Rapid progression of aortic stenosis in a 3-month-old infant with bicuspid aortic valve and DeSanto-Shinawi syndrome

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ABSTRACT

A 3-month-old female was diagnosed at 1 month of age with DeSanto-Shinawi syndrome (DSS) and bicuspid aortic valve with trivial stenosis. The aortic valve stenosis progressed to severe within 2 months and required balloon aortic valvuloplasty. This is the first case of aortic stenosis (AS) associated with DSS, and the syndrome may be the reason for the rapid worsening of AS in this case.

Keywords: Aortic stenosis, chromosome 10p12-p11, Desanto-Shinawi syndrome

INTRODUCTION

Aortic stenosis (AS) due to bicuspid aortic valve is the most common cause of left ventricular outflow obstruction in children. The worsening of AS is usually gradual, and the usual rate of increase of aortic valve gradient is 3–7 mmHg per year due to fibrosis and calcification of the aortic valve.[1]

DeSanto-Shinawi syndrome (DSS) is a rare neurodevelopmental disorder described by DeSanto *et al.* in 2015. The syndrome is characterized by global developmental delay, gastrointestinal and ocular abnormalities, and characteristic dysmorphic facial features.[2] It is associated with loss of function of *WAC* gene. Although there are a few cases reports of association of congenital heart diseases in DSS, the presence of aortic valve stenosis with DSS has not been reported.[3-6] This is the first case report describing the rapid progression of AS in a short period of time in a patient with DSS.

CASE REPORT

A 3-month-old female with DSS had been diagnosed with severe AS. She was born at 30 weeks via C-section, weighing 1140 g at birth, and was admitted to the neonatal intensive care unit. She had constipation, failure to thrive, feeding intolerance, and persistent emesis along with micrognathia, and mild facial dysmorphisms. Chromosomal microarray was obtained and showed 5.30 Mb interstitial deletion of chromosome 10p12.2-p12.1 region including the *WAC* and *ANKRD26* genes.

An echocardiogram performed at 3 weeks of age showed a bicuspid aortic valve [Figure 1] with aortic valve diameter of 4.8 mm (Z score: –1.2) and trivial AS (mean gradient: 13 mmHg) [Figure 2a]. There was no evidence of aortic valve insufficiency. A small patent foramen ovale with left-to-right shunt was also present. The left ventricle was normal in size and systolic function. The aortic arch was normal, with no evidence of coarctation.

She had worsening of the systolic ejection murmur, and a repeat echocardiogram was obtained at 3 months of age, which showed severe AS with peak and mean gradients of 134 mmHg and 69 mmHg, respectively [Figure 2b]. The aortic valve leaflets were moderately thickened, and there

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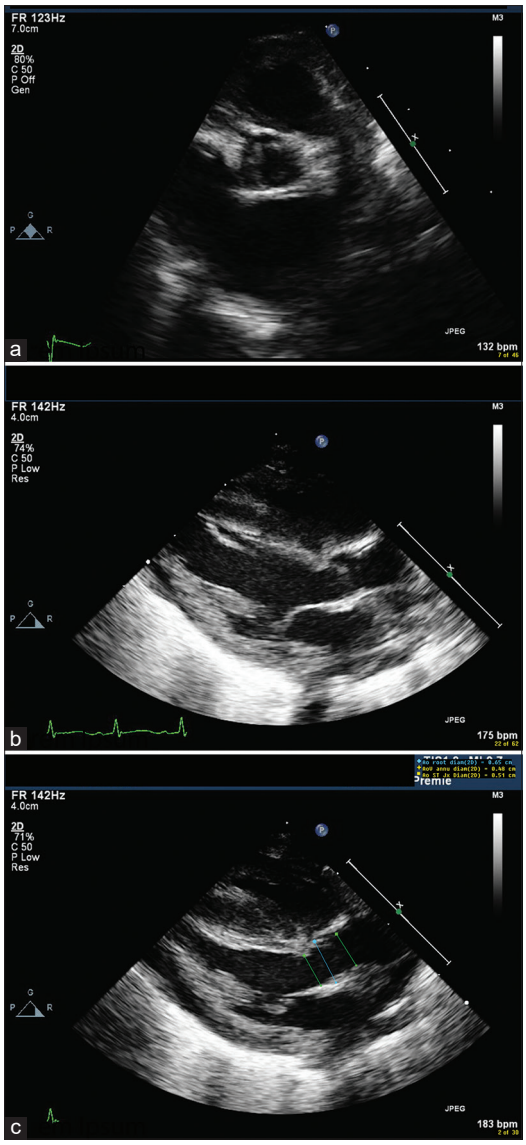

Figure 1: (a) Short-axis parasternal view showing the bicuspid aortic valve with fusion of right and left coronary cusps. (b) Long-axis parasternal view showing bicuspid aortic valve with the doming tips of the valve cusps. (c) Long-axis parasternal view prior to balloon aortic valvuloplasty with measurement. Aortic annulus diameter 6.7 mm (z score: −0.26), aortic root diameter 9.2 mm (z score: −0.46), and aortic sinotubular junction diameter 10 mm (z score: 2.1)

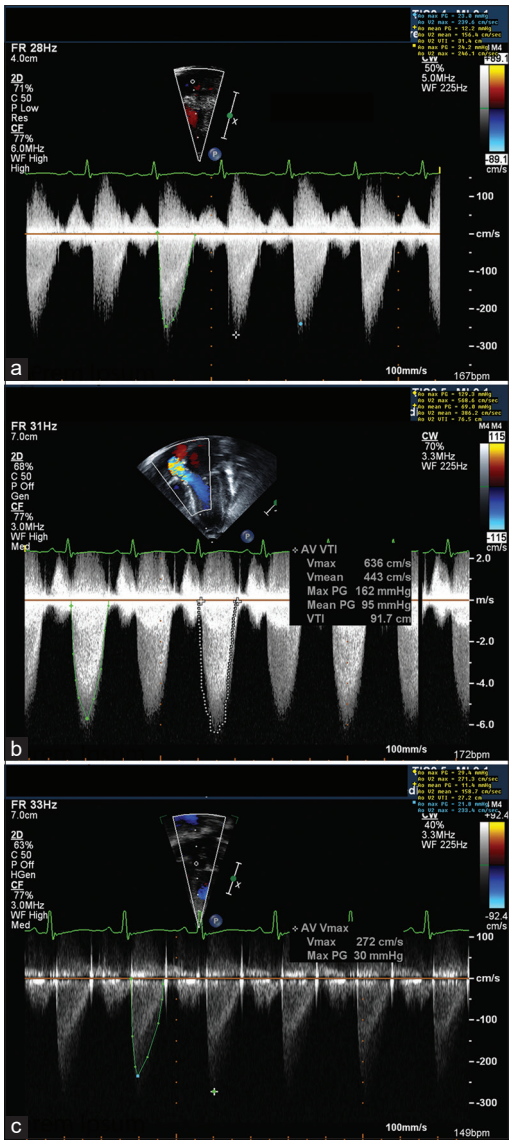

Figure 2: (a) Continuous Doppler imaging from apical five-chamber view, at 3 weeks of age, showing a peak gradient of 23 mmHg and a mean gradient of 13 mmHg across the aortic valve. (b) Continuous Doppler imaging at 3 months of age, showing a peak gradient of 134 mmHg and a mean gradient of 69 mmHg across the aortic valve. (c) Postballoon valvuloplasty showing a peak gradient of 29 mmHg and a mean gradient of 11 mmHg

was mild poststenotic dilation of the ascending aorta along with mild concentric left ventricular hypertrophy. The left ventricular systolic function was normal.

Cardiac catheterization and balloon valvuloplasty were performed at 3 months of age, and simultaneous left ventricle and ascending aorta pressure measurement during the procedure showed a systolic peak gradient of 80 mmHg across the aortic valve. Balloon aortic valvuloplasty with a 6 mm × 2 cm Tyshak II balloon catheter (NuMED, Hopkinton, New York, USA) was performed. The balloon was inflated across the aortic valve on two occasions to a maximum of 5 atmospheres. After the procedure, the peak gradient improved significantly to 20–25 mmHg across the aortic valve, and there was no evidence of aortic insufficiency [Figure 2c]. Follow-up echocardiogram performed 1 month after the valvuloplasty continued to show mild AS with a mean gradient of 22 mmHg and peak systolic gradient of 40 mmHg across the aortic valve. The left ventricle continued to have normal size and systolic function.

DISCUSSION

There are few case reports of congenital heart diseases associated with interstitial deletions at 10p12p11,

which include patent ductus arteriosus, coarctation of the aorta, ventricular septal defect, pulmonary valve stenosis, and bicuspid aortic valve.[3,7] Shahdadpuri *et al.* reported a patient with multiple small ventricular septal defects with biventricular hypertrophy and a bicuspid aortic valve with moderate aortic coarctation requiring balloon dilatation.[7] However, this is the first case of association of DSS with rapid progression of AS requiring intervention reported in published literature.

DSS is a newly discovered genetic disorder characterized by global developmental delay apparent in infancy or early childhood and associated with characteristic dysmorphic facial features, such as broad forehead, depressed nasal bridge with bulbous nasal tip, and deep-set eyes. It is associated with loss-of-function mutations in *WAC*, which encodes a 647 amino acid protein involved in multiple cell processes, including transcription regulation, autophagy, Golgi reformation, and centrosome-independent microtubule generation within the spindle.[2] The patient reported has an interstitial deletion of chromosome 10p12.2-p12.1 region. This deletion contains at least 41 genes, including *WAC* gene implicated in DSS and *ANKRD26* gene in pathogenic variants of which have been associated with *ANKRD26*-related thrombocytopenia, a mild-to-moderate lifelong thrombocytopenia with normal platelet size and no syndromic associations.[8] Among the genes encompassed in 10p12.2-p12.1 region, only these two genes are associated with autosomal dominant genes, which would be the highest likelihood to be affected by a singular microdeletion. However, other microdeletions of the genes in this region could be associated with the cardiac involvement in this patient. In fact, 8 out of 20 previously reported patients with deletion at 10p12 had congenital heart disease.[2,3,5-7,9,10] Among these patients, only two patients had a bicuspid aortic valve.[3,7]

Our patient was diagnosed with bicuspid aortic valve with trivial stenosis at 3 weeks of age but rapidly progressed to severe AS within a 2-month period. There are some diseases which are associated with calcific AS at a younger age and with rapid progress such as Paget disease or end-stage renal disease. However, our patient did not have any of these conditions. DSS may be a potential new genetic syndrome which accelerates the progression of AS. Therefore, we suggest closely follow patients with DSS with aortic valve disease for disease progression.

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Conflicts of interest

There are no conflicts of interest.

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