Cardiology in the Young

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Rapid progression of mitral valve disease in a child with Noonan syndrome

Pezad N. Doctor[1], David K. Lawrence[2] and Amrit Misra[2]

[1]Department of Pediatrics, Children's Hospital of Michigan, Detroit, MI, USA and [2]Division of Pediatric Cardiology, Department of Pediatrics, Children's Hospital of Michigan, Detroit, MI, USA

Brief Report

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Author for correspondence:
Pezad Doctor, MD, Department of Pediatrics, Children's Hospital of Michigan, 3901 Beaubien Boulevard, Detroit, MI 48201, USA.
Tel: +1 203 868 6048.
E-mail: pezaddactor@gmail.com

Abstract

Noonan syndrome is the second most common genetic syndrome associated with congenital heart disease after Trisomy 21. The two most common cardiac lesions associated with Noonan syndrome are pulmonary stenosis and hypertrophic cardiomyopathy. Although the incidence of mitral valve disease in Noonan syndrome ranges between 2 and 6%, rapid progression of mitral valve dysplasia causing severe mitral valve regurgitation and left atrial dilatation is seldom seen. Most cases of mitral valve disease have been diagnosed either on routine echocardiographic surveillance or when presented with heart failure symptoms. We describe an 18-month-old boy with Noonan syndrome presenting in atrial flutter due to a massively enlarged left atrium caused by severe mitral valve regurgitation which developed and progressed in less than 17 months.

Noonan syndrome is a genetically heterogeneous disorder with an incidence ranging from 1 in 1000 to 1 in 2500 live births.[1] Cardiovascular disorders are known to occur in as high as 80–90% of patients with Noonan syndrome.[2] Pulmonary stenosis, hypertrophic cardiomyopathy, atrial septal defects, and patent ductus arteriosus are more common, whereas mitral valve disease, aortic root dilatation, aortic valve stenosis, coarctation of aorta, and tetralogy of Fallot are much rarer.[3] Due to the rarity of mitral valve disease in this cohort, its clinical presentation, management, and prognosis are not well known.[4] In our case, rapid progression of mitral valve dysplasia led to left atrial dilatation and recurrent atrial tachyarrhythmia, emphasising the need for close follow-up to allow prompt identification and prevent complications.

Case

The presented patient was born at 32 weeks gestation with a perinatal history significant for polyhydramnios, bilateral hydro-nephrosis, and in-utero cocaine exposure. He was noted to have dysmorphic features which included low-set ears, frontal bossing, low nasal bridge with transverse crease, and a large anterior fontanelle in the neonatal period. Genetic analysis identified a pathogenic heterozygous mutation in *RAF1* (c.770C > T, p. Ser257Leu) gene confirming the diagnosis of Noonan syndrome. An echocardiogram performed at 1 month of age was notable for a small patent ductus arteriosus, a patent foramen ovale, and a normal mitral valve (Fig. 1a and b). The size and function of the left ventricle was normal. A follow-up echocardiographic assessment at 3 months of age revealed mild dysplasia of the mitral valve leaflets with mild insufficiency. The patient did not return for a scheduled 3-month follow-up.

At 18 months of age, he presented to the emergency department secondary to increased work of breathing, increased precordial activity, fussiness, and decreased oral intake for 1 day. On presentation, his heart rate was 235 beats/minute, respiratory rate 52/minute, blood pressure 72/48 mmHg, and oxygen saturation 98% in room air. Chest radiogram showed cardiomegaly with upturned cardiac apex and pulmonary vascular congestion. Electrocardiogram was notable for a regular, narrow complex tachyarrhythmia (Fig. 2). Intravenous adenosine administration unmasked flutter waves, confirming the diagnosis of atrial flutter with 3:1 ventricular conduction. The child underwent synchronised electrical cardioversion, successfully converting him to sinus rhythm. An echocardiogram revealed a moderately dysplastic mitral valve with prolapse of the anterior leaflet causing severe mitral insufficiency (Fig. 1c and d). The posterior leaflet motion appeared to be limited and was adherent to the inferolateral wall of the left ventricle. The mitral valve leaflets were thickened with no apparent cleft present. The chordal attachments did not appear to obstruct the left ventricular outflow tract. The left atrium was massively dilated (Fig. 1c). He had mild left ventricular hypertrophy with posterior wall thickness measuring 8.5 mm (z score: +3.5) and interventricular septum measuring 6.7 mm (z score: +1.9) with mild left ventricular dilation visually (left ventricle internal diameter of 27 mm; z score: −0.28 in diastole and 13 mm; z score: −2.4 in systole). He was admitted to the paediatric intensive care unit for the management of heart failure symptoms. Diagnostic cardiac catheterisation was performed which showed small left-to-right shunts via a patent foramen ovale and tiny patent ductus arteriosus, yielding a net pulmonary-to-systemic blood flow ratio of 1.3. The left atrial and left ventricular end diastolic pressures were 12 and

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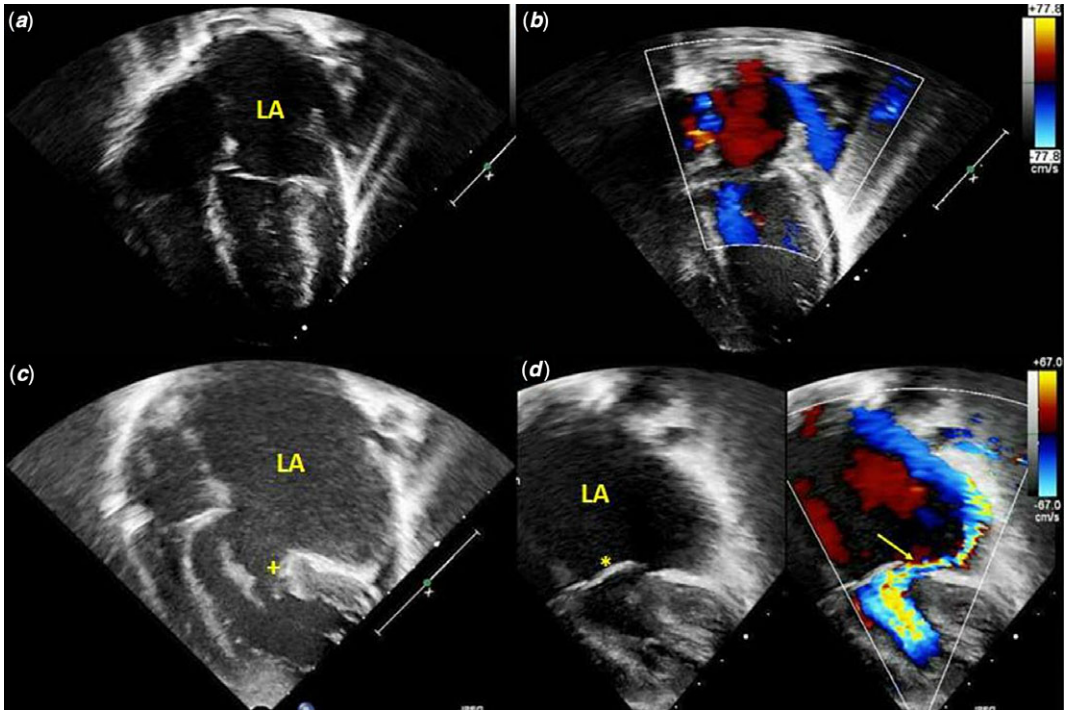

Figure 1. (***a***) Apical four-chamber view at 1 month of age shows normal size left atrium. (***b***) Focused color Doppler imaging shows a competent mitral valve with no regurgitation across it. (***c***) Apical four chamber view at 18 months of age shows massively dilated left atrium with dysplastic posterior leaflet of mitral valve (plus sign) adherent to the inferolateral wall of the left ventricle. (***d***) Focused color Doppler imaging shows eccentric jet of mitral regurgitation (arrow) with prolapse of the anterior leaflet of mitral valve (asterisk).

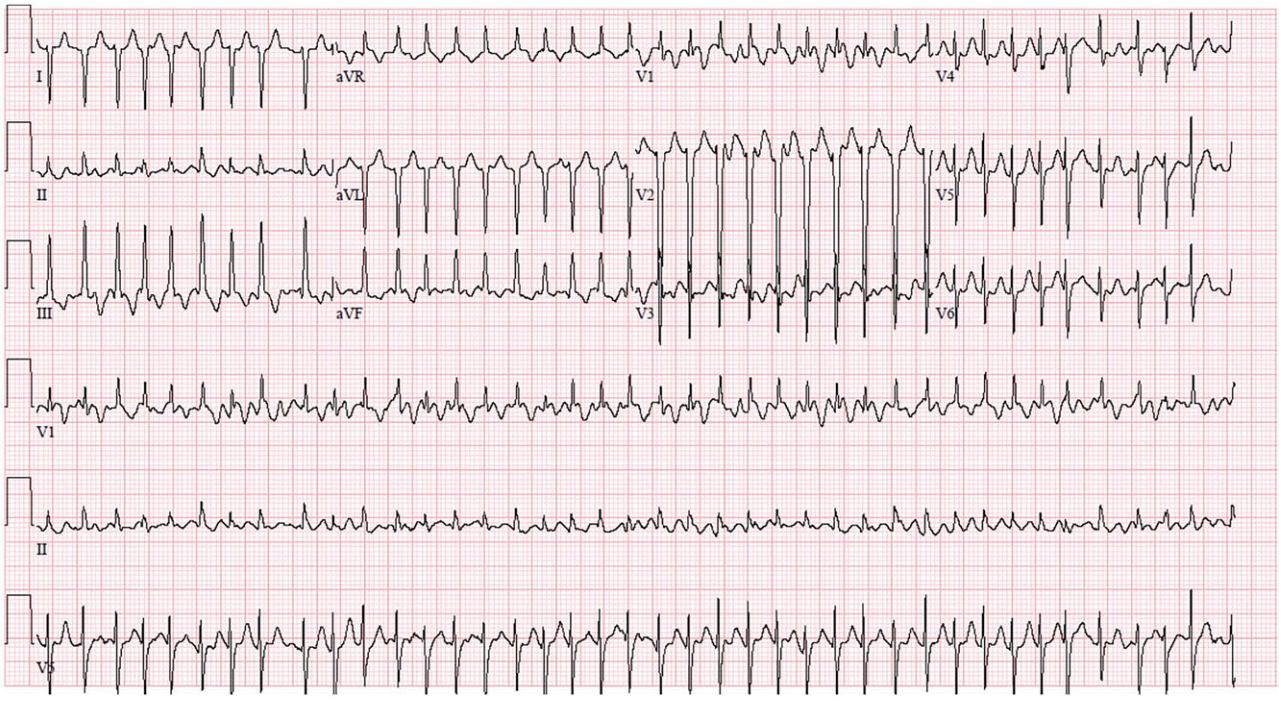

Figure 2. Electrocardiogram shows regular narrow complex tachyarrhythmia with a ventricular rate of 230 beat per minute.

15 mmHg, respectively. There was no significant gradient across the right or left ventricular outflow tracts. His symptom improved significantly and was discharged home on oral amiodarone, furosemide, and enalapril with close follow-up in the clinic. However, he had recurrent episodes of atrial flutter requiring hospital admission at 22 and 23 months of age. Presently, the cardiovascular surgical team is evaluating him for mitral valve replacement and Cox-Maze procedure.

Discussion

The reported incidence of mitral valve disease in Noonan syndrome ranges from 2 to 6%.[2,5,6] In the last 2 decades, a few studies have elucidated genotypic–phenotypic correlation with important prognostic implications.[2] *PTPN11* gene mutation is the most common gene affecting 40–50% of the cases whereas *RAF1* gene mutations account for 3–17% of the cases with Noonan syndrome.

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In a case series, mitral valve anomaly was noted in about 13% of cases with a mutation in the *RAF1* gene.[3] Genetic sequencing in our patient revealed a pathogenic mutation in the *RAF1* gene.

Different mitral valve abnormalities have been reported in Noonan syndrome. In a post-mortem case series, grossly thickened and loose myxomatous mitral valve leaflets with shortened chordae and diminished interchordal space were noted.[7] Another series described partial atrioventricular canal defects and anomalous insertion of mitral valve over the interventricular septum.[4] Annular dilation and prolapse of the mid portion of anterior mitral leaflet causing mitral regurgitation have also been reported.[11] Our patient had thickened, dysplastic mitral valve leaflets, with prolapse of the anterior mitral leaflet leading to severe regurgitation, as well as a posterior valve leaflet that was tethered to the lateral left ventricular wall.

Most cases of mitral valve disease in Noonan syndrome have been detected via routine echocardiographic surveillance or following presentation with symptoms of heart failure.[8–11] Some cases have also presented as sub-aortic obstruction due to anomalous insertion of the anterior mitral valve leaflet into the left ventricular outflow tract.[4] Our case presented with atrial tachyarrhythmia due to an enlarged left atrium from severe mitral valve insufficiency. His left ventricle end-diastolic pressure was mildly elevated (15 mmHg). Therefore, his left ventricle hypertrophy was unlikely to cause severe left atrial dilatation. It was interesting to note that his mitral valve disease progressed rapidly as the echocardiogram performed at 1 month of age displayed no abnormalities of the mitral valve or left atrial dilation. Mild mitral valve dysplasia with mild accompanying insufficiency was noted 2 months following his initial echocardiogram. Unfortunately, the patient was lost to follow-up. A case of rapidly progressing enlargement of the left atrium and left ventricle due to worsening mitral regurgitation over 1 year was reported in an 18-year-old woman with Noonan syndrome.[8] She was detected on routine follow-up and was asymptomatic at the time of diagnosis. However, that patient had mitral insufficiency characterised as "moderate" on her prior examination.

Our patient was discharged home on oral amiodarone after his initial hospital stay at 18 months of age. Despite adherence and dose escalation of amiodarone, he developed recurrent episodes of symptomatic atrial flutter at 22 and 23 months of age requiring cardioversion and hospitalisation. This was expected due to his massively enlarged left atrium providing a substrate for atrial flutter. He is presently under evaluation for mitral valve replacement and Cox-Maze procedure for recurrent atrial flutter. Due to the paucity of data with regards to the clinical presentation, progression, and management of mitral valve disease in Noonan syndrome, close monitoring is essential for early identification and timely intervention.

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Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards. No human or animal experimentation was done.

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