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Williams-Beuren's Syndrome in an Indian Child : A Case Report

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ABSTRACT :

Williams-Beuren syndrome or Williams Syndrome (WS), is an uncommon disorder with a prevalence of 1 per 20,000 live births. It is exemplified by multiple congenital heart defects (CHD), particularly supravalvular aortic stenosis (SVAS) and/or supravalvular pulmonary stenosis (SVPS), with or without peripheral pulmonary arterial obstruction accompanied by dysmorphic facial features (ELFIN FACIES) and several other structural anomalies of skeletal, renal organs etc. The diagnosis is confirmed by the deletion of chromosome 7q11.23 determined by the FISH technique. We are reporting a case of WS in a 3-year-old Indian male child who was referred to us for evaluation of incidental detection of a heart murmur. The child had classical ELFIN FACIES accompanied by a ejection systolic murmur (3/6) in left and right upper sternal borders with radiation to carotids. Transthoracic echocardiography (TTE) demonstrated SVAS at an atypical location in the ascending aorta in association with a bicuspid aortic valve.

Typically, a child presenting with elfin facies alongwith SVAS should raise a high index of suspicion of WS. However, genetic testing for confirmation of WS, being very expensive, is not available in majority of hospitals in India. Consequently, due to paucity of funds, FISH test was not performed in our patient.

Keywords: Dysmorphic facies, Mitral Regurgitation, Williams Syndrome; Chromosome 7q11.23; Elfin Facies; Supravalvular aortic stenosis.

Introduction

WS is a rare developmental disorder that affects multiple organs of the body. Its estimated prevalence is 1 per 20,000 live births in the united states [1]. Typically patients of WS have CHDs, which characteristically includes SVAS (Figure 1) and/or SVPS [2, 3].

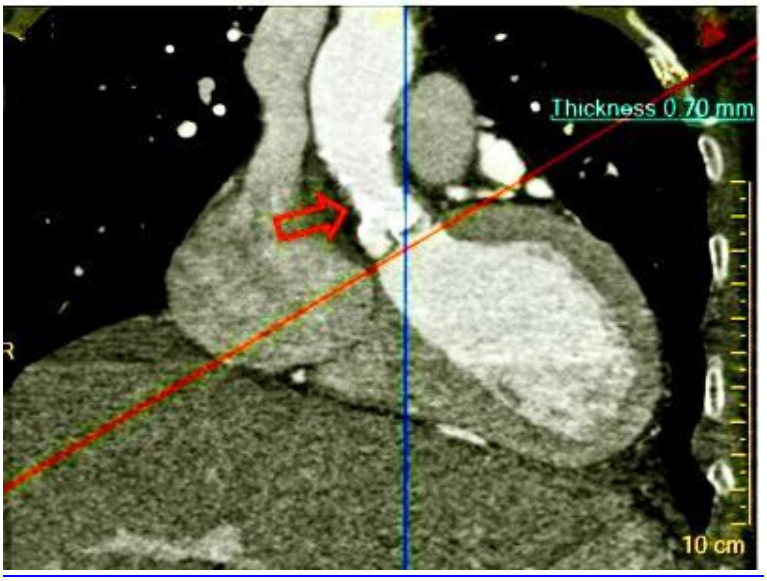


Figure 1: Cardiac CT of Supravalvular Aortic Stenosis. The red arrows points to the zone of obstruction.

Conventionally, SVAS can be of three types:

(i) discrete hourglass type, (ii) discrete diaphragm or membranous type and, (iii) diffuse hypoplasia [4-7].

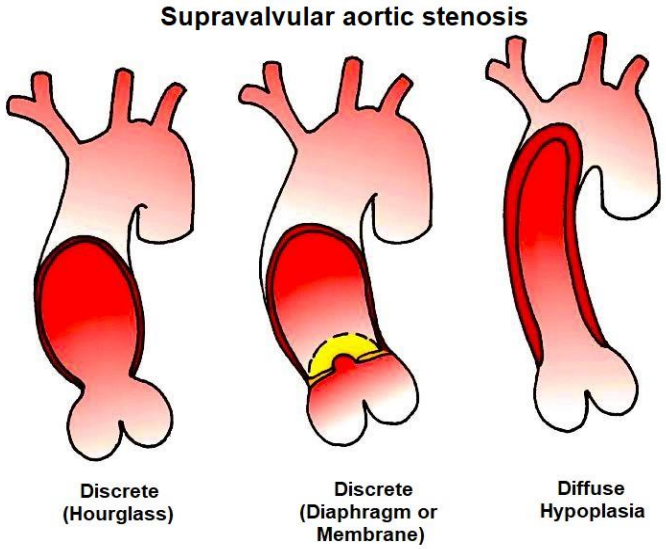


Figure 2: Supravalvular Aortic Stenosis: three different types.

WS patients may be afflicted with hypertension due to either stenosis of renal artery or unknown causes [2]. WS diagnosis is confirmed by the deletion of chromosome 7q11.23 (Figure 3) determined by the FISH (fluorescent in situ hybridization) test [8, 9]. FISH test is extremely expensive [10] and consequently majority of patients are unable to afford it.

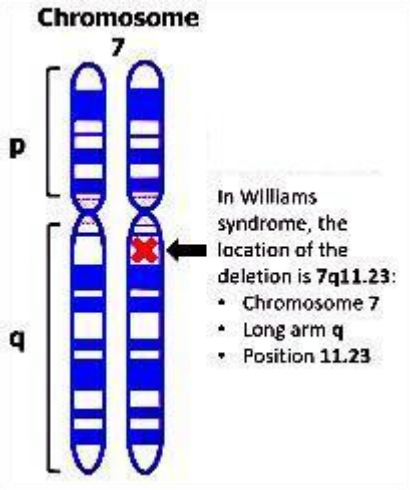


Figure 3: Deletion of gene 7q11.23 in Williams Syndrome.

Mutation occurs in elastin gene (ELN), and the deletion of ELN gene in WS patients, perhaps, is the dominant reason for the cardiovascular phenotype [11] (Figure 4).

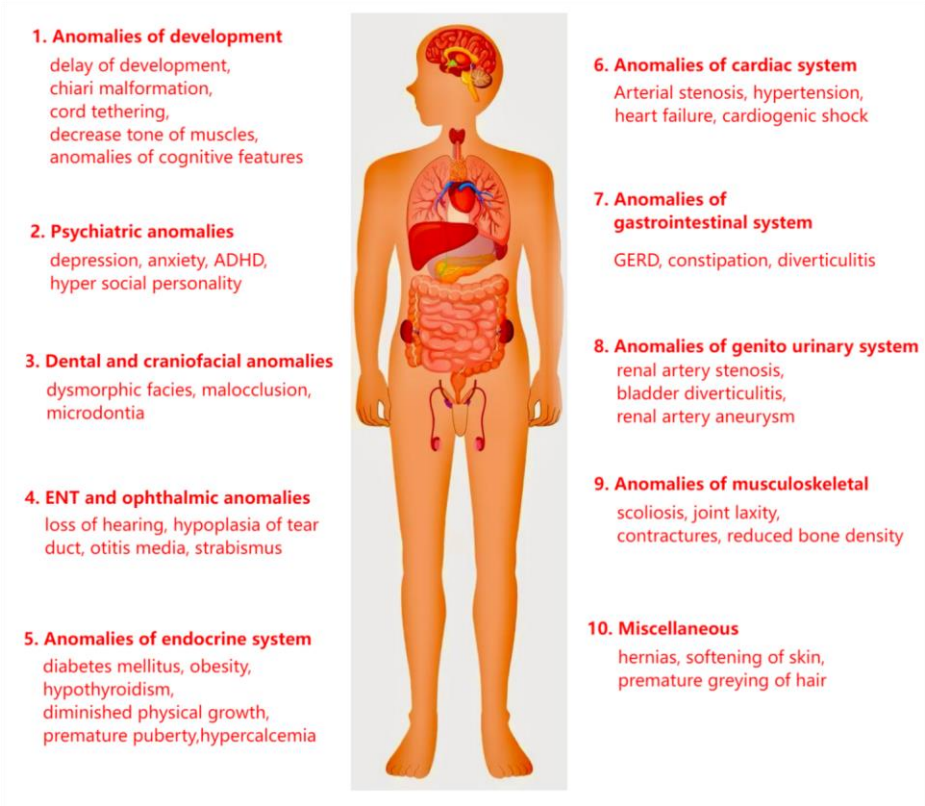


Figure 4: Williams Syndrome: cardiovascular phenotype

TTE is the current imaging of choice in patients with CHD [12]. TTE is advantageous over other non-invasive imaging tools [12] particularly Cardiac CT and Cardiac MRI due to multiple reasons:

(i) relatively cheap, affordable

(ii) versatile

(iii) portability and can be performed at beside in extremely sick patients

(iv) wide availability and accessibility

(v) non-invasive and safe

(vi) real time imaging

(vii) rapid delivery of results

(viii) no radiation exposure

(ix) comprehensive cardiac assessment of structural and functional abnormalities

Thus for the detection of CHD, we comprehensively conducted a color doppler TTE and were able to effectively diagnose SVAS in association with bicuspid aortic valve in our patient.

Case Report

A three year old, healthy looking Indian male child was referred to us for evaluation of incidental detection of systolic murmur over precordium. The parents denied any symptom related to cardiovascular system - breathlessness, cyanosis, failure to thrive or recurrent chest infections, etc.

The child's weight was 4.5 kg, height was 90 cm, BP was 80/50 mmHg, HR was 120/min, respiratory rate was 16/min and SPO2 was 97% at room air. Cardiovascular examination revealed apical impulse in the 5th intercostal space, just medial to the mid-clavicular line. A grade 3/6 ejection systolic murmur was best heard in the right sternal edge, in the IIIrd intercostal space with radiation to cervical region. IInd HS was normal. No clicks or gallop sound were heard.

The child had typical "Elfin facies" with the presence of multiple features (Figure 5):

- Prominat forehead
- Widely spaced eyes
- Bilateral epicanthal folds

- Suken nasal bridge
- Upturned nose
- Fullsome cheeks
- Patulous lips
- Small chin

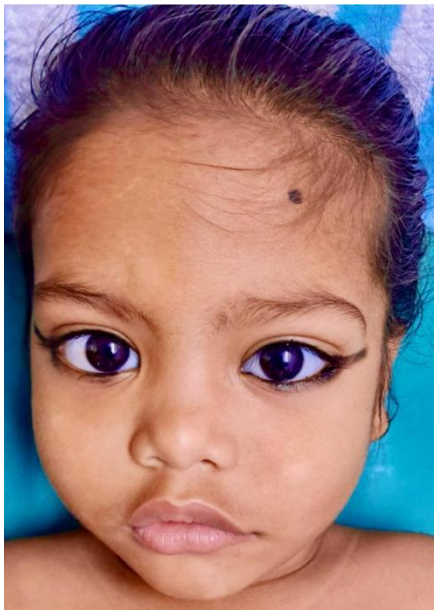


Figure 5: Facial appearance of our index patient.

Xray chest (PA) view demonstrated levocardia with normal pulmonary blood flow (Figure 6).

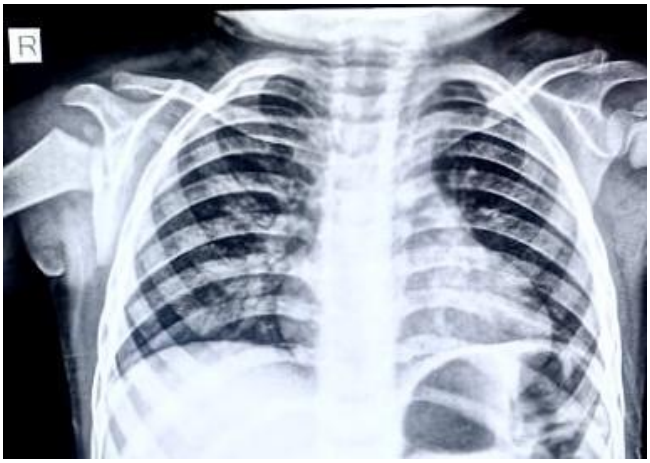


Figure 6: X-ray chest (PA) view- Levocardia with normal pulmonary blood flow.

Resting ECG was normal (Figure 7). There was normal sinus rhythm with a normal QRS axis and ventricular rate of 120/min.

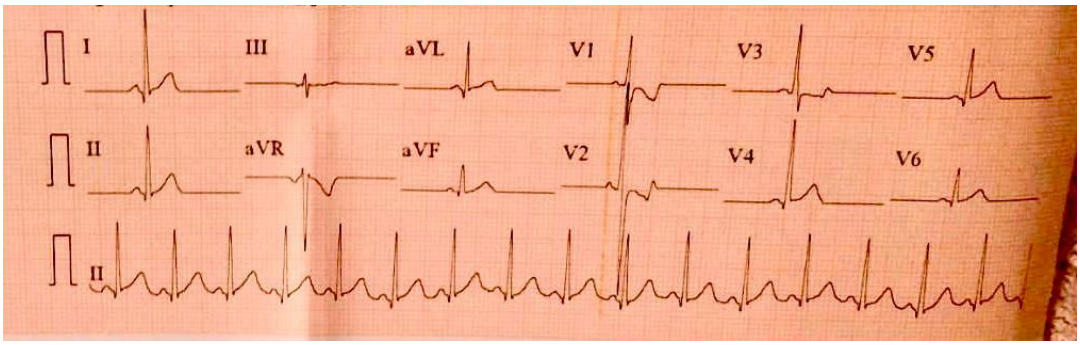


Figure 7: Resting ECG. ECG was normal. It showed sinus rhythm with a normal QRS axis and a ventricular rate of 120/min.

Transthoracic Echocardiography

The echocardiography system - My Lab X7 4D XStrain, Esaote, Italy, was utilized for performing echocardiographic measurements and evaluations using a pediatric probe. Sequential segmental transthoracic echocardiography was performed in the classical subcostal, parasternal long axis (LX), parasternal short axis (SX), 4-Chamber (4CH), 5-Chamber (5CH) and suprasternal views.

M-mode Echocardiography

M-mode echocardiography of left ventricle was performed and the estimated measurements are outlined in Table 1, Figure 8.

Table 1: Calculations of M-mode echocardiography

Measurements	**LV**
IVS d	4.4 mm
ID d	36.3 mm
PW d	4.8 mm
IVS s	7.5 mm
ID s	23.9 mm
PW s	8.8 mm
EF	64 %
%FS	34 %
EDV	55.7 ml
ESV	20.0 ml
SV	35.7 ml
Mass	39 g
IVS, interventricular septum, ID, internal dimension; PW, posterior wall, d, diastole; s, systole; FS, fractional shortening; EDV, end-diastolic volume; ESV, end systolic volume; SV, stroke volume; EF, ejection fraction.	

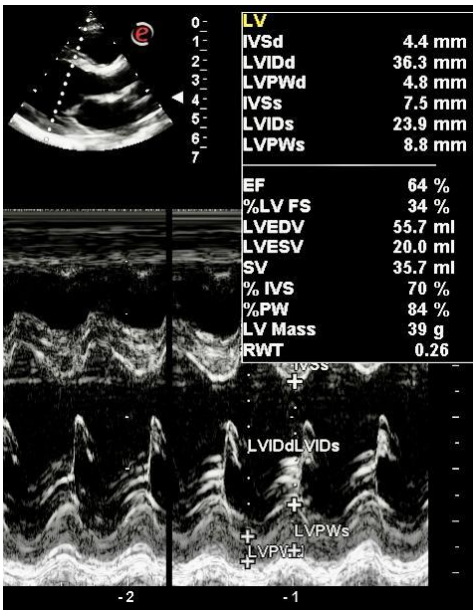


Figure 8: M-mode measurements of LV.

Summary of M-mode echocardiography

LV systolic dimensions and systolic function were normal. LV mass was 39 gm and LVEF was 64 %.

2-Dimensional-Transthoracic Echocardiography

Transthoracic echocardiography (TTE) was systemically maneuvered by the sequential segmental approach (SSA) and the echocardiographic characteristics which were demonstrated are enumerated below:

- Levocardia
- Situs solitus
- AV concordance
- VA concordance
- Concordant d-bulboventricular loop
- Normally related great arteries
- Confluent pulmonary arteries
- Normal systemic and pulmonary venous drainage.
- **Supravalvular aortic stenosis**

1. In the suprasternal view, a conspicuous discrete membrane is identified, at the junction of ascending and arch of aorta (Figure 9). Additionally, the branches of arch of aorta were originating normally from the aortic arch, without any obstruction.
2. The region of insertion of supravalvular aortic membrane (SAM) demonstrated localized narrowing (Figure 10). Ascending aorta dimension in the mid part was 12.5 m and at the narrowed zone was 8.5 mm.
3. On color flow mapping (CFM) in the suprasternal view, a highly turbulent, mosaic pattern flow is displayed across supravalvular membrane (Figure 11).
4. On continuous flow doppler (CWD) analysis peak/mean gradient across SAM was 34.9/17.5 mmHg, suggestive of moderate obstruction (Figure 12).

- Supravalvular pulmonary stenosis was not detected (Figure 13) and similarly no obstruction was discovered in the proximal coronary or renal arteries.
- Mitral Regurgitation

The anterior and posterior mitral valve leaflets were large and thickened (Figure 14A, B) causing mild mitral regurgitation (Figure 14C). The MR jet area was 0.62 sqcm.

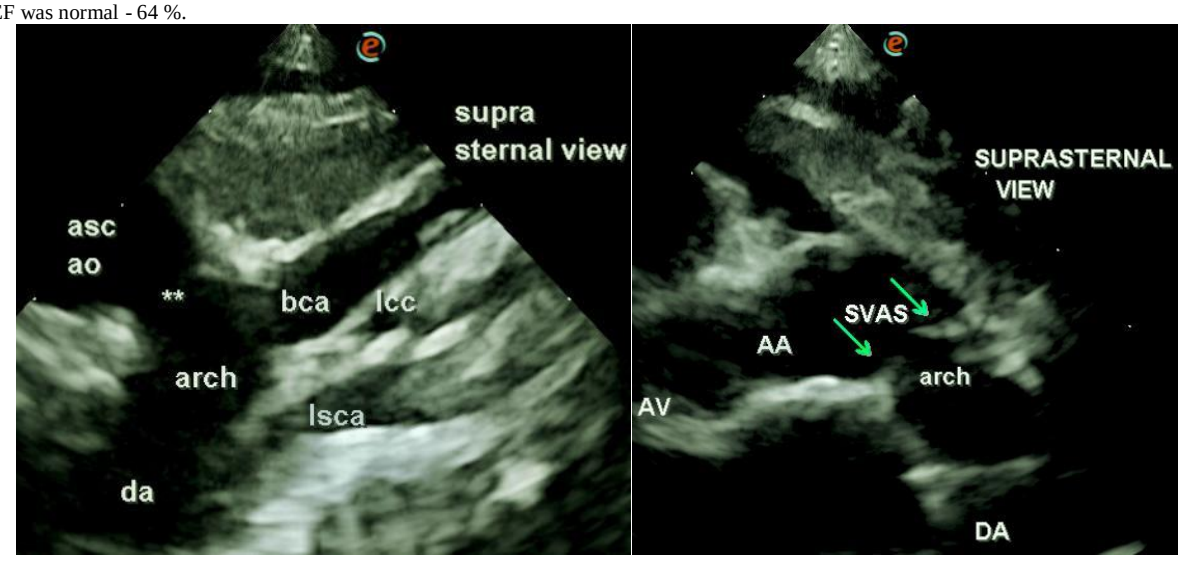
- Bicuspid Aortic Valve

A conspicuous, non stenotic bicuspid aortic valve was also detected (Figure 15).

- Left Ventricular Functions

There was normal biventricular systolic functions and dimensions.

LVEF was normal - 64 %.



(A) **(B)**

Figure 9: Supravalvular aortic membrane is recognized (**) at the junction of ascending and arch of aorta.

Moreover, the branches of arch of aorta are visualized, originating normally from the arch, without any stenosis; (B) Supravalvular aortic stenosis- A distinctive, discrete membrane is displayed at the junction of ascending and arch of aorta; SVAS, supravalvular aortic stenosis; AV, aortic valve; AA, ascending aorta, DA, descending aorta; bca, brachiocephalic artery, lcc, left common carotid artery, lsca, left subclavian artery.

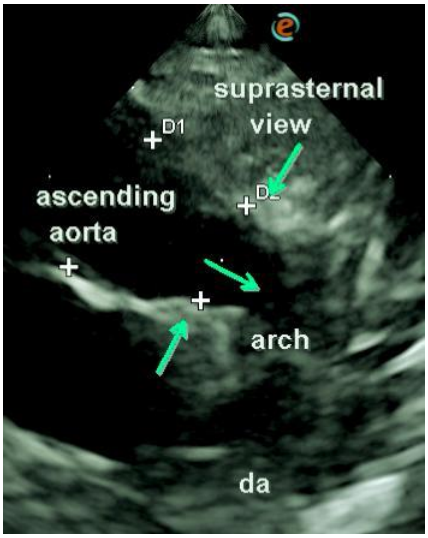


Figure 10: Suprasternal view revealed localized narrowing of ascending aorta just proximal to the site of discrete membrane.

The dimensions at the mid part ascending aorta and proximal to the site of membrane was 12.5 mm and 8.5 mm respectively.

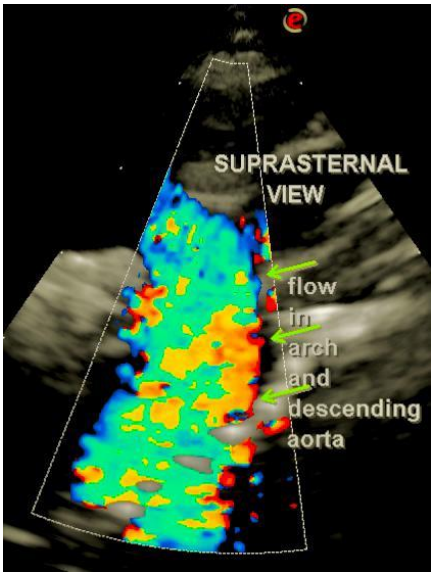


Figure 11: Color flow across supravalvular stenosis- In the suprasternal view, a highly turbulent mosaic pattern flow is illustrated, in the region of aortic arch and descending aorta, consistent with obstruction across supravalvular aortic membrane.

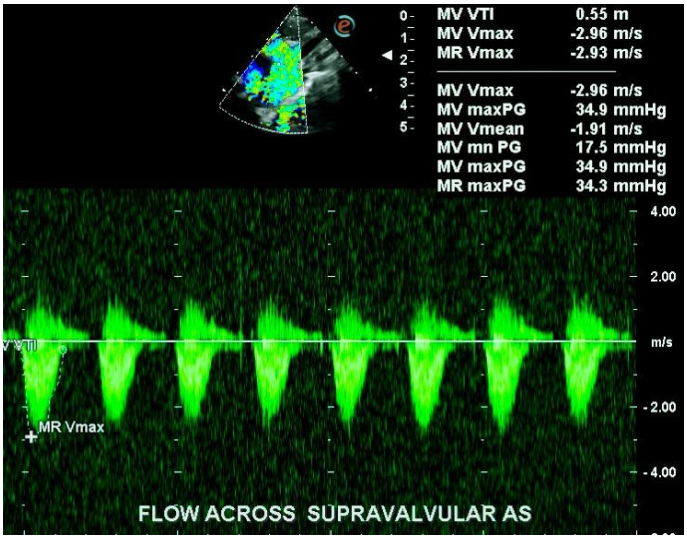


Figure 12: Continuous flow Doppler analysis across the supravalvular aortic membrane. Continuous flow Doppler showed peak/ mean gradient

of 34.9/ 17.5 mmHg , suggestive of moderate obstruction.

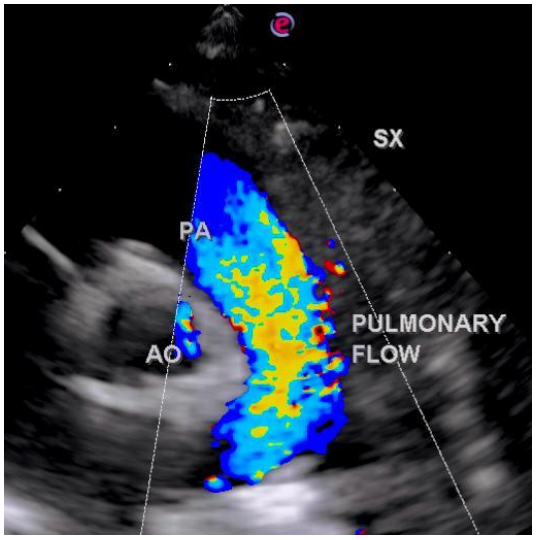
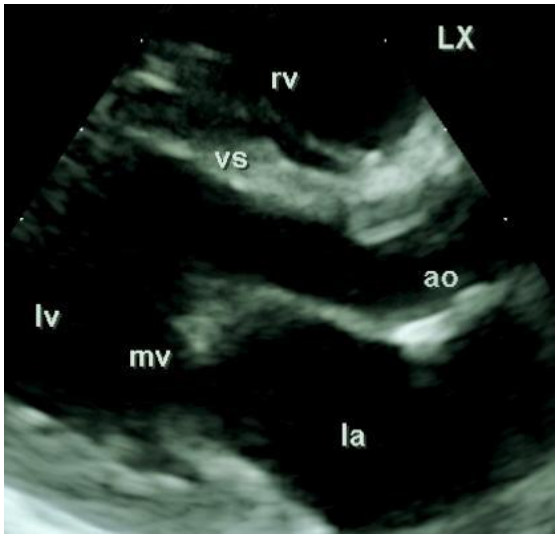
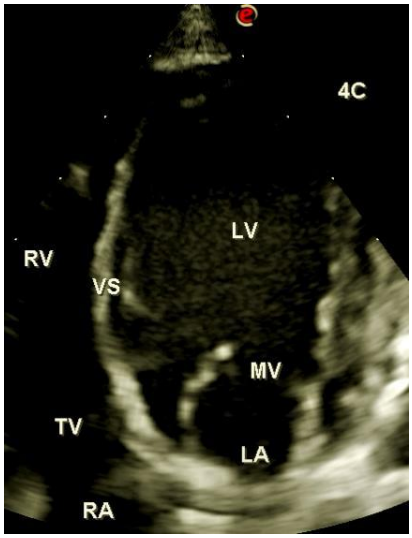


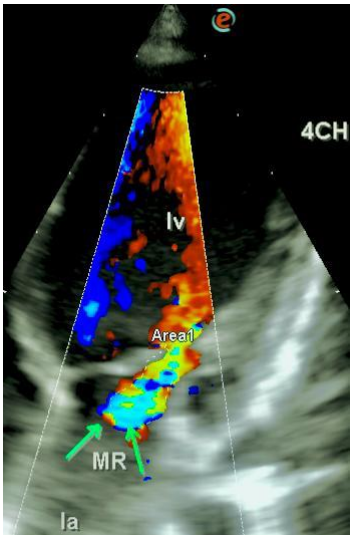
Figure 13: Color flow mapping across RV outflow tract. There was non turbulent flow across right ventricular outflow tract and pulmonary arteries. No supravalvular pulmonary stenosis was identified.



(A)



(B)



(C)

Figure 14: Mitral regulation. (A) In the parasternal LX and (B) apical 4CH views anterior and posterior mitral valve leaflets were elongated and markedly thickened; (C) Mild mitral regurgitation jet was delineated with a jet area of 0.62 sqcm.

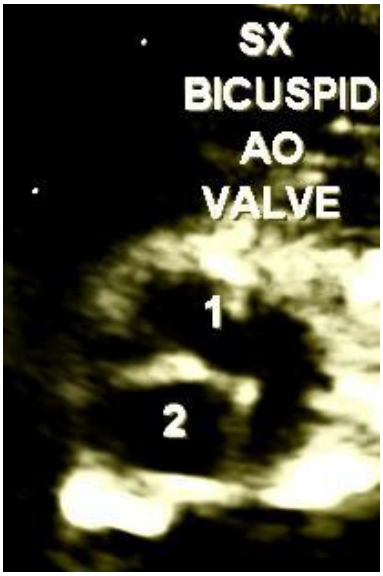


Figure 15: Bicuspid aortic valve.

In the SX view a distinct bicuspid aortic valve was located. There was no stenosis present.

Summary of Transthoracic Echocardiography

On TTE our index patient exhibited discrete, membranous SVAS. It was situated at an atypical location; at the junction of ascending and arch of aorta, with narrowing of minute zone of ascending aorta prior to the membranous SVAS. Non stenotic bicuspid aortic valve was also depicted. Proximal coronary arteries were normally delineated. No ostial stenosis, aneurysm or dilatation was recognized. The systolic function and dimensions of LV were normal.

Discussion

Our patient afflicted with WS displayed characteristic elfin facies and SVAS. TTE is highly sensitive for diagnosing SVAS [7]. TTE was performed in our index patient and it demonstrated moderate SVAS at an atypical location in the ascending aorta. The SVAS was a discrete, membranous obstruction at the junction of ascending and arch of aorta. We did a detailed search of the literature and could not come across a similar case report.

The association of SVAS, SVPS and peculiar facies has been described as Williams' syndrome [13]. Our patient had SVAS and typical elfin facies, even though SVPS was not demonstrated.

SVAS prevalence in approximately 1 of 25,000 live births [14] and accounting for approximately 0.5% of congenital heart diseases cases, but only 30–50% of patients with supravalvular aortic stenosis have WS [15, 16] and about 20 % of cases are familial, and the remaining cases, appear to be sporadic. In our patient, SVAS was not isolated and also had elfin facies and bicuspid aortic valve. Bicuspid aortic valve is associated with WS in 5-12 % of cases [5].

SVAS is frequently diagnosed during evaluation of an asymptomatic heart murmur [17, 18]. Systolic murmur is similar to valvular aortic stenosis, most prominent at upper right and left sternal border with radiation to neck and carotids [19].

Significant SVAS if left untreated, may lead to cardiac hypertrophy followed by heart failure [20]. Although balloon dilation [21] and stent treatment [22] of SVAS has been reported, the close proximity to the aortic valve and coronary artery orifices are noteworthy obstacles, nonetheless, currently surgical correction is the choice treatment. The presence of symptoms warrants prompt consideration for operation surgery [17, 23]. In our case, there was a moderate SVAS and there were no signs of cardiac hypertrophy or heart failure; thus surgery was not necessary. SVAS patients are closely followed up by regular echocardiography and if stenosis gets worse, then surgery may be unavoidable.

Conclusion

Cardiovascular abnormalities are present in about 80% of the cases of WS most frequently SVAS and SVPS. It is suggested that WS should be kept as a differential diagnosis in a child detected to be having a distinctive systolic murmur in presence of dysmorphic facial features.

Our case is of unique with membranous SVAS involving the junction of ascending and arch of aorta accompanied by elfin facies. Because the patient was asymptomatic with a moderate gradient across SVAS, hence, no intervention was advised and we suggested to the parents a regular follow up of the

child with TTE at an yearly interval, to know the progression of obstruction. Hence, it won't be inappropriate to say that WS not only stings and deletes the genes, simultaneous, it may corrode the heart resulting in cardiac lesions.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

Statement of ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee of Prakash Heart Station, Nirala nagar, Lucknow.

Statement of informed consent

Informed consent was obtained from the patient for publication of this case report and accompanying images.

Acknowledgement

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REFERENCES :

1. Moris CB. and Mervis CA. Wiliams syndrome and related disorders, Annual Review of Genomics and Human Genetics. 2000;1:461–484.
2. Kececioglu D, Kotthoff S, and Vogt J. Williams-Beuren syndrome: a 30-year follow-up of natural and postoperative course, European Heart Journal. 1993;14:1458–1464.
3. Eronen M, Peippo M, Hiippala A, Raatikka M, Arvio M, Johansson R, and Kähkönen M. Cardiovascular manifestations in 75 patients with Williams syndrome, Journal of Medical Genetics. 2002;39:554–558.
4. Sabzi F, Heidari A, Faraji R. Congenital combined atresia of the left main coronary with supravalvar aortic stenosis. Ann Card Anaesth. 2018;21:423-426.
5. Collins RT. Cardiovascular disease in Williams syndrome. Curr Opin Pediatr. 2018;30:609-615.
6. Carr M, Curtis S, Marek J. Educational Series In Congenital Heart Disease: Congenital left-sided heart obstruction. Echo Res Pract. 2018;5:R23-R36.
7. Yuan SM. Congenital heart defects in Williams syndrome. Turk J Pediatr. 2017;59:225-232.
8. Elçioglu N, Mackie-Ogilvie C, Daker M, Berry AC. FISH analysis in patients with clinical diagnosis of Williams syndrome. Acta Paediatr. 1998;87:48-53.
9. Metcalfe K, Rucka AK, Smoot L, Hofstadler G, Tuzler G, McKeown P, Siu V, Rauch A, Dean J, Dennis N, Ellis I, Reardon W, Cytrynbaum C, Osborne L, Yates JR, Read AP, Donnai D, and Tassabehji M. Elastin: mutational spectrum in supravalvular aortic stenosis, European Journal of Human Genetics. 2000; 8:955–963.
10. Leme DE, Souza DH, Mercado G, Pastene E, Dias A, Moretti-Ferreira D. Assessment of clinical scoring systems for the diagnosis of Williams-Beuren syndrome. Genet Mol Res. 2013;12:3407-11.
11. Frangiskakis JM, Ewart AK, Morris CA, Mervis CB, Bertrand J, Robinson BF, Klein BP, Ensing GJ, Everett LA, Green ED, Pröschel C, Gutowski NJ, Noble M, Atkinson DL, Odelberg SJ, and Keating MT, LIM-kinase1 hemizygosity implicated in impaired visuospatial constructive cognition, Cell. 1996;86:59–69.
12. Huang SJ, McLean AS. Appreciating the strengths and weaknesses of transthoracic echocardiography in hemodynamic assessments. Cardiol Res Pract. 2012;2012:894308.
13. Matsumoto AH, Delany DJ, Parker LA, and Ney KA, "Massive hemoptysis associated with isolated peripheral pulmonary artery stenosis," Catheterization and Cardiovascular Diagnosis, 1987;13, 313–316, .
14. Ewart AK, Morris CA, Ensing GJ, et al., "A human vascular disorder, supravalvular aortic stenosis, maps to chromosome 7," Proceedings of the National Academy of Sciences of the United States of America, 1993;90:3226–3230.
15. Wiliams JC, Barratt-Boyes BG, and Lowe JB, "Supravalvular aortic stenosis," Circulation, 1961;24:1311–1318.

16. Beuren AJ, Schulze C, Eberle P, Harmjanz D, and Apitz J, "The syndrome of supravalvular aortic stenosis, peripheral pulmonary stenosis, mental retardation and similar facial appearance," The American Journal of Cardiology, 1964;13:471–483.
17. Stamm C, Kreutzer C, Zurakowski D, et al., "Forty-one years of surgical experience with congenital supravalvular aortic stenosis," Journal of Thoracic and Cardiovascular Surgery, 1999;118:874–885.
18. Keane JF, Fellows KE, and LaFarge CG, "The surgical management of discrete and diffuse supravalvar aortic stenosis," Circulation, 1976;54:112–117.
19. French JW and Guntheroth WG, "An explanation of asymmetric upper extremity blood pressures in supravalvular aortic stenosis: the Coanda effect," Circulation,1970;42:31– 36.
20. Cherniske EM, Carpenter TO, Klaiman C et al., "Multisystem study of 20 older adults with Williams syndrome," American Journal of Medical Genetics A, 2004;131:255–264.
21. Jacob JLB, Coehlo WMC, Machado NCS, and Garzon SAC, "Initial experience with balloon dilatation of supravalvar aortic stenosis," British Heart Journal, 1993;70:476–478.
22. De Lezo JS, Pan M, Medina A, Segura J, Pavlovic D, and Romero M, "Acute aortic insufficiency complicating stent treatment of supravalvular aortic stenosis: successful release of trapped leaflets by wiring the stent," Catheterization and Cardiovascular Interventions, 2004;61:537–541.
23. Hazekamp MG, Kappetein AP, School PH et al., "Brom's three-patch technique for repair of supravalvular aortic stenosis," Journal of Thoracic and Cardiovascular Surgery, 1999;118:252–258.