripheral pulmonary arterial stenosis tended to improve during follow-up. The new finding in our work is the high prevalence of atypical cardiac malformations, particularly ventricular septal defect, which should stimulate further genetic studies to elucidate the role in cardiac development of contiguous genes in the Williams-Beuren critical region. Systemic hypertension was common even in the absence of aortic coarctation, and was often unresponsive to antihypertensive therapy. About one-quarter of our patients with cardiac disease underwent surgery, and the overall mortality rate was quite low.

References

1. Morris CA, Demsey SA, Leonard CO, Dilts C, Blackburn BL. Natural history of Williams-Beuren syndrome: physical characteristics. J Pediatr 1988; 113: 318–326.
2. Francke U. Williams-Beuren syndrome: genes and mechanisms. Hum Mol Genet 1999; 8: 1947–1954.
3. Edelmann L, Prosnitz A, Pardo S, et al. An atypical deletion of the Williams-Beuren syndrome interval implicates genes associated with defective visuospatial processing and autism. J Med Genet 2007; 44: 136–143.
4. Bruno E, Rossi N, Thuer O, Cordoba R, Alday LE. Cardiovascular findings, and clinical course, in patients with Williams syndrome. Cardiol Young 2003; 13: 532–536.
5. Pascual-Castroviejo I, Pascual-Pascual SI, Moreno Granado F, et al. Williams-Beuren syndrome: presentation of 82 cases. An Pediatr (Barc) 2004; 60: 530–536. Spanish.

6. Zalzstein E, Moes CA, Musewe NN, Freedom RM. Spectrum of cardiovascular anomalies in Williams-Beuren syndrome. Pediatr Cardiol 1991; 12: 219–223.

7. Hallidie-Smith KA, Karas S. Cardiac anomalies in Williams-Beuren syndrome. Arch Dis Child 1988; 63: 809–813.

8. Sugayama SM, Moises RL, Wagenfur J, et al. Williams-Beuren syndrome: cardiovascular abnormalities in 20 patients diagnosed with fluorescence in situ hybridization. Arq Bras Cardiol 2003; 81: 462–473.

9. American Academy of Pediatrics: Health care supervision for children with Williams syndrome. Pediatrics 2001; 107: 1192–1204; Erratum in: Pediatrics 2002; 109: 329.

10. Kim YM, Yoo SJ, Choi JY, Kim SH, Bae EJ, Lee YT. Natural course of supravalvar aortic stenosis and peripheral pulmonary arterial stenosis in Williams' syndrome. Cardiol Young 1999; 9: 37–41.

11. Dridi SM, Foucault Bertaud A, Igondjo Tchen S, et al. Vascular wall remodeling in patients with supravalvar aortic stenosis and Williams-Beuren syndrome. J Vasc Res 2005; 42: 190–201.

12. Tassabehji M. Williams-Beuren syndrome: a challenge for genotype-phenotype correlations. Hum Mol Genet 2003; 12 Spec No 2: R229–R237.

13. Eronen M, Peippo M, Hiippala A, et al. Cardiovascular manifestations in 75 patients with Williams syndrome. J Med Genet 2002; 39: 554–558.

14. Amenta S, Sofocleous C, Kolialexi A, et al. Clinical manifestations and molecular investigation of 50 patients with Williams syndrome in the Greek population. Pediatr Res 2005; 57: 789–795.

15. Geggel RL, Gauvreau K, Lock JE. Balloon dilation angioplasty of peripheral pulmonary stenosis associated with Williams syndrome. Circulation 2001; 103: 2165–2170.

16. Brown JW, Ruzmetov M, Vijay P, Turrentine MW. Surgical repair of congenital supravalvar aortic stenosis in children. Eur J Cardiothorac Surg 2002; 21: 50–56.

17. Medley J, Russo P, Tobias JD. Perioperative care of the patient with Williams syndrome. Paediatr Anaesth 2005; 15: 243–247.

18. Ferencz C, Rubin JD, McCarter RJ, et al. Congenital heart disease: prevalence at livebirth. The Baltimore-Washington Infant Study. Am J Epidemiol 1985; 121: 31–36.

19. Broder K, Reinhardt E, Ahern J, Lifton R, Tamborlane W, Pober B. Elevated ambulatory blood pressure in 20 subjects with Williams syndrome. Am J Med Genet 1999; 83: 356–360.

20. Giordano U, Turchetta A, Giannotti A, Digilio MC, Virgilii F, Calzolari A. Exercise testing and 24-hour ambulatory blood pressure monitoring in children with Williams syndrome. Pediatr Cardiol 2001; 22: 509–511.

21. Martyn CN, Greenwald SE. Impaired synthesis of elastin in walls of aorta and large conduit arteries during early development as an initiating event in pathogenesis of systemic hypertension. Lancet 1997; 350: 953–955.

22. Mackenzie HS, Brenner BM. Fewer nephrons at birth: a missing link in the etiology of essential hypertension? Am J Kidney Dis 1995; 26: 91–98.