Case study

Cardiovascular Abnormalities in Williams-Beuren Syndrome

Abstract

We present different cases of cardiovascular abnormalities in 3 patients with WS aged between 8months 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. Hemizygosity at the elastin gene locus on this chromosome has been demonstrated to be the cause of the vascular lesions in WS [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 8months and 7 years.

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. She 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, Vmax = 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 WS.

The surgical technique consisted on the inspection of the pulmonary valve through a transverse pulmonary arteriotomy, in order to determine the state of the valve cusps, degree of fusion of the commissures, and the diameter of the valve anulus. The obstruction was relieved by making a longitudinal incision, from the center of the transverse arteriotomy, to cut across the anulus into the outflow tract. A shield shaped Dacron gusset was then sutured into the T-shaped arterial and outflow incision. A post bypass gradient of no more than 35 mm Hg was regarded as acceptable in post operative echocardiography. Routine follow-up controls showed excellent cardiovascular performance with no evidence of pulmonary incompetence, normal cardiac silhouette in the chest x-ray, and signs of minimal right ventricular hypertrophy.

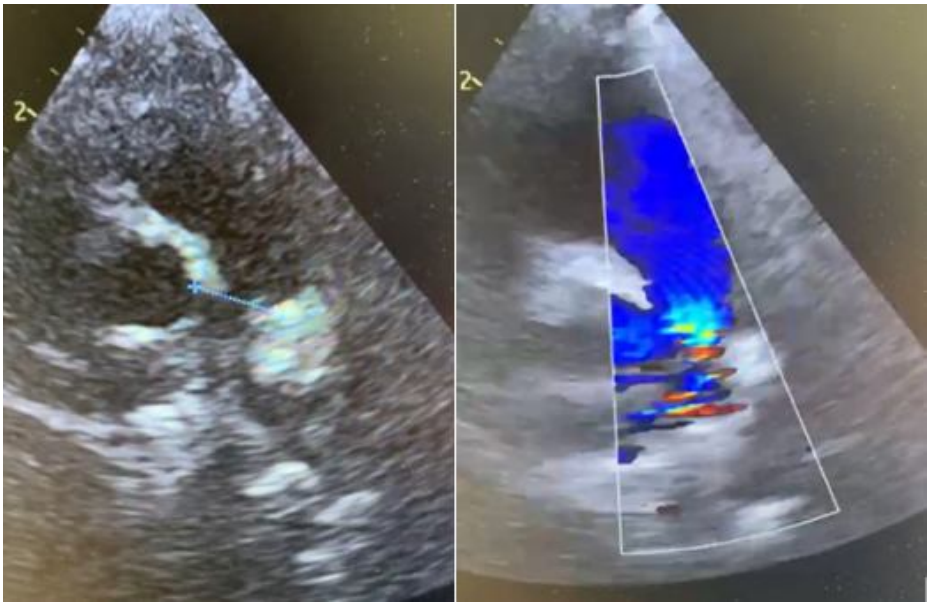

Fig**.** 2. Right parasternal short axis view at the pulmonic valve level showing the increased velocity of flow was associated with the stenosis, which was not apparent at the level of the pulmonic valve.

Patient 2:

Ryad, 6-years-old child, the only child of unrelated parents, without a family history of WB-S or congenital heart disease. This patient presented to us with the characteristic 'elfin facies´ which is shown in the image (fig 3) as having a large mouth, widely spaced eyes, patulous lips, broad forehead with a short and upturned nose. We also noted features of moderate intellectual disability with poor social interaction and a very limited vocabulary. He was also irritable and appeared restless at times.

Contrast-enhanced computed tomography (CCT) indicated a partial hourglass-shaped narrowing of the ascending aorta. Lesions associated with supravalvular stenosis of the pulmonary artery, patent ductus arteriosus, and aortic coarctation were ruled out by the CCT.

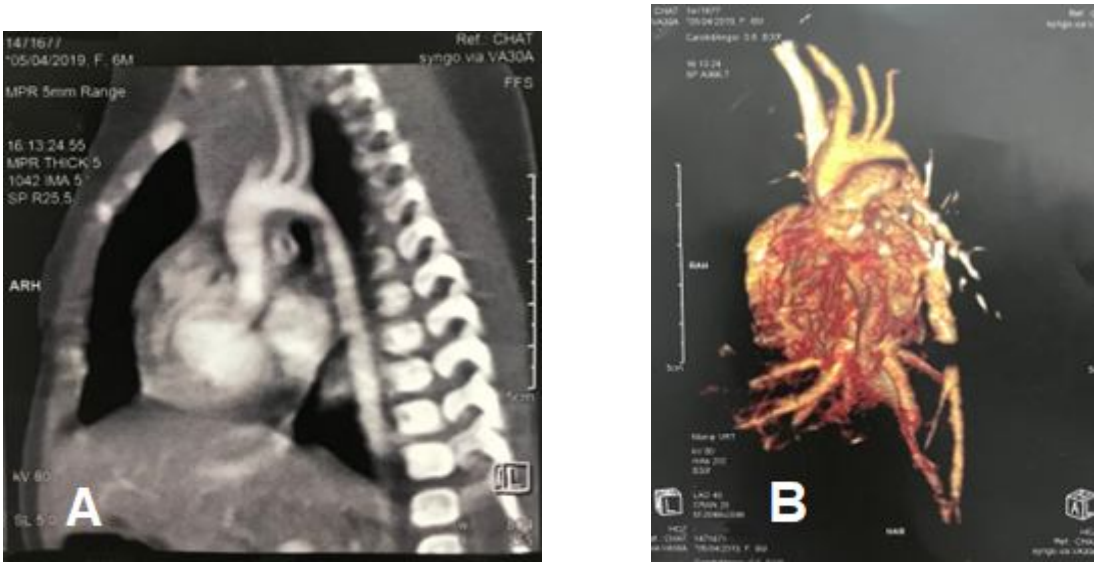

Fig. 3. A. The contrast-enhanced computed tomography (CCT) scan shows a partial hourglass-shaped narrowing of the ascending aorta. B. Three-dimensional reconstruction of the contrast-enhanced computed tomography reveals SVAS.

The cardiovascular examination showed an ejection systolic murmur with no associated ejection click. 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 mm Hg.

The surgical procedure consisted on extended aortoplasty with a patch in the shape of an inverted Y with extensive endarterectomy. A longitudinal aortotomy was extended from the non-stenotic segment of ascending aorta distal to the supravalvular stenosis, deep into the right and noncoronary sinuses of Valsalva. The supravalvular ridge was excised carefully, and procedures on the aortic valve, root and subvalvular region were performed if necessary. The aorta was then augmented with a Y-shaped patch using continuous non-absorbable monofilament suture.

Patient 3:

Amal, a 2-year-old girl presented to us with history of dyspnea and cyanosis for the past 8 months. On cardiovascular examination, her pulse rate was 120 per minute, blood pressure was 100/56 mmHg, a systolic ejection murmur was heard in the second left intercostal space. The patient had a typical face with bulge forehead and speech problem; although she had a good auditory rote memory and could follow orders.

The Electrocardiography showed right ventricular hypertrophy. Chest X-ray revealed right atrial and right ventricular hypertrophy. Combined two-dimensional echocardiography and continuous wave Doppler examination were carried out which revealed along with a stenotic pulmonary valve, and restricted systolic excursion. Peak gradient across the pulmonary valve was 140 mmHg and mean gradient was 60 mmHg. No Patent Foramen Oval or Atrial Septal Defect was found to explain cyanosis in this case.

Percutaneous pulmonary balloon valvuloplasty was performed. We inserted a 5F umbilical vein

catheter into the femoral vein. The pulmonary valve annulus measured 6.48, with the narrowest site about 2.3 mm (Fig. 6). We twice dilated the pulmonary valve by Tyshak 6.0 balloon under the pressure of 3–4 atm. After completion of the procedure, the narrow site of the pulmonary valve measured 4.2 mm. Percutaneous oxygen saturation was well improved (up to 96%). The total fluoroscopic time was 10 mins, and the total procedure time was about 60 mins.
Six days after the procedure, the patient was discharged from the hospital without any complications. At her last follow-up at the out-patient department (3 years old), the patient looked comfortable with the percutaneous oxygen saturation of 94%

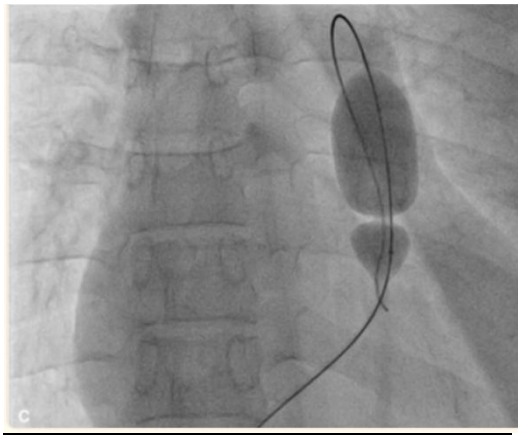

Fig. 4. Successful percutaneous balloon pulmonary valvuloplasty with Accura balloon over Amplatz wire.

III. Discussion:

Williams-Beuren Syndrome was first described by Dr. J. C. P. Williams in 1961 and Dr. Beuren in 1964. This 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 hemizygosity of the elastin gene is responsible for the typical vasculopathy of WBS, 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 WS 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] Cardiovascular defects are the most common cause of death in patients with WBS [7], structural cardiovascular abnormalities occur in 80% of all WBS patients

and are present in up to 93% of WBS patients presenting in the first year of life [8-9]. SVAS occurs in approximately 55% of patients with WBS who present in the first year of life and 45% of those who present thereafter [8-9]. Branch pulmonary artery stenosis occurs in approximately 60% of patients presenting in the first year of life and about 40% of those who present thereafter [8-9]. Valve abnormalities and septal defects are very unusual [5]. It is not uncommon to find an association of several heart lesions in the same WS patient. It was reported by Del Pasqua et al [10], that typical cardiac defects were present in 94 of their 113 patients (83%) and atypical defects were present in 19 patients (17%). They also reported that among typical congenital heart defects, SVAS was found in 73 of 113 patients (64.6%), pulmonary stenosis (both valvular and peripheral) was found in 51 of 113 (45.1%), while aortic coarctation and mitral valvar prolapse were each found in 7 patients (6.2%). Other nonstructural cardiovascular issues are usual in patients with WS. Of those, hypertension, occurring in 40–50% [11]. Renal artery stenosis, major cause of hypertension has been reported to occur in 7–58% of patients with WS [8, 12, 13]. Although, some patients do not have an identifiable cause for hypertension. The risk of sudden death has increased, it is 25–100 times more common in patients with WS than the general population [14] with the cause being incompletely understood.

Most patients are first diagnosed due to dysmorphic features and/or associated congenital heart defects. The typical phenotype of WS is difficult to detect in early life and most newborns are identified when typical cardiac defects are present [15]. A study of 75 patients with WS concluded that cardiovascular signs or symptoms were evident in approximately 50% of their patients when they were newborns. Of these, 77% were found to have arterial vasculopathy or intracardiac defects, suggesting that typical cardiac anomalies aid in making a rapid diagnosis of WS when other characteristic features still remain unrecognized [5-15]. 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 [16]. 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. Angiotensin converting enzyme inhibitors are relatively contraindicated in the renal artery stenosis (RAS), as they pose a risk of renal dysfunction [17]. However, calcium channel blockers of the dihydropyridine class are effective medications for the treatment of hypertension in WS and do not pose a risk in the setting of RAS [18]. B-blockers are another option for hypertension management, and they may have additional benefits of potentially decreasing the risk of ventricular arrhythmia and sudden death [18]. The treatment for SVAS includes the dilation or amplification of the stenotic segment of aortic or coronary wall, which is sometimes repaired with pericardial patches [19]. In cases of PAS, there is the

possibility of stent placement [2]. In 58% of cases, a surgery is required, depending on the severity of pulmonary artery stenosis [20]. A previous study showed that, with time, PAS tends to improve spontaneously and SVAS to progress [5, 14].

IV. Conclusion:

Cardiovascular abnormalities are the most common manifestations of infantile WS 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. The assessment and long follow-up of WS patients by several specialties is of good relevance due to the high prevalence of multisystem manifestations and complications.

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