

CASE REPORT

Williams syndrome associated with complete atrioventricular septal defect

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Heart 2003;89:e15 (<http://www.heartjnl.com/cgi/content/full/89/5/e15>)

Williams syndrome is a genetic disorder associated with characteristic facies, supraaortic stenosis, peripheral pulmonary stenosis, mental retardation, hypertension, premature aging of skin, and congenital cardiac defects. Many cardiac defects such as bicuspid aortic valve, mitral valve regurgitation, coarctation of the aorta, and ventricular or atrial septal defects are linked to the syndrome. Complete atrioventricular septal defect has rarely been associated with Williams syndrome and only one necropsy case has been reported in the literature. The long term follow up of Williams syndrome associated with complete atrioventricular septal defect is reported. During a 10 year follow up period, the pressure gradient in the ascending aorta did not increase despite narrowing of the ascending aorta as identified on an aortogram.

Williams syndrome is a genetic disorders that occurs in 1 in 20 000–50 000 live births. It is also a developmental disorder involving the vascular system, the connective tissue, and the central nervous system and associated with cardiac anomalies. Herein we report a rare case of Williams syndrome associated with complete atrioventricular septal defect.

CASE REPORT

A 13 year old girl was admitted to our hospital for the postoperative examination. She had undergone repair of cardiac defects in our hospital when she was 3 years old. She was born at 42 weeks of gestation weighting 2200 g. She had a characteristic face with elfin features and mental retardation. On admission for surgical repair, systolic ejection murmur and mitral regurgitant murmur were heard. The second heart sound was fixedly split and the pulmonary second sound was accentuated. A chest x ray showed an increased cardiothoracic

ratio of 0.63 and an increased pulmonary vasculature. An ECG showed left axis deviation and right ventricular hypertrophy.

Right ventricular pressure was high at 94/0 mm Hg. The main pulmonary arteriogram showed supraaortic, branch, and peripheral stenoses (fig 1). The left ventriculogram showed goose neck sign (fig 2). An aortogram showed supraaortic stenosis but there was no pressure gradient in the ascending aorta (fig 2). The diagnosis of Williams syndrome with associated complete atrioventricular septal defect was based on her characteristic face, supraaortic stenosis, and goose neck sign on the left ventriculogram. The complete atrioventricular septal defect was repaired with the two patch method and the main pulmonary artery was enlarged with a bovine pericardial patch to relieve the supraaortic pulmonary stenosis. The postoperative pressure measured immediately after complete cardiac repair had decreased from the preoperative high right ventricular pressure of 90/0 mm Hg to 60/0 mm Hg as a result of the decreased systolic pressure in the main pulmonary artery. However, the systolic pressure of the right and left pulmonary arteries did not change because the peripheral pulmonary stenosis could not be corrected because of anatomical restrictions. There was also no pressure gradient in the ascending aorta. Postoperative cardiac catheterisation, performed in this admission 10 years after surgical repair of the cardiac defect, showed that the right ventricular pressure was 62/0 mm Hg, which had not changed from the previous postoperative study. There was also no pressure gradient in the ascending aorta. Before the second admission, fluorescence in situ hybridisation analysis detected the hybridisation signal on only one chromosome 7 in this patient.

DISCUSSION

Williams and colleagues¹ reported on four patients with the triad of characteristic facies, mental retardation, and supraaortic stenosis in 1961. Features of this disorder are congenital heart disease, hypertension, premature aging of the

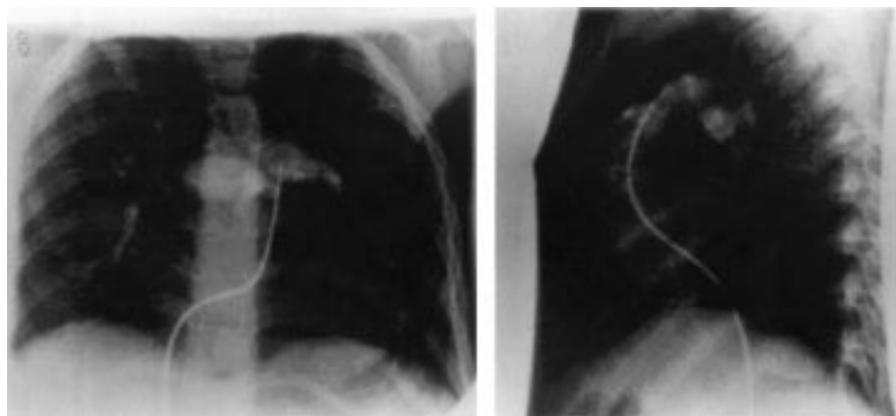


Figure 1 Main pulmonary arteriogram showing supraaortic, branch, and peripheral stenoses.

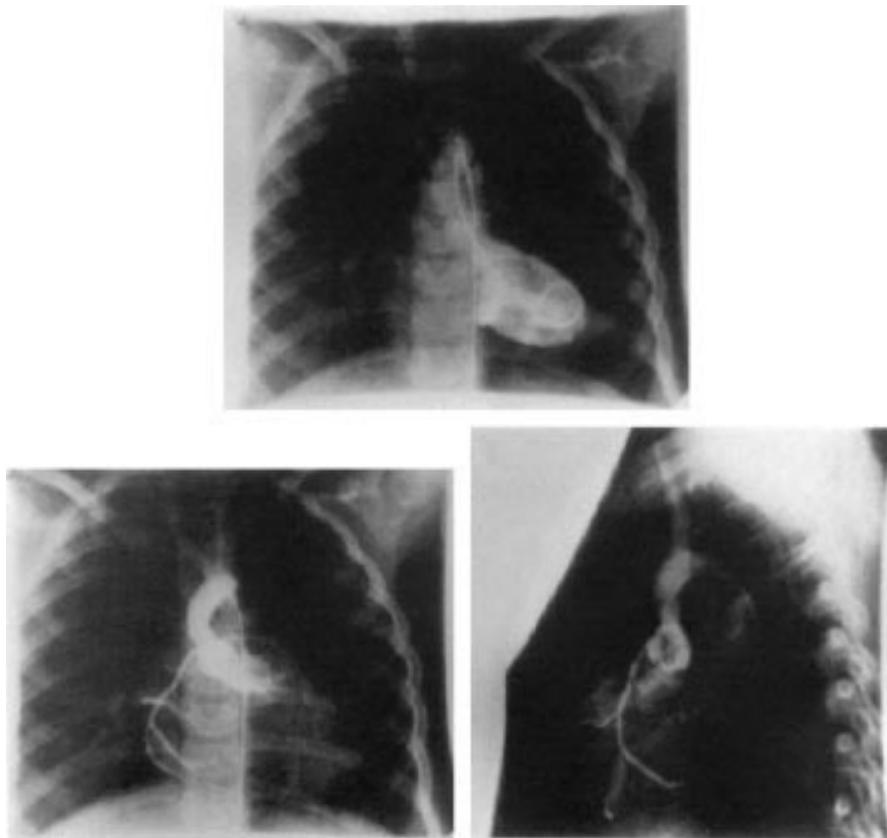


Figure 2 Top: left ventriculogram showing goose neck sign. Bottom: aortograms showing supralvalvar aortic stenosis.

skin, dysmorphic facial features, infantile hypercalcaemia, a gregarious personality, and mental retardation. Subsequently, Beuren and colleagues² noted the frequent association of peripheral pulmonary stenosis. Occasionally, Williams syndrome is associated with other congenital abnormalities such as bicuspid aortic valve, mitral valve regurgitation, coarctation of the aorta, and ventricular or atrial septal defects. Jones and colleagues³ evaluated 19 patients with Williams syndrome and found five with pulmonary stenosis, two with ventricular septal defect, two with atrial septal defect, and one with valvar aortic stenosis. Extracardiac defects other than supralvalvar aortic stenosis were three instances of peripheral pulmonary stenosis, three of aortic hypoplasia, and two of mesenteric and coeliac artery stenosis. Mitral valve disease rarely accompanied Williams syndrome. Becker and colleagues⁴ reported mitral valve thickening in three cases of supralvalvar aortic stenosis. Akcoral and associates⁵ reported that mitral valve prolapse was accompanied by supralvalvar aortic stenosis in only four cases, including their reported case. Mitral regurgitation was rarely accompanied by supralvalvar aortic stenosis syndrome or Williams syndrome.⁶ Hanya and colleagues⁷ reported on a necropsy case of supralvalvar aortic stenosis associated with complete atrioventricular septal defect, to our knowledge for the first time in the literature. They also reported no pressure gradient in the ascending aorta, as in our case. They considered that no pressure gradient in the ascending aorta was due to a left to right shunt that was produced by the complete atrioventricular septal defect. However, in contrast to Hanya's report, in our case 10 years after complete repair there was also no pressure gradient in the ascending aorta despite dissolution of the intracardiac shunt after complete repair.

Genetic study of Williams syndrome discovered complete deletion of the elastin gene on chromosome 7. Complete atrioventricular septal defect was often associated with Down's syndrome, but it sometime occurs alone without

trisomy 21. Although the vast majority of patients with the clinical features of Down's syndrome have complete trisomy 21, in a minority portions of chromosome 21 are duplicated. Molecular and cytogenetic mapping of small duplication has suggested that the atrioventricular septal defect critical region maps to a 4–5 Mb interval at 21q22.1-qter.^{8,9} Inoue and colleagues¹⁰ introduced a human chromosome 21 into mouse embryonic stem cells. Differentiation into cardiomyocytes was delayed in the embryonic stem cells with an entire human chromosome 21. However, when a human chromosome with deletion at 21q22.1 was transferred, cardiomyocyte differentiation was normal. From a genetic viewpoint, the cause of solitary complete atrioventricular septal defect without Down's syndrome is not understood. In the present study, Williams syndrome seems to be associated with complete atrioventricular septal defect by chance because the affected genetic site of Williams syndrome is different from that of Down's syndrome. To our knowledge, this is the first description in the literature of a long follow up period of Williams syndrome associated with complete atrioventricular septal defect. During 10 years' follow up, the pressure gradient in the ascending aorta did not increase despite the narrowing of the ascending aorta seen on the aortogram.

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Accepted 19 December 2002

REFERENCES

- 1 Williams JCP, Barratt-Boyes BG, Lowe JB. Supralvalvar aortic stenosis. *Circulation* 1961;**24**:1311–8.

- 2 **Beuren AJ**, Apitz J, Harmjanz D. Supravalvular aortic stenosis in association with mental retardation and a certain facial appearance. *Circulation* 1962;**24**:1235–40.
- 3 **Jones KL**, Smith DW. The Williams elfin facies syndrome: a new perspective. *J Pediatr* 1975;**86**:718–23.
- 4 **Becker AE**, Becker MJ, Edwards JE. Mitral valvular abnormalities associated with supravalvular aortic stenosis: observations in 3 cases. *Am J Cardiol* 1972;**29**:90–4.
- 5 **Akcoral A**, Ozaksoy D, Oran B, *et al.* A new and rare form of Williams' syndrome. *Acta Paediatr Jpn* 1993;**35**:247–51.
- 6 **Vazquez AM**, Colonel L, Zuberbuhler JR, *et al.* Mitral insufficiency in association with the syndrome of idiopathic hypercalcemia of infancy. *J Pediatr* 1968;**73**:907–10.
- 7 **Hanya S**, Natsuaki M, Morikawa T, *et al.* Case of supravalvular aortic stenosis syndrome associated with complete endocardial cushion defect. *Kyobu Geka* 1974;**27**:425–32.
- 8 **Korenberg JR**, Bradley C, Disteché CM. Down syndrome: molecular mapping of the congenital heart disease and duodenal stenosis. *Am J Hum Genet* 1992;**50**:294–302.
- 9 **Korenberg JR**, Chen XN, Schipper R, *et al.* Down syndrome phenotypes: the consequences of chromosomal imbalance. *Proc Natl Acad Sci U S A* 1994;**91**:4997–5001.
- 10 **Inoue T**, Shinohara T, Takehara S, *et al.* Specific impairment of cardiogenesis in mouse ES cells containing a human chromosome 21. *Biochem Biophys Res Commun* 2000;**273**:219–24.