East African Medical Journal Vol. 95 No. 8 August 2018
WILLIAMS-BEUREN SYNDROME: A RARE PRESENTATION OF AORTIC HYPOPLASIA
Del-Rossi Sean Quadros, MD, MMed, Department of Pediatrics and Child Health, Aga Khan University Hospital, Nairobi. P.O. Box 45680-00100 Nairobi, Kenya. Naushad Karim, MBChB, MMed, Department of Radiology, Aga Khan University Hospital, Nairobi. Fathimath Amal Abdul Sattar, MD, MMed, Department of Anaesthesia, School of Medicine, University of Nairobi.
Corresponding Author: Dr Sean Del-rossi Quadros, P.O. Box 45680-00100 Nairobi, Kenya
Email: dellychka@hotmail.com

WILLIAMS-BEUREN SYNDROME: A RARE PRESENTATION OF AORTIC HYPOPLASIA

D. S. Quadros, N. Karim, and F. A. A. Sattar

ABSTRACT

William-Beuren syndrome (WBS) is a rare genetic disorder resulting from a micro-deletion of the elastin gene located on the long arm of chromosome 7 (7q11.23). Characterized by typical elfin facies, mental deficiency, overfriendly personality and occasionally infantile hypercalcemia together with various eye, teeth, cardiovascular, renal and skeletal abnormalities. Herein, we describe two cases of diffuse narrowing of the entire aorta, with associated pulmonary artery narrowing. To the best of our knowledge, these two cases of aortic hypoplasia associated with WBS are the first to be reported in the region.

INTRODUCTION

William-Beuren syndrome (WBS), first described independently by Williams et al. [1] in 1961 and Beuren et al. [2] in 1962, is a rare genetic disorder characterized by typical elfin-like facies, mental deficiency, an overfriendly personality and occasionally infantile hypercalcemia together with various cardiovascular, skeletal, teeth, eye and renal abnormalities. [1-4] William-Beuren syndrome, both sporadic and familial cases are considered as a result of a micro-deletion of the elastin gene located on the long arm of chromosome 7 (7q11.23), which is routinely confirmed by detecting elastin hemizygosity by flouresence in situ hybridization (FISH). [5-6]

The abnormal deposition of elastin during cardiovascular embryogenesis, leads to a wide spectrum of cardiovascular abnormalities seen within this syndrome. A review analysis, by Karuna et al. [7] using computed tomography imaging of the various cardiovascular abnormalities seen in WBS, demonstrated that the most common anomaly was supravalvular aortic stenosis (SVAS), pulmonary arterial stenosis (PAS) and mitral valve prolapse (MVP). Less frequent abnormalities observed included coarctation of aorta (COA), ventricular septal defect (VSD), patent ductus arteriosus (PDA), subaortic stenosis and hypertrophic cardiomyopathy (HCM). Similar findings were reported in a clinical study by Del Pasqua et al., [8] where typical cardiac defects were seen in 83% of the patients and atypical defects seen in 17% of patients. They also reported that among the typical congenital defects, SVAS was found in 65% of cases

and PS, both peripheral and valvular, found in 45% of cases. Intracardiac lesions are rare in WBS patients as reported by Pober et al., [9] Nakamoto et al., [10] Shimamoto et al. [11] and Park et al. [12]

The middle aortic syndrome, characterized by diffuse narrowing of the aorta between the arch and the iliac bifurcation with renal and visceral branch involvement is a common finding in patients with WBS, however, not regarded as a typical cardiovascular abnormality in most previous published data. Radford et al. [13] reported diffuse narrowing of the thoracic and abdominal aorta present in about 55% of WBS patients. This narrowing causes hypertension and abdominal angina. The diagnosis of middle aortic syndrome was defined by Raford et al. as diffuse narrowing of descending aorta with a measured gradient of >20mmHg across a narrowing and associated with visceral or renal arterial stenosis.

Herein, we describe two cases of diffuse narrowing of the aorta with no localized narrowing seen, the first case was an isolated diffuse aortic narrowing with no associated cardiovascular defect while the second case was associated with peripheral pulmonary artery narrowing.

CASE REPORT

Our first case (patient 1), a 4-year-old male referred due to features of attention deficit and hyperactivity disorder (ADHD) with syndromic features, and the second case (patient 2), a 3-year-old female referred for cardiac screening due to a cardiac murmur. Clinical examination of both patients demonstrated typical elfin facies and appeared overfriendly and happy with no associated skeletal, renal or ocular abnormalities. Cardiac auscultation revealed a continuous murmur over the lung fields in patient 2. A 2-D echocardiogram demonstrated a structurally normal heart in both patients with bilateral branch pulmonary artery narrowing seen in Patient one and right pulmonary artery (RPA) stenosis seen in Patient 2. Micro-deletion of the elastin gene located on the long arm of chromosome 7 (7q11.23) was confirmed for both patients using flouresence in situ hybridization (FISH) using the Vysis LSI Williams syndrome (elastin gene) region probe. A Computer tomography (CT) angiography was done for both patients to further delineate the cardiac anatomy.

Patient 1, (Figures 1 and 2), demonstrated a hypoplastic aorta from the sinotubular junction up to the visualized upper abdominal aorta. Aortic sinus measured 14mm x 15mm x 17mm, (Z-score: 1.18), sinotubular junction; 9mm (Z-score: -4.44), ascending aorta; 8mm (Z-score: -5.15), isthmic region; 8.5mm (Z-score: -0.5), descending aorta; 8mm (Z-score: -0.9), aorta at the level of the diaphragm; 6mm (Z-score -7.7). The celiac axis, superior mesenteric artery and bilateral renal arteries were all reduced in caliber. The main pulmonary artery (MPA) measured 15mm (Z-score: 0.3). Right pulmonary artery; 6mm (Z-score: -2.4), while the left pulmonary artery measured 7mm (Z-score: -0.7). There was no other cardiac abnormality reported.

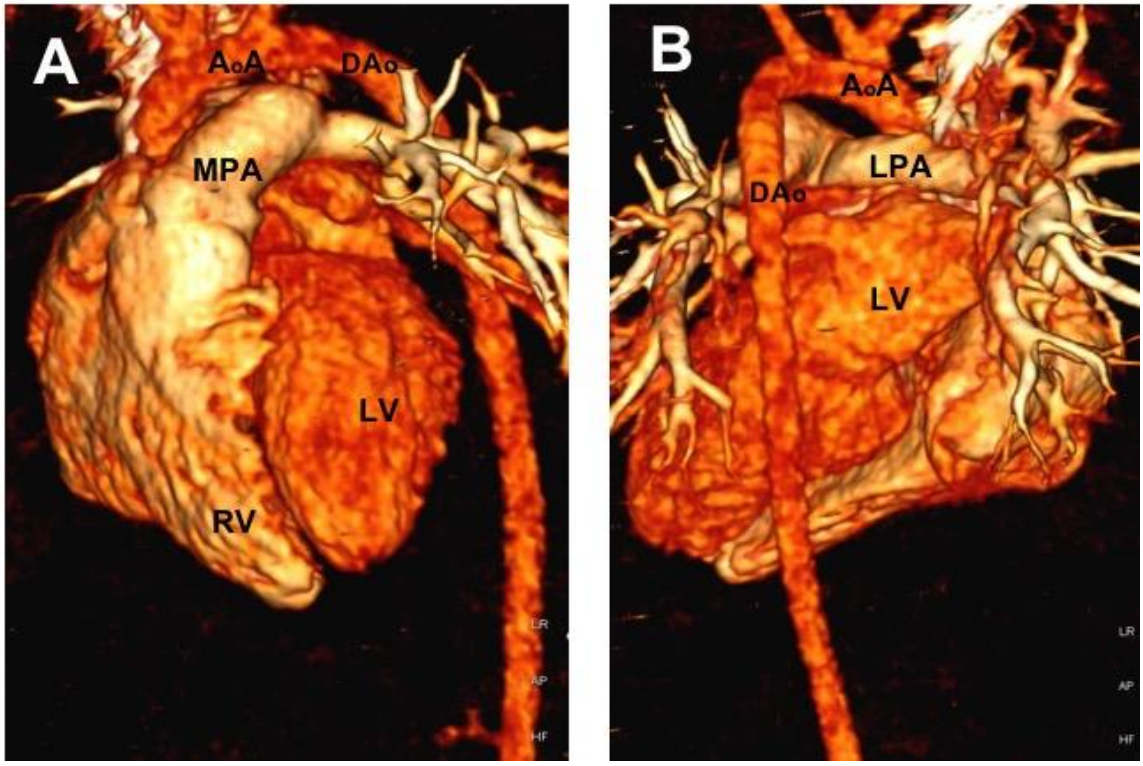

FIGURE 1

3D reformats of CT pulmonary angiogram in Oblique lateral view (figure 1A) and Posterior view (figure 1B) demonstrating diffuse narrowing of the aorta when compared to the pulmonary trunk. MPA; Main Pulmonary Artery, AoA; Aortic Arch, DAo; Descending Aorta, RV; Right Ventricle, LV; Left Ventricle.

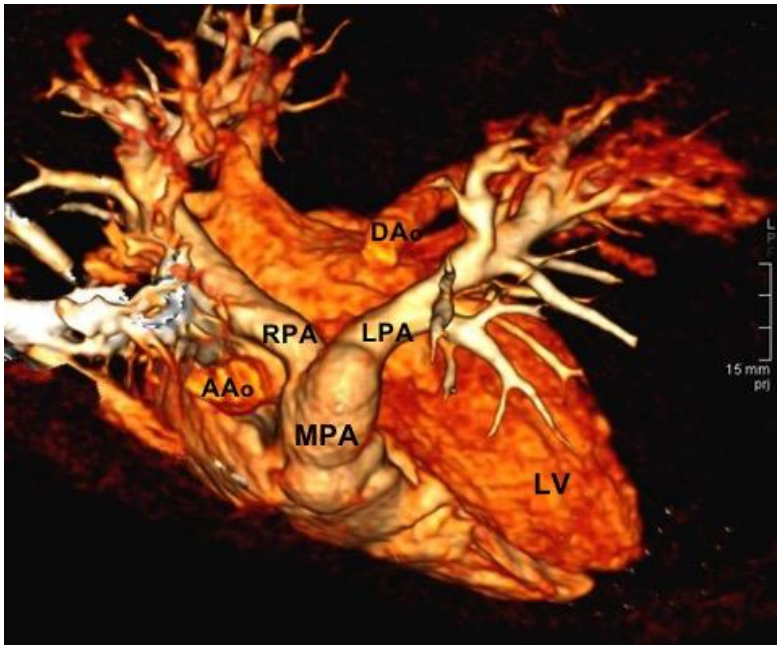

FIGURE 2

3D reformats of CT pulmonary angiogram with cropping of the aortic arch demonstrating normal caliber of the pulmonary trunk, right and left pulmonary arteries. Narrowing of the ascending and descending thoracic aorta is seen when compared to the pulmonary trunk and right and left main pulmonary arteries. MPA; Main Pulmonary Artery, LPA; Left Pulmonary Artery, RPA; Right Pulmonary Artery, AAo; Ascending Aorta, DAo; Descending Aorta, LV; Left Ventricle.

Patient 2, (Figures 3 and 4), demonstrated a hypoplastic aorta from the supravalvular region (sinotubular junction) up to the upper abdominal aorta. Aortic sinus; 16mm x 17mm x 18mm (Z-score: -0.2), sinotubular junction; 8.6mm (Z-score: -4.5), ascending aorta; 9mm (Z-score: -3.6), isthmic region; 8.7mm (Z-score; -0.1), descending aorta; 8.1mm (Z-score:0.5), aorta at the level of the diaphragm; 8mm (Z-score: -0.6). The celiac axis, superior mesenteric artery and bilateral renal arteries were all reduced in caliber. The main pulmonary artery (MPA) was normal in caliber measuring 18mm (Z-score: 1.8). There was focal narrowing at the origin of the right pulmonary artery with the narrowest portion measuring 4mm (Z-score: -3.7), the left pulmonary artery measured 10mm (Z-score: 1.0), in diameter with no focal stenosis seen. There was no other cardiac abnormality reported. (Figures 3 and 4)

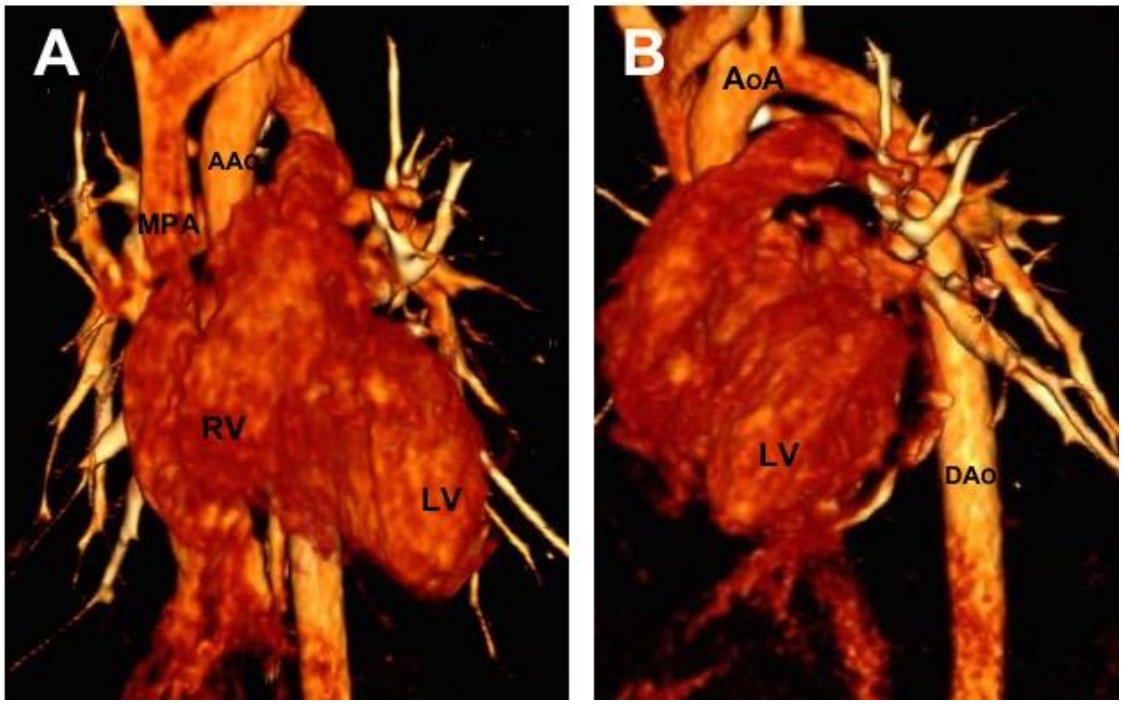

FIGURE 3

3D reformats of CT pulmonary angiogram in Oblique Anterior view (figure 1A) and Oblique Lateral view (figure 1B) demonstrating diffuse narrowing of the aorta. MPA; Main Pulmonary Artery, AoA; Aortic Arch, DAo; Descending Aorta, RV; Right Ventricle, LV; Left Ventricle.

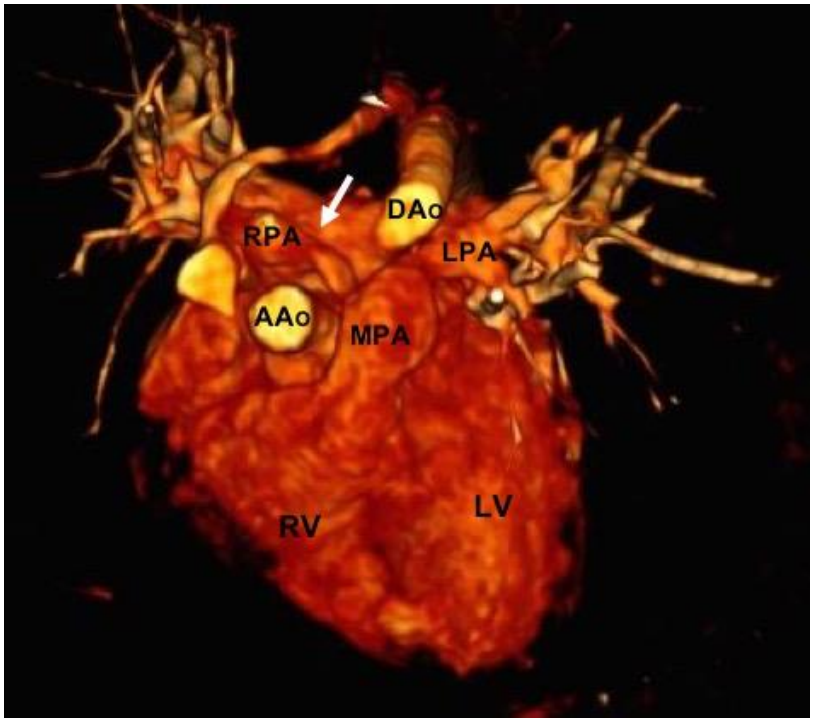

FIGURE 4

3D reformats of CT pulmonary angiogram with cropping of the aortic arch demonstrating normal caliber of the pulmonary trunk and left pulmonary arteries with focal narrowing of the right pulmonary artery (arrow). Narrowing of the ascending and descending thoracic aorta is seen when compared to the pulmonary trunk. MPA; Main Pulmonary Artery, LPA; Left Pulmonary Artery, RPA; Right Pulmonary Artery, AAo; Ascending Aorta, DAo; Descending Aorta, LV; Left Ventricle. RV; Right Ventricle.

DISCUSSION

Cardiovascular lesions are an important cause of both morbidity and mortality among patients with Williams-Beuren syndrome. Several studies have focused on supravalvular aortic stenosis (SVAS) and pulmonary artery stenosis (PAS) as the main cardiovascular lesions and have demonstrated that PAS tends to improve spontaneously, whereas SVAS was generally found to be progressive. Scheiber et al. [14] demonstrated in an echographic study, that in addition to the major cardiac features seen in WBS, the severity of other cardiac anomalies can also change over time and emphasized the importance of regular cardiac follow-up.

Incidence of hypertension among patients with WBS and associated Middle Aortic Syndrome and aortic hypoplasia has been shown to be high. Radford et al. [13] reported an incidence of 61% in a follow-up series of patients with Middle Aortic Syndrome. Similar results were reported by Morris et al. [3] who also reported that the incidence of hypertension in WBS increases with age. The mechanism of hypertension has been shown to be due to the contribution from the stiff thick arterial wall, which lacks elastin and also from renal artery stenosis and associated renal abnormalities. [13] Thoracic and abdominal angiography together with demonstration of any hemodynamic gradients at various sites is necessary when assessing patient with WBS.

In the two patients that we have reported, both had significant aortic narrowing with associated right pulmonary artery stenosis in one patient. CT images demonstrated a

uniformly narrowing of the entire aorta to the level of the renal bifurcation with no evidence of regional coarctation. We will follow-up both patients closely and plan for cardiac trans catheter hemodynamic assessment at a later date.

To the best of our knowledge, these two cases of aortic hypoplasia associated with WBS are the first to be reported in the region. Our intention is to highlight the importance of having a high degree of suspicion of WBS to avoid misdiagnosis that often leads to loss of follow-up of these children leading to increased morbidity and even mortality. Asymptomatic children with WBS also need continued follow-up as these cardiac lesions tend to change or progress over time.

CONCLUSION

Williams-Beuren syndrome remains to be unrecognized in newborns especially those without typical phenotypic features, therefore, it is recommended that all babies with any dysmorphic features must be examined by cardiac ultrasound. There is high risk of sudden cardiac death, and most of these children will require either surgical or trans catheter cardiac interventions. A considerable number of cardiac pathology may not manifest until later in adult age and the symptoms may be absent or non-specific, thus hampering adequate treatment. Therefore, it is a recommendation that all patients diagnosed with WBS with or without symptoms, have a lifelong follow-up with a cardiologist.

REFERENCES

1. Williams JCP, Barratt-Boyes BG, Lowe JB. Supravalvular aortic stenosis. Circulation 1961; 21: 1311-8.
2. Beuren AJ. Supravalvular aortic stenosis: a complex syndrome with and without mental retardation. Birth Defects: OAS VIII 1962; 5: 45-56.
3. Morris CA, Demsey AS, Leonard CO, Dilts C, Blackborn. Natural history of Wil- liams syndrome: physical characteristics. J Pediatr 1988; 113: 318-26.
4. Jones, KL, Smith, DW. The Williams elfin facies syndrome. J Pediatr 1975; 86: 718-23.
5. Lowery MC, Morris CA, Ewart A, et al. Strong correlation of elastin deletions, detected by FISH, with Williams syndrome: evaluation of 235 patients. Am J Hum Genet 1995; 57: 49-53.
6. Nickerson E, Greenberg F, Keating MT, McCaskill C, Shaffer LG. Deletions of the elastin gene at 7q11.23 occur in 90% of patients with Williams syndrome. Am J Hum Genet 1995; 56: 1156-61.
7. Karuna MD, Tarek SM, Sven GL, Shehla J, Abduallah SA, Edward YL. Williams-Beuren Syndrome: Computed Tomography Imaging Review. Pediatr Cardiol. 2014;35:1309-1320
8. Del Pasqua A, Rinelli G, Toscano A, 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.
9. Pober BR. Williams-Beuren syndrome. N Engl J Med 2010; 362: 239-252.
10. Nakamoto S, Saga T, Shinohara T. Williams syndrome associated with complete atrioventricular septal defect. Heart 2003; 89: e15.
11. Shimamoto T, Ikeda T, Koshiji T, et al. A successful surgical repair of total anomalous pulmonary venous connection associated with Williams syndrome. Kyobu Geka 1997; 50: 405-408.
12. Park HK, Heinle JS, Morales DL. Williams syndrome and obstructed total anomalous pulmonary venous return: a previously unreported association. Ann Thorac Surg 2012; 94: 289-291.
13. Radford DJ, Pohlner PG (2000) The middle aortic syndrome: an important feature of Williams' syndrome. Cardiol Young 10: 597–602
14. Scheiber D, Fekete G, Urban Z, et al. Echocardiographic findings in patients with Williams-Beuren syndrome. Wien Klin Wochenschr 2006; 118: 538-542.