

# Cardiovascular Abnormalities in Williams-Beuren Syndrome

## **Abstract**

We present different cases of cardiovascular abnormalities in 3 patients with WS aged between 8 months and 7 years. Williams-Beuren Syndrome is characterized by specific facial dysmorphism that may look like an “elfin face”, congenital heart diseases, cognitive disorder, social personality disorder and endocrinological abnormalities. WBS is generally sporadic, it is caused by de novo deletions, and has a recurrence risk lower than 5%. Early diagnosis of this syndrome is important to start therapy for other medical problems that may develop. Lifelong cardiac follow up is necessary because of the risks of developing vasculopathy or arterial hypertension. The importance of research during the neonatal period is pointed up in order to reduce morbidity and mortality rates and ensure a better quality of life during the development of these children.

Keywords: Williams-Beuren Syndrome, arterial hypertension, morbidity, social personality disorder

## **I. Introduction:**

“Williams syndrome (WS), also known as Williams-Beuren syndrome (WBS), is a rare genetic disorder, with a prevalence of 1/7500-1/20,000 live births. It is characterized by congenital heart defects, dysmorphic facies, skeletal and renal anomalies, cognitive disorder, social personality disorder, and neonatal hypercalcemia. It is resulting from the deletion of approximately 28 genes on chromosome 7q11.23. Hemizygoty at the elastin gene locus on this chromosome has been demonstrated to be the cause of the vascular lesions in Williams syndrome” [1]. “The most frequent cardiovascular anomalies in WS were supravalvar aortic stenosis (SAVS) and pulmonary arterial stenosis (PAS)” [2]. We present different cases of cardiovascular abnormalities in 3 patients with WS aged between 8 months and 7 years old.

## **II. Case presentations:**

### **Patient 1:**

Naoual, 8-month-old female, the second out of 2 children of non-consanguineous parents, with no relevant family history. The baby was born by spontaneous vaginal delivery at 39 weeks of an uncomplicated pregnancy, average birth weight and height. The sitting was acquired at the age of 7 months. Her parents consult for cyanotic spells during feedings since birth with weight

stagnation. The patient was in a good general condition, and had a typical face with bulge forehead, a flattened nasal bridge with an anteverted nares, periorbital fullness, a long philtrum and full cheeks. The cardiovascular examination revealed a harsh systolic murmur at the level of the aortic and pulmonary area.



Fig. 1. Characteristic "elfin facies" in our patient

A 2D echocardiography study was performed showing pulmonary stenosis of the right pulmonary artery at the origin and on the proximal part 4 mm,  $V_{max} = 4.6$  m/s and acceleration on the aortic isthmus of 4.6 m/s, without aortic obstruction. The interventricular and interatrial septa are intact, with normal filling pressure and good LV function without dilatation or hypertrophy of the 2 ventricles. Cytogenetic analysis by the fluorescence in situ hybridization technique "FISH" showed a microdeletion of 7q11.23 which is specific for Williams syndrome. The surgical technique consisted on the inspection of the pulmonary valve through a transverse pulmonary arteriotomy. A longitudinal incision was made, then a Dacron gusset was sutured into the arterial incision.

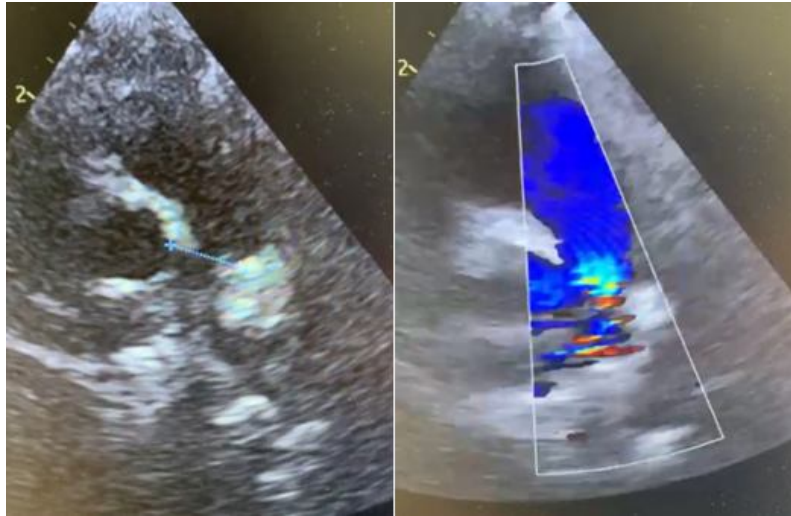


Fig. 2. Right parasternal short axis view at the pulmonic valve level showing an increase of flow velocity associated with the stenosis.

Patient 2:

Ryad, 6-years-old child, the only child of unrelated parents, without a family history of WBS or congenital heart disease. He came to us with the characteristic 'elfin facies', with a large mouth, wide-set eyes, broad forehead with a short and upturned nose. He had mild intellectual disability with poor social interaction. The CT-scan indicated a partial narrowing of the ascending aorta.

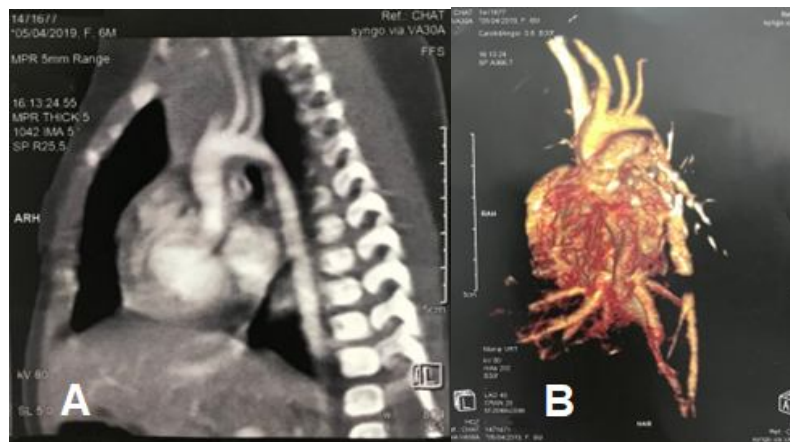


Fig. 3. A. The CT scan shows a partial hourglass-shaped narrowing of the ascending aorta. B. 3D reconstruction shows SVAS.

The cardiovascular examination showed an ejection systolic murmur. There was a disparity in blood pressure between the 2 arms, the right arm systolic blood pressure tended to be higher than in the left arm by 22 mmHg. FISH analysis showed a microdeletion of chromosome 7q11.23. The surgical repair of SVAS consisted on extended aortoplasty with extensive endarterectomy.

### Patient 3:

Amal, a 2-year-old girl presented to us with history of dyspnea and cyanosis for the past 8 months. The cardiovascular examination showed a systolic ejection murmur, her pulse rate was 120 per minute, blood pressure was 100/56 mmHg. The patient had a typical face of Williams syndrome. FISH analysis revealed the 7q11.23 microdeletion. The Electrocardiography showed right ventricular hypertrophy. Chest X-ray revealed right atrial and right ventricular hypertrophy. A 2D Echocardiography study revealed a stenotic pulmonary valve. The Peak gradient across the pulmonary valve was 140 mmHg and mean gradient was 60 mmHg. Percutaneous pulmonary balloon valvuloplasty was performed.

### **III. Discussion:**

“Williams-Beuren Syndrome is characterized by specific facial dysmorphism that may look like an elfin face, congenital heart diseases, cognitive disorder, social personality disorder and endocrinological abnormalities. WBS is generally sporadic, it is caused by de novo deletions, and has a recurrence risk lower than 5%” [3]. “A few cases of vertical transmission have been reported [4]. The syndrome is confirmed by detecting a deletion at chromosome 7q11.23 by fluorescence in situ hybridization (FISH). The genes mapping to this region have been defined and include the elastin gene. Some reports suggest that hemizyosity of the elastin gene is responsible for the typical vasculopathy of Williams-Beuren Syndrome, such as supravalvular aortic stenosis and pulmonary arterial stenosis” [1-2-5]. “Deficient elastin may be responsible for other connective tissue abnormalities of WS, which includes hoarse voice, soft skin, lax ligaments, hernias, and joint abnormalities. The facial gestalt of Williams Syndrome is unique, featuring a broad forehead, bitemporal narrowing, a flattened nasal bridge with an upturned nose, periorbital fullness, a stellate pattern of the irises, a long philtrum with a wide mouth and full lips, full cheeks, pointed chin and dental malocclusion with small widely spaced teeth”. [6] “Structural cardiovascular abnormalities occur in 80% of all WBS patients and are the most common cause of death in patients with this syndrome” [7-8-9]. “The most frequent cardiovascular anomalies in WS are supravalvar aortic stenosis and pulmonary arterial stenosis” [2]. Valve abnormalities and septal defects are very unusual [5]. It is not uncommon to find an association of different heart lesions in the same Williams Syndrome patient. It was reported by Del Pasqua et al [10], that 83% of their patients had typical cardiac defects (64.6% SVAS, 45.1% PAS), while 17% had atypical defects. Other nonstructural cardiovascular issues, such as hypertension, are usual in patients with WS. Renal artery stenosis, major cause of hypertension has been reported to occur in 7–58% of patients with WS [8, 12, 13].

“Most patients are first diagnosed due to dysmorphic features and/or associated congenital heart defects. Physicians should pay more attention to specific facial features, as in certain cases the classical cardiovascular manifestations may be absent and consequently, diagnosis can be

delayed. Early diagnosis of this syndrome is important to start therapy for other medical problems that may develop" [14]. Lifelong cardiac follow up is necessary because of the risks of developing vasculopathy or arterial hypertension.

Treatment is aimed at correcting the congenital heart defects. Medical therapies are directed toward treatment of hypertension such as calcium channel blockers of the dihydropyridine class and B-blockers. The treatment for SVAS involves the dilation of the stenotic section of aortic or coronary wall [15]. In cases of PAS, there is possibility of stent placement [2]. A previous study showed that, with time, PAS tends to improve spontaneously and SVAS to progress [5, 16].

#### **IV. Conclusion:**

Cardiovascular abnormalities are the most common manifestations of infantile Williams-Beuren syndrome and occur with greater frequency than previously reported. The importance of research during the neonatal period is pointed up in order to reduce morbidity and mortality rates and ensure a better quality of life during the development of these children.

#### **Ethical Approval:**

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

#### **Consent**

As per international standard or university standard, parentals' written consent has been collected and preserved by the author(s).

#### **REFERENCES:**

1. Keating MT. Genetic approaches to cardiovascular disease: supra-avalvular aortic stenosis, Williams syndrome, and long-QT syndrome. *Circulation* 1995; 92:142-7.
2. Bruno E, Rossi N, Thüer O, Córdoba R, Alday LE. Cardiovascular findings, and clinical course, in patients with Williams syndrome. *Cardiol Young* 2003; 13:532-536.
3. Pankau R, Siebert R, Kautza M, Schneppeheim R, Gosch A, Wessel A, et al. Familial Williams-Beuren syndrome showing varying clinical expression. *Am J Med Genet* 2001; 98:324 –329.
4. Scherer SW, Gripp KW, Lucena J, Nicholson L, Bonnefont JP, et al: Observation of a parental inversion variant in a rare Williams-Beuren syndrome family with two affected children. *Hum Genet* 2005;117(4):383–388.

5. Eronen M, Peippo M, Hiippala A, Raatikka M, Arvio M, et al. Cardiovascular manifestations in 75 patients with Williams syndrome. *J Med Genet* 2002; 39:554–8.
6. Morris CA. Introduction: Williams syndrome. *Am J Med Genet Part C Semin Med Genet* 2010;154C:203–208.
7. Pober BR. Williams-Beuren syndrome. *N Engl J Med*. 2010; 362:239–252.
8. Collins RT, Kaplan P, Somes GW, Rome JJ. Long-term outcomes of patients with cardiovascular abnormalities and Williams syndrome. *Am J Cardiol*. 2010; 105:874–878.
9. Collins RT, Kaplan P, Somes GW, Rome JJ. Cardiovascular abnormalities, interventions, and long-term outcomes in infantile Williams syndrome. *J Pediatr*. 2010 ;156 :253–258.e1.
10. Del Pasqua A, Rinelli G, Toscano A, Lacobelli R, Digilio C, Marino B, et al. New findings concerning cardiovascular manifestations emerging from long-term follow-up of 150 patients with the Williams-Beuren-Beuren syndrome. *Cardiol Young* 2009; 19: 563-567.
11. Broder K, Reinhardt E, Ahern J, Lifton A, Tambrorlane W, Pober B. Elevated ambulatory blood pressure in 20 subjects with Williams syndrome. *Am J Med Genet* 1999; 83:356–360.
12. Committee on Genetics. American Academy of Pediatrics: healthcare supervision for children with Williams syndrome. *Pediatrics* 2001; 107: 1192–1204.
13. Bouchireb K, Boyer O, Bonnet D, Brunelle F, Decramer S, Landthaler G, et al. Clinical features and management of arterial hypertension in children with Williams–Beuren syndrome. *Nephrol Dial Transplant* 2010; 25:434–438.
14. Huarte N, García-Guereta L, and Lapunzina P. Williams-Beuren syndrome: Usual face, unusual heart. *Open Journal of Genetics*, 2013, 3, 79-81.
15. Actis Dato GM, La Torre M, Caimmi P, Actis Dato A Jr, Centofanti P, Ottino GM, et al. Williams-Beuren syndrome. Long-term results of surgical treatments in six patients. *J Cardiovasc Surg (Torino)* 1997;38(2):125-9.
16. Wessel A, Gravenhorst V, Buchhorn R, Gosch A, Partsch C-J, et al. Risk of sudden death in the Williams–Beuren syndrome. *Am J Med Genet* 2004;127A:234–237.