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WILLIAMS SYNDROME: ELFIN FACIES WITH SUPRAVALVULAR AORTIC STENOSIS: A RARE CASE REPORT

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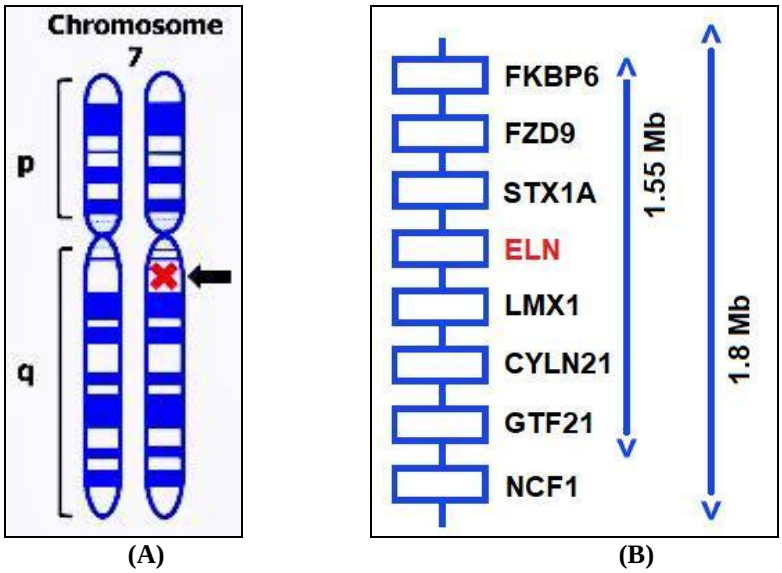
ABSTRACT

We are reporting a rare case of Williams Syndrome (WS) in a three year old female child based on the characteristic facial dysmorphism (ELFIN FACIES) and a significant aortic ejection murmur at the left sternal edge. Transthoracic echocardiography (TTE) disclosed a discrete membranous supravalvular aortic stenosis (SVAS) at an unusual location in the ascending aorta. Due to the presence of above features there was high suspicion of WS. However, genetic testing for confirmation of WS, could not be performed due to the paucity of funds.

KEYWORDS: Williams Syndrome; Chromosome 7q11.23; Elfin Facies; Supravalvular aortic stenosis.

INTRODUCTION

WS is an exceptionally rare autosomal dominant syndrome comprising of variable and myriads of abnormalities including elfin facial dysmorphism, SVAS, peripheral pulmonary artery stenosis, deficient mental ability, short stature, dental malformation, infantile hypercalcemia, etc.[1] The definitive diagnostic feature of WS is microdeletion in chromosome region 7q11.23, enclosing the elastin gene determined by fluorescent in situ hybridization (FISH) test[2, 3] (Figure 1).



(A) (B)

Figure 1: Williams Syndrome: Diagrammatic illustration of deletion of genes on the chromosome 7. (A) Red cross sign denotes the location of deletion 7q11.23; (B) microdeletion in 7q11.23 enclosing the Elastin gene - ELN.

SVAS and/or supravalvular pulmonary and peripheral pulmonary artery stenosis are the commonest cardiac aberrations in WS[3] and about 80 % of cases of WS are reported to be afflicted with a structural cardiac defect[4], particularly SVAS (Figure 2).

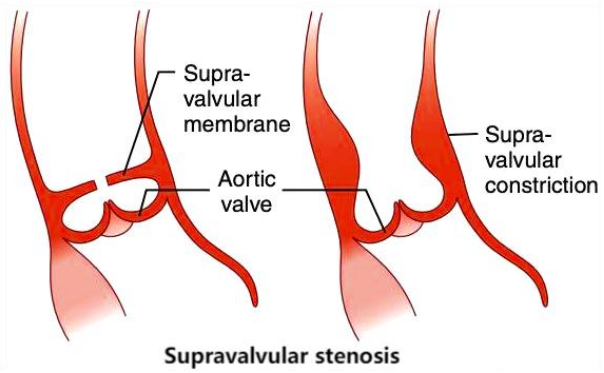


Figure 2: Diagrammatic portrayal of typical location of SVAS.

In clinical practice the presence of combination of typical elfin facies accompanied by SVAS and or pulmonary stenosis may be considered to be strongly suggestive of WS. FISH test is very expensive[5], and therefore in India, FISH test is not conducted in majority of hospitals, due to the paucity of funds.

CASE REPORT

A healthy looking male child of about three years of age 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 left sternal edge, in the IIIrd intercostal space. IInd HS was normal. No clicks or gallop sound were heard.

The child had typical "Elfin facies" with the presence of multiple features (Figure 3).

- Prominat forehead
- Widely spaced eyes
- Bilateral epicanthal folds
- Suken nasal bridge
- Upturned nose
- Fullsome cheeks
- Patulous lips
- Small chin

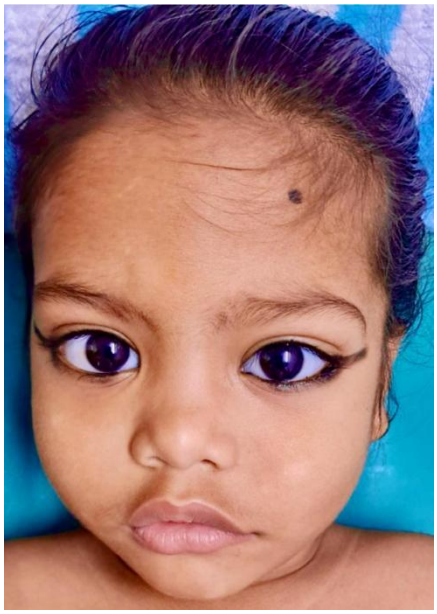


Figure 3: Facial appearance of our index patient.

Xray chest (PA) view demonstrated levocardia with normal pulmonary blood flow (Figure 4).

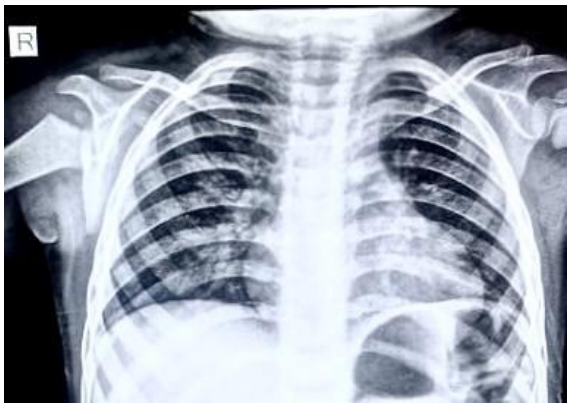


Figure 4. X-ray chest (PA) view- Levocardia with normal pulmonary blood flow.

Resting ECG was normal (Figure 5). There was normal sinus rhythm with a normal QRS axis and ventricular rate of 120/min.

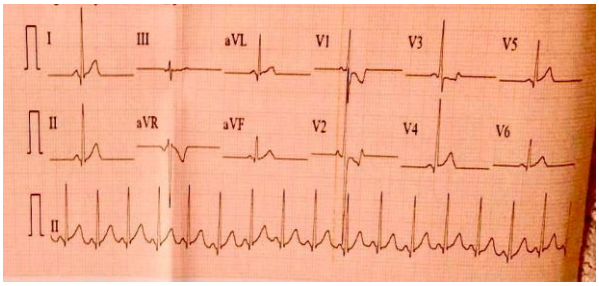


Figure 5: Resting ECG. ECG was normal. It showed sinus rhythm with a normal QRS axis and ventricular rate of 120/min.

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 6.

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.

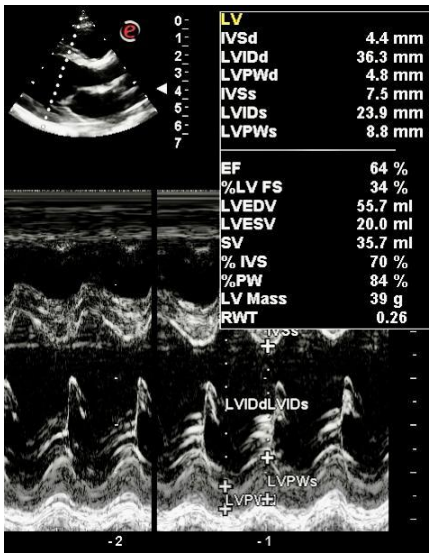


Figure 6: M-mode measurements of LV.

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 performed 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 7). Additionally, the branches of arch of aorta were normally originating from the arch, without any obstruction.
2. The region of insertion of supravalvular aortic membrane (SAM) demonstrated localized narrowing (Figure 8). 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 9).
4. On continuous flow doppler (CWD) analysis peak/mean gradient across SAM was 34.9/17.5 mmHg, suggestive of moderate obstruction (Figure 10).

- Supravalvular pulmonary stenosis was not detected (Figure 11) 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 12A, B) causing mild mitral regurgitation (Figure 12C). The MR jet area was 0.62 sqcm.

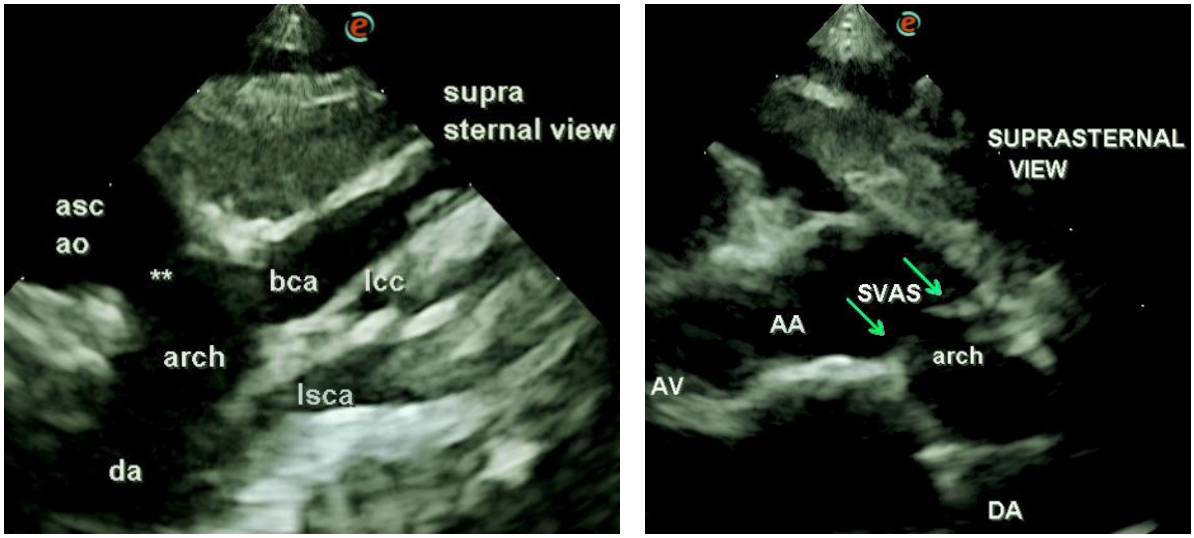
- **Bicuspid Aortic Valve**

A conspicuous, non stenotic bicuspid aortic valve was also detected (Figure 13).

- **Left Ventricular Functions**

There was normal biventricular systolic functions and dimensions.

LVEF was normal - 64 %.



(A) (B)

Figure 7: 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.

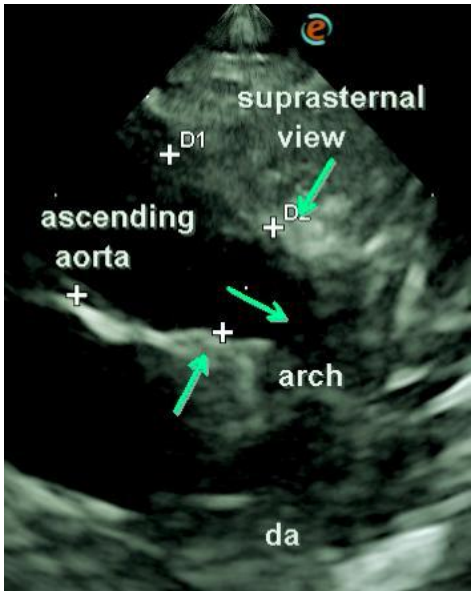


Figure 8: Suprasternal view revealed localized narrowing of ascending aorta just proximal to the site of discrete membrane. The dimensions at the mid part ascending aorta and proximal to the site of membrane was 12.5 mm and 8.5 mm respectively.

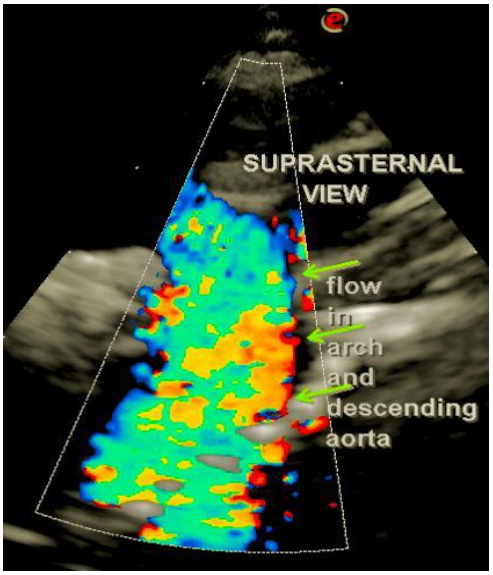


Figure 9: Color flow across supravalvular stenosis- In the suprasternal view, a highly turbulent mosaic pattern flow is illustrated, in the region of aortic arch and descending aorta, consistent with obstruction across supravalvular aortic membrane.

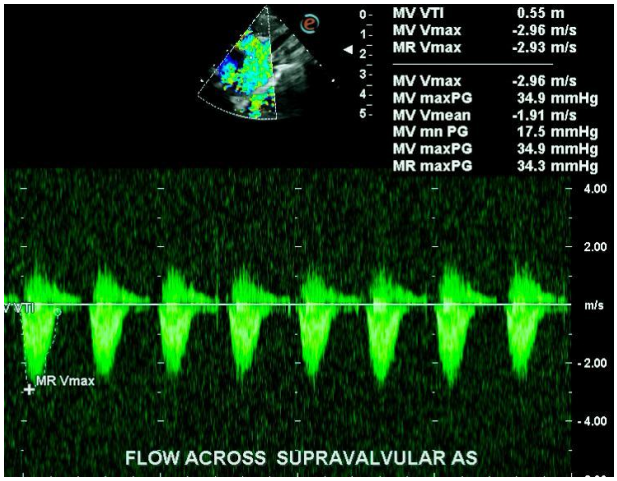


Figure 10. Continuous flow Doppler analysis across the supravalvular aortic membrane. Continuous flow Doppler showed peak/ mean gradient of 34.9/ 17.5 mmHg , suggestive of moderate obstruction.

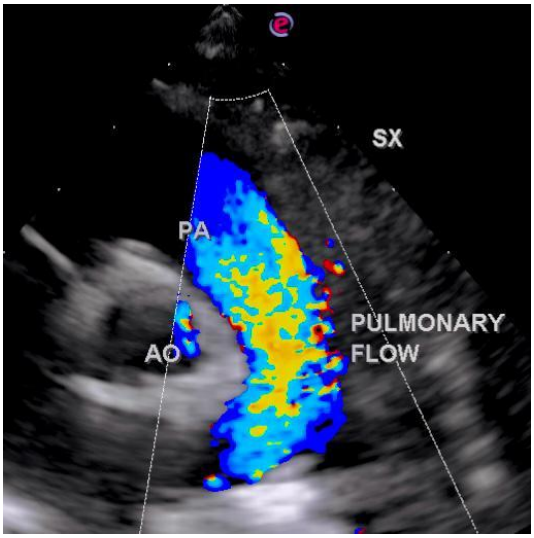
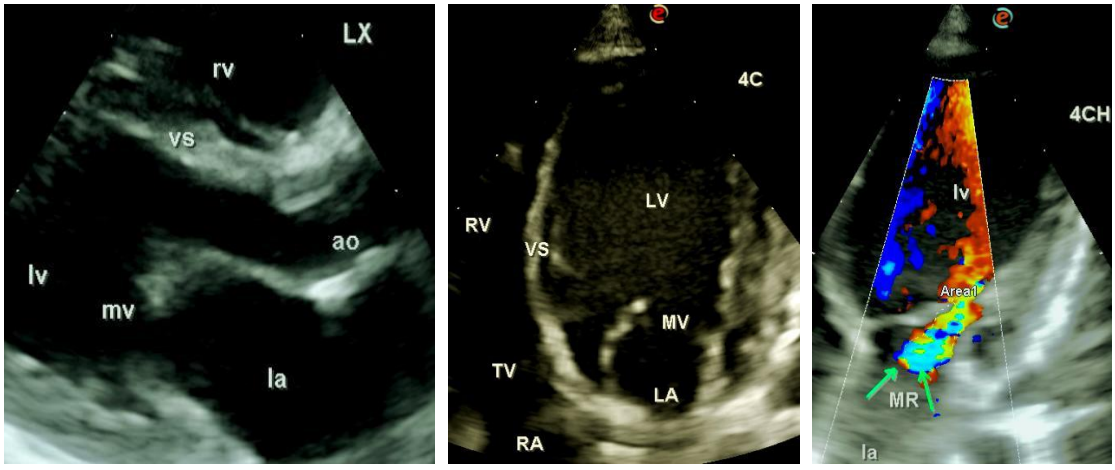


Figure 11: Color flow mapping across RV outflow tract. There was non turbulent flow across right ventricular outflow tract and pulmonary arteries. No supravalvular pulmonary stenosis was identified.



(A) (B) (C)

Figure 12: 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.

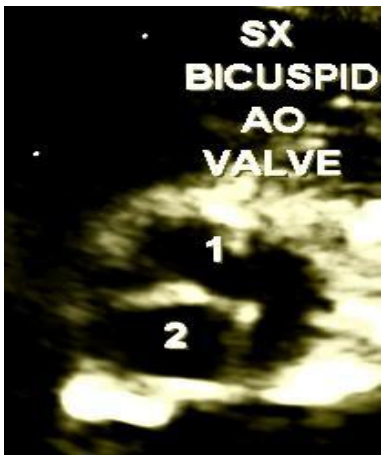


Figure 13: Bicuspid aortic valve. In the SX view a distinct bicuspid aortic valve was located. There was no stenosis present.

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

WS typically is defined by the presence of "ELFIN FACIES", SVAS and/or pulmonary stenosis (generally peripheral pulmonary stenosis) and confirmed by microdeletion of elastin gene on chromosome 7q11.23[4], by the FISH test.[5]

Consequences of deletion of elastin gene

Decreased aortic elastin causes marked pathological aberrations in the aortic wall causing progressive stenosis.[6] The pathological changes occurring are mentioned below.

- Reduced aortic elasticity
- Dysfunction of the endothelium
- Proliferation of Intima
- Increased amounts of fibrous tissue causing fibrosis
- Excessive proliferation of intima and media
- Circumferential growth is reduced
- Progressive secondary thickening of medial wall
- Striking proliferation of cellular matrix
- Excessive axial growth

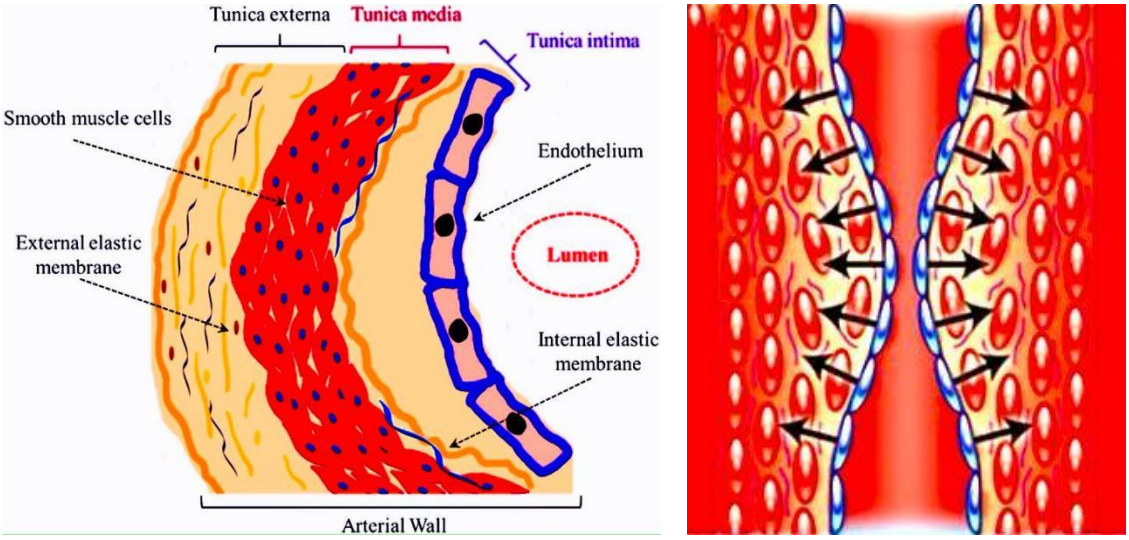


Figure 14: Elastin arteriopathy in Williams syndrome. (A) Anatomy of normal arterial wall [9]; (B) Pathological anatomy of elastin arteriopathy.[6]

Williams Syndrome - arterial narrowing sites

The various locations of arterial stenosis are mentioned in Table 2.

Table 2: Williams syndrome - locations of arterial stenosis [4]
SVAS, discrete hourglass type or a diffuse long segment stenosis
Supravalvular pulmonary artery stenosis
Branch and peripheral pulmonary artery stenosis
Coronary ostial stenosis
Stenosis of thoracic aorta (coarctation at aortic isthmus/long segment stenosis)
Renal arterial stenosis, at the origin of renal arteries.
Systemic arterial stenosis in the arteries of neck, limbs, abdominal aorta, mesenteric arteries, and intracranial vessels.

Structural abnormalities associated with WS.

Several structural anomalies are found in association with WS. They are outlined in Table 3.

Table 3: Cardiovascular anomalies in association with Williams Syndrome [8]	
Cardiovascular anomalies	**Percentage**
Supravalvar aortic stenosis	35-65%
Peripheral pulmonary artery stenosis	37-61%
Long-segment stenosis of the thoracic aorta°	6-14%
Ventricular septal defect	8-21%
Supravalvar pulmonary stenosis	12%
Abnormal mitral valve	20%
Mitral valve prolapse	15%
Mitral valve regurgitation	14%
Abnormal aortic valve	18%
Aortic insufficiency	10%
Abnormal aortic valve cusps	7%
Bicuspid aortic valve	5-12%
Valvar aortic stenosis	4%
Coronary artery anomalies	11-27%

Ostial stenosis	5-9%
Dilated coronary arteries	19-23%
ALCAPA	Rare
Atrial septal defect	3-6%
Ebstein anomaly	Rare
Tetralogy of Fallot	Rare
Total anomalous pulmonary venous return	Rare
Complete atrioventricular canal defect	Rare
Double-chambered right ventricle	Rare
Aortopulmonary window	Rare
Interrupted aortic arch	Rare
Pulmonary artery sling	Rare
ALCAPA, anomalous left coronary artery arising from the pulmonary artery.	

Our index patient demonstrated SVAS at an unusual location of ascending aorta. We have carried out an intensive search of the literature and could not find a similar case report. Even though association of bicuspid aortic valve in WS is rare - 5-12 %[8], however, in our patient non-stenotic bicuspid aortic valve was also detected.

CONCLUSION

Practising physicians, non-invasive cardiologist and general practitioners at large, must contemplate of WS in an infant or child presenting with facial dysmorphism and a systolic murmur over precordium. It is respectfully suggested that a detailed clinical examination alongwith resting ECG and TTE must be performed to confirm the presence of SVAS and/or supravalvular pulmonary stenosis. We must remember that fundamentally, SVAS is an elastin arteriopathy and not confined to aorta or pulmonary arteries.

WS is a progressive disease and may involve multiple and atypical locations. Therefore all patients of WS will require regular ongoing cardiovascular assessment and follow up.

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