Ibrahim Card Med J 2014;4(1): 42-47

Williams Syndrome presenting with Supra-valvular Aortic Stenosis: A Case Report

S. M. Shaheedul Islam[1], F. Aaysha Cader[2], M. Maksumul Haq[3], Md. Rokonujjaman[4], Sahela Nasrin[5]

ABSTRACT

Williams Syndrome is described in children presenting with Supra-valvular Aortic Stenosis (SVAS) and typical dysmorphic 'Elfin facies' with characteristic neurocognitive profile. SVAS, a congenital narrowing of the ascending aorta, occurs sporadically but can also occur as a component of Williams Syndrome, with which it shares similar genetic microdeletion of the elastin gene on chromosome 7q11.23, responsible for the vasculopathy as well as certain morphological features of the syndrome. We report the case of a 5 year old girl, who presented with chest pain and a heart murmur, along with typical 'Elfinfacies', whose investigation led to the diagnosis of SVAS presenting with Williams Syndrome.

Key Words: Williams Syndrome, Supra-Valvular Aortic Stenosis (SVAS). Chromosome 7q11.23.

INTRODUCTION

Williams Syndrome, also known as Williams-Beuren Syndrome (WBS) is a relatively rare familial multi-system disorder occurring in 1/10,000 individuals, and first described by J.C.P. Williams[1] in 1961, followed shortly thereafter by A. J. Beuren.[2] Best known for its association with the Supra-valvular Aortic Stenosis (SVAS), the disorder encompasses mental retardation with a peculiar neurocognitive profile, dysmorphic facies and body features, and occasional hypercalcaemia especially in infancy.[3] SVAS is a congenital narrowing of the ascending aorta which can occur sporadically, as a manifestation of elastin arteriopathy, as an autosomal dominant condition, or as one component of Williams syndrome. SVAS is caused by translocations, gross deletions and point mutations that disrupt the elastin gene (ELN) on chromosome 7q11.23. Functional hemizygosity for elastin is known to be responsible for the vasculopathy in SVAS patients with gross chromosomal abnormalities involving ELN.[4,5]

In 1993 it was reported that the genetic cause of WBS also involved the same chromosome, involving de novo deletions of the elastin gene,[6] with another study reporting that deletions of the elastin gene at 7q11.23 occur in approximately 90% of patients with Williams Syndrome.[7] This chromosomal basis now permits a laboratory-based diagnostic test, so that the diagnosis no longer rests solely on clinical criteria.

Authors' Information:

1 **Dr. S. M. Shaheedul Islam,** MBBS, DCH (DU), FCPS (Ped), Fellowship in Pediatric Cardiology, Associate Professor & Consultant in Pediatric Cardiology, Ibrahim Cardiac Hospital & Research Institute (ICHRI), Dhaka.

2 **Dr. F. Aaysha Cader,** MBBS, MRCP (UK), Assistant Registrar in Cardiology, ICHRI, Dhaka.

3 **Prof. M. Maksumul Haq,** MBBS, FCPS, FRCP, FACP, Professor & Head, Department of Cardiology, ICHRI, Dhaka.

4 **Dr. Md. Rokonujjaman,** MBBS, MS (Cardiovascular & Thoracic surgery), Fellowship in Congenital & Pediatric Cardiac Surgery (ESCORTS Hospital, India & Seoul National University Hospital, South Korea), Assistant Professor & Associate Consultant, ICHRI, Dhaka.

5 **Dr. Sahela Nasrin,** MBBS, MCPS (Med), MD (Card), Associate Consultant & Assistant Professor, ICHRI, Dhaka.

Address of Correspondance: **Dr. S. M. Shaheedul Islam,** MBBS, DCH (DU), FCPS (Ped), Fellowship in Pediatric Cardiology, Associate Professor & Consultant in Pediatric Cardiology, Ibrahim Cardiac Hospital & Research Institute (ICHRI), Dhaka, **Cell:**+88 01711362927, **E-mail:** shaheedul.islam@yahoo.com

The syndrome is routinely confirmed by detecting elastin hemizygosity by fluorescence in situ hybridisation (FISH),[6] although DNA dosage techniques such as quantitative PCR, multiplex ligation-dependent probe amplification, and chromosomal microarray, may soon become confirmatory tests of choice.[8] We report here the case of a 5 year-old Bangladeshi girl who presented with chest pain and a heart murmur, with investigation findings being consistent with SVAS, along with typical morphological faces and neurocognitive profile consistent with Williams Syndrome.

Case Report

A 5 year old Bangladeshi girl presented with chest pain for 2 years, increasing at night, frequent respiratory tract infection over the last year and failure to thrive. She demonstrated growth retardation, weighing just 13 kg with a height of 106 cm. She was the youngest of 3 siblings, the rest of whom were well, and her mother confirmed delays in developmental milestones from an early age, including difficulty in speech. Although she had good auditory rote memory she had difficulty speaking out words and sentences.

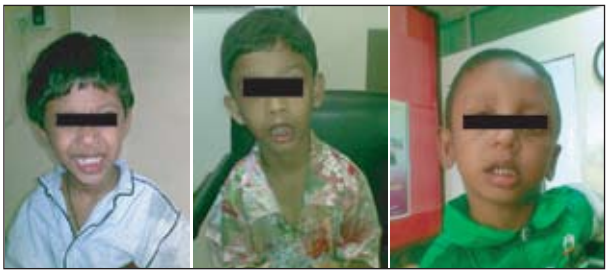

FIGURE 1: Typical facies in children presenting with Williams Syndrome

Of distinct note however, was extremely sociable nature. The child displayed morphological features of Williams Syndrome described by Williams,[1] such as full face, broad forehead, eyes set well apart, wide mouth, and pointed chin, consistent with the typical 'Elfin facies'. She also had prominent ears and malocclusion of the teeth, along with a dental abscess (Figure 1).

On physical examination, heart rate was 106 beats/min, regular with good volume pulses but low volume in left radial pulse. Blood pressure was 120/80 mmHg in right arm; 80/50 mmHg in left arm; 120/80 mmHg in both lower limbs. There was a heaving left ventricular apex beat with thrill and a loud systolic ejection murmur in the aortic area that radiated to the bilateral carotid arteries. ECG revealed sinus tachycardia and short PR interval. Chest X-ray showed no abnormality. Echo demonstrated supra-valvular aortic stenosis (pressure gradient 80 mmHg). Aorta was arising from left ventricle (LV) with hour-glass narrowing of ascending aorta at sinotubular junction (STJ), aortic root 17 mm, narrowest part being 8mm, arch was left and normal, without coarctation (Figure 2). There was concentric LVH with good LV systolic function (EF-75%) and normal right ventricle (RV). Pulmonary arteries arose from RV with normal main pulmonary artery (MPA) and confluent branches. Right pulmonary artery (RPA) was mildly hypoplastic. Interarterial and interventricular septa were intact. Pulmonary Artery Systolic Pressure (PASP) was 25 mmHg. Great arteries were normally related.

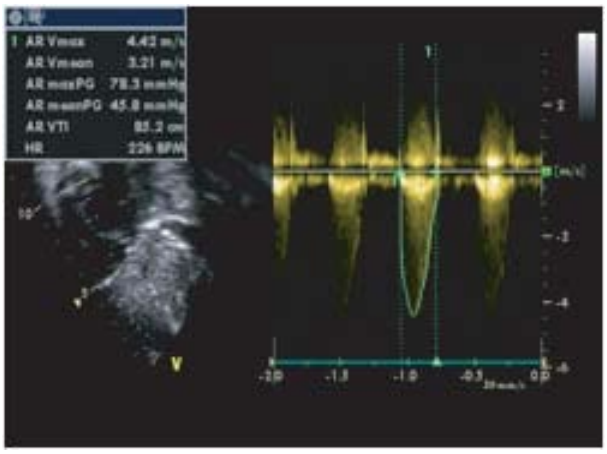

FIGURE 2: (a) CW spectral tracing

Cardiac catheterization was done and pressures were as follows: RV pressure was 33/05(EDP), femoral artery pressure 125/65/93, Aorta 121/60/85, LV 225/05(EDP). LV aortogram revealed concentric hypertrophy of LV, with severe

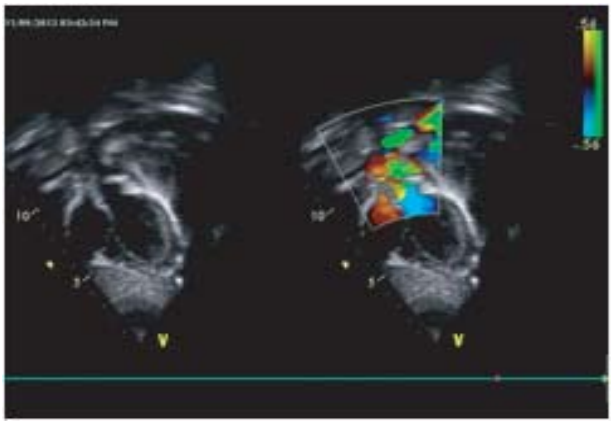

FIGURE 2: *(b) Simultaneous 2D echo & colour flow image*

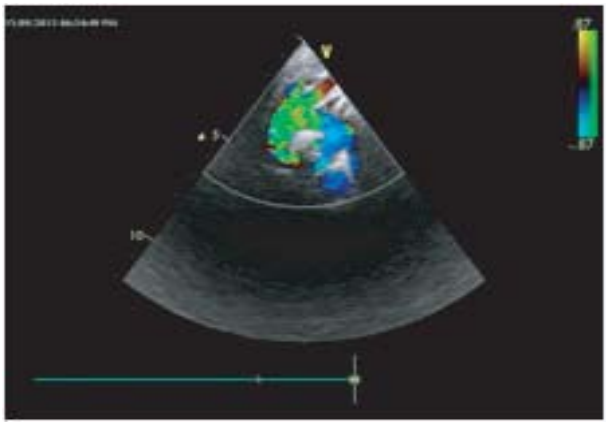

FIGURE 2: *(c) Colour Doppler showing Coanda effect*

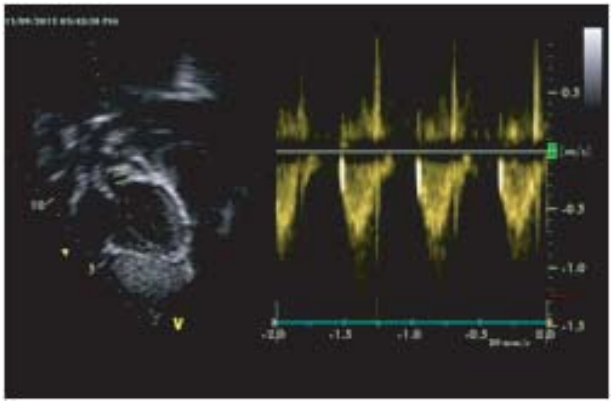

FIGURE 2: *(d) PW sampling*

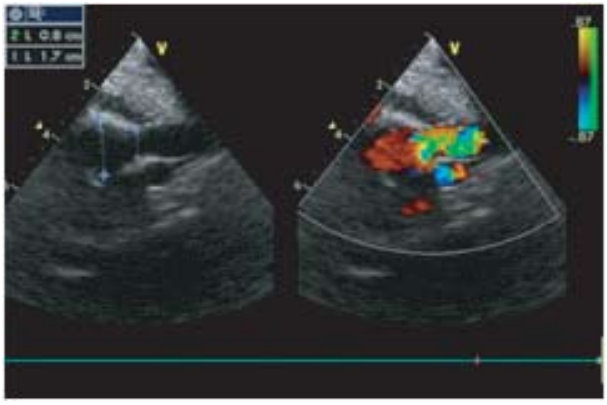

FIGURE 2: *(e) Hour-glass deformity of ascending aorta*

stenosis at sino-tubular junction (STJ) - aortic annulus-11 mm, root 13 mm, STJ 5 mm. STG Aortogram revealed supra-valvular narrowing; arch and descending aorta showing no stenotic lesion (Figure 3). Renal arteries were of normal caliber. Coronary arteries appeared normal. Good contractile trabeculated RV, MPA and branch PAs were of good size with good arborization and no visible stenotic lesion. These findings were confirmed on CT aorto-pulmonary angiogram which revealed: aortic annulus 18.2 mm, mildly narrow segment of about 5.5 mm & 7.5 mm width noted at or just above the sino-tubular junction; ascending aorta 12.5 mm; arch of aorta 11 mm; descending aorta 8.6 mm. Pulmonary arteries: MPA 16.3 mm, RPA 11.8 mm, LPA 10.8 mm (Figure 4). Image quality was suboptimal due to motion artifact.

Blood biochemistry including CBC, ESR, serum electrolytes and renal function tests were all within normal limit, as was serum calcium: 9.3mg/dl (normal 8.4 - 10/2mg/dl). The typical phenotypical features, combined with the findings

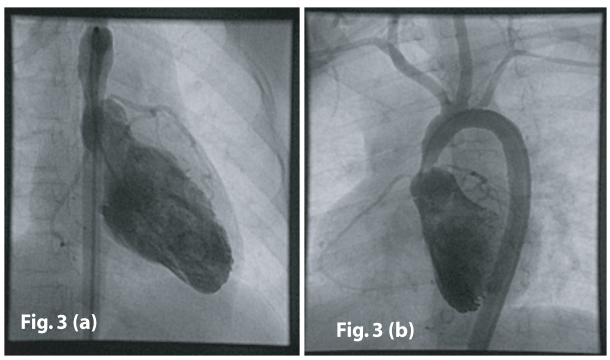

FIGURE 3: *(a) LV graphy and (b) Root aortogram showing supra-valvular aortic stenosis.*

CASE REPORT

of SVAS led us to the diagnosis of Williams Syndrome, however the condition should ideally have been confirmed by genetic evaluation demonstrating the 7q11.23 microdeletion on FISH test, with which our centre is unfortunately unequipped. This child is currently on Propranolol and definitive surgical repair in the form of augmentation of ascending aorta has been planned.

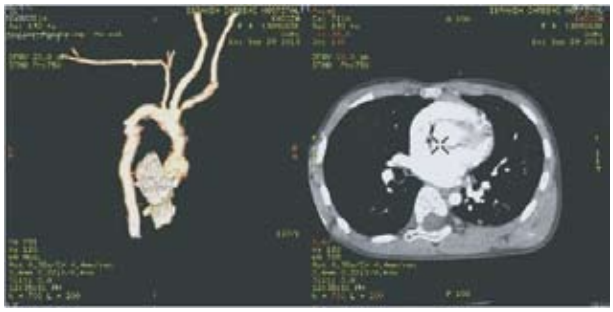

FIGURE 4: *CT angiogram demonstrating supra-valvular aortic stenosis.*

Discussion

Williams Syndrome is an arteriopathy involving both systemic and pulmonary arteries. However pulmonary lesions grow out with the child, although aortic lesions worsen with time, with high incidence of sudden cardiac death (SCD) inaffected children of Williams Syndrome if left unattended. SVAS is a fixed form of congenital left ventricular outflow tract (LVOT) obstruction that occurs as a localized or diffuse narrowing of the ascending aorta beyond the superior margin of the sinuses of Valsalva.[9] Although SVAS is estimated to occur in approximately 1 in 25,000 live births[10] and accounts for approximately 0.5% of congenital heart diseases cases, the sporadic form of SVAS is the most common, with only 30-50% of patients with SVAS having Williams Syndrome.[11]

There are 3 commonly recognized forms of SVAS: the hour-glass type, hypoplastic type and tubular form.[12] The commonest type, seen in 50-75% of cases as well as in our patient, is the external hourglass deformity of the aorta with a corresponding luminal narrowing at a level just distal to the coronary artery ostia. As a consequence of the severe degree of obstruction to the egress of blood from the left ventricle, the wall of this chamber usually shows pronounced concentric hypertrophy,[12] as is manifested in this child's echo and catheterization findings. In contrast to aortic and subaortic valvular stenosis, in SVAS, the origins of the coronary arteries lie proximal (as opposed to distal) to the obstruction site, and are therefore subjected to the same systolic pressure as the LV. Consequently, they become dilated and tortuous over time, with hypertrophy and intimal thickening, predisposing them to premature atherosclerosis.[12]

We also found unequal systolic blood pressure in the upper extremities, which has been frequently reported with SVAS, and is an important diagnostic sign. This can be explained by the mechanism of the Coanda effect. In valvular aortic stenosis, the velocity of the jet is quickly dissipated beyond the stenotic orifice, preventing any sustained high-velocity stream. However, the smooth, annular narrowing of SVAS creates a "step" between the orifice and the ascending aortic wall which enhances the natural affinity of a jet for a boundary wall and conserves the kinetic energy of the jet stream. In most patients with SVAS, the jet of blood flow has a preferential trajectory into the brachiocephalic vessels, as the high-velocity stream is along the right aortic wall, causing disproportionately high pressure in the right arm.[13]

Although the sporadic form of SVAS is the most common, most pediatric patients present because of a heart murmur or the features of Williams Syndrome. Symptoms caused by SVAS usually develop in childhood, and rarely in infancy.[14] Patients with Williams Syndrome may also develop systemic hypertension, involvement of joints, peripheral pulmonary artery stenosis, coarctation of aorta, and mitral insufficiency.[15]

In addition to their distinctive facial appearance, which also includes wide mouth, full cheeks, long

philtrum, small nose, delicate chin and dental abnormalities,[8] children with Williams Syndrome tend to have growth retardation as well as mild to moderate mental retardation. Particularly notable is the pattern of intellectual peaks and valleys, referred to as the Williams syndrome cognitive profile, with relative strengths in selected language domains and a prominent weakness in the visuospatial domain.[16] They are generally social and friendly demeanour coexists with anxiety (especially anticipatory anxiety), phobias, and perseverative tendencies.[17,18]

Dyspnea on exertion, angina, and syncope develop in the course of the disease if SVAS is untreated, and indicate at least a moderate degree of LVOT obstruction. Although the coronary arteries revealed no abnormality in our case, the involvement of coronaries later on may cause angina to arise early and more often than in other obstructive LVOT lesions. Our patient also presented with chest pain; therefore, cases such as these presenting with angina and syncope in childhood should prompt immediate investigation, particularly echocardiography.[14]

Two dimensional and Doppler echocardiography is a highly sensitive tool in the diagnosis of SVAS; Hallidie-Smith et al demonstrated that all patients of Williams' Syndrome showed echocardiographic evidence of SVAS.[19] However, better delineation of its anatomy and physiology can be obtained by cardiac catheterization with angiography and CT and MR imaging. Nevertheless caution must be exercise in the administration of sedative during CT angiogram in these children as Ketamine needs to avoid due to its tendency to increase Supravalvular resistance and decrease cardiac output further. Definitive treatment of SVAS involves surgery. Operative techniques for repair of SVAS have utilized patch aortoplasty that may involve augmentation of 1-3 of the aortic sinuses.[20,21] The symmetric inverted 3-sinus patch plasty has resulted in improved outcome in one large series.[22]

Although genetic confirmation could not be made owing to the unavailability of FISH testing in our centre, we have substantial reason to conclude that this is indeed a case of Williams Syndrome presenting with SVAS, as she demonstrates the typical morphological features described by Williams' in addition to supportive neurocognitive profile (i.e. developmental delay especially in speech; good in rote memory, very social & friendly).

Conclusion

Although Williams Syndrome is not a common diagnosis encountered, it should be strongly suspected in children presenting with typical 'William facies' and mental retardation presenting with a heart murmur, as the diagnosis of SVAS should be made early in order to institute prompt therapy and prevent complications.

REFERENCES

1. Williams JC, Barratt-Boyes BG, Lowe JB. Supravalvular aortic stenosis. *Circulation* 1961;24:1311-18.
2. Beuren AJ, Apitz J, Harmjanz D. Supravalvular aortic stenosis in association with mental retardation and a certain facial appearance. *Circulation* 1962;26:1235-40.
3. Morris CA, Demsey SA, Leonard CO, Dilts C, Blackburn BL. Natural history of Williams syndrome. *J Pediatr* 1988;113:318-26.
4. Metcalfe K, Rucka AK, Smoot L, Hofstadler G, Tuzler G, McKeown Pet al. Tassabehji. Elastin: mutational spectrum in supravalvular aortic stenosis. *Eur J Hum Genet* 2000;8(12):955-63.
5. Ewart AK, Jin W, Atkinson D, Morris CA, Keating MT. Supravalvular aortic stenosis associated with a deletion disrupting the elastin gene. *J Clin Invest* 1994;93(3): 1071-77.
6. Ewart AK, Morris CA, Atkinson D, Jin W, Sternes K, Spallone P et al. Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. *Nat Genet* 1993;5(1):11-6.
7. Nickerson E, Greenberg F, Keating MT, McCaskill C, Shaffer LG. Deletions of the elastin gene at 7q11.23 occur in about 90% of patients with Williams syndrome. *Am J Hum Genet* 1995;56(5):1156-61.
8. Pober BR, Johnson M, Urban Z. Mechanisms and treatment of cardiovascular disease in Williams-Beuren syndrome. *J Clin Invest* 2008;118(5):1606-15.
9. Micale L, Turturo MG, Fusco C, Augello B, Jurado LA, Izzi C et al. Identification and characterization of seven novel mutations of elastin gene in a cohort of patients affected by supravalvular aortic stenosis. *Eur J Hum Genet* 2010;18(3):317-23.

10. Ewart AK, Morris CA, Ensing GJ, Loker J, Moore C, Leppert M et al. A human vascular disorder, supravalvular aortic stenosis, maps to chromosome. *Proc Natl Acad Sci USA* 1993;90(8):3226-30.

11. Zamani H, Babazadeh K, Fattahi S, Mokhtari-Esbuie F. Williams-Beuren's Syndrome: A Case Report. *Case Rep Med* 2012;2012:585726.

12. Edwards JE. Pathology of left ventricular outflow tract obstruction. *Circulation* 1965;31:586-99.

13. French JW, Guntheroth WG. An explanation of asymmetric upper extremity blood pressures in supravalvular aortic stenosis: the Coanda effect. *Circulation* 1970;42(1):31-6.

14. Krishnan A, Singh GK. Pediatric Supravalvular Aortic Stenosis [Internet]. [updated 2015 Aug 26; cited 2015 July 15].

Available from:http://emedicine.medscape.com/article/892252-overview#aw2aab6b2b2aa.

15. Eronen M, Peippo M, Hiippala A, Raatikka M, Arvio M, Johansson R et al. Cardiovascular manifestations in 75 patients with Williams Syndrome. *J Med Genet* 2002; 39(8):554-58.

16. Mervis CB, Robinson BF, Bertrand J, Morris CA, Klein-Tasman BP, Armstrong SC. The Williams syndrome cognitive profile. *Brain Cogn* 2000;44(3):604-28.

17. Dykens EM. Anxiety, fears, and phobias in persons with Williams syndrome. *Dev Neuropsychol* 2003;23(1-2): 291-316.

18. Cherniske EM, Carpenter TO, Klaiman C, Young E, Bregman J, Insogna Ket al. Multisystem study of 20 older adults with Williams syndrome. *Am J Med Genet A* 2004;131(3):255-64.

19. Hallidie-Smith KA, Karas S. Cardiac anomalies in Williams-Beuren syndrome. *Arch Dis Child* 1988;63(7): 809-13.

20. Hazekamp MG, Kappetein AP, Schoof PH, Ottenkamp J, Witsenburg M, Huysmans HA et al. Brom's three-patch technique for repair of supravalvular aortic stenosis. *J Thorac Cardiovasc Surg* 1999;118(2):252-58.

21. Stamm C, Friehs I, Moran AM, Zurakowski D, Bacha E, Mayer JE et al. Surgery for bilateral outflow tract obstruction in elastin arteriopathy. *J Thorac Cardiovasc Surg* 2000;120(4):755-63.

22. Stamm C, Kreutzer C, Zurakowski D, Nollert G, Friehs I, Mayer JE et al. Forty-one years of surgical experience with congenital supravalvular aortic stenosis. *J Thorac Cardiovasc Surg* 1999;118(5):874-85.