CASE REPORT

Prolapse of all cardiac valves in Noonan syndrome

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SUMMARY

Noonan syndrome is an autosomal dominant disorder with genetically heterogeneous inheritance. The incidence of cardiac abnormalities is higher in patients with Noonan syndrome and approximately 80% patients with Noonan syndrome are reported to have cardiac abnormalities during their lifetimes. However, polyvalvular disease in Noonan syndrome is rare. In this case-report, we describe a case of a young man whose features were strongly suggestive of Noonan syndrome and who was diagnosed with prolapse of all four cardiac valves after 22 years of uneventful survival.

BACKGROUND

Noonan syndrome (NS) is an autosomal dominant genetic disorder with an estimated incidence between 1 in 1000 to 1 in 2500 live-births.¹ It is a

genetically heterogeneous disorder. Although several causative genes of NS, namely PTPN11 (50%), SOS1 (10–15%), KRAS (2%), NRAS (<1%), SHOC2 (<1%), RAF1 (5–10%), CBL (<1%), RIT1 and BRAF, have been identified, approximately 30% of cases still have unexplained aetiology.^{2–5} However, next-generation sequencing proves helpful in identifying rare variants (ie, RASA2, NF1, MAP2K1, MAP3K8, SPRY1) associated with NS.⁵

The incidence of structural cardiac abnormalities is higher in NS.⁶ Although virtually all types of cardiac defects have been reported in NS, pulmonary valve stenosis with dysplastic leaflets is the most common cardiac anomaly.^{6–8} The prolapse of mitral valve (either isolated or in association with other cardiac anomalies) has been reported.⁹ There are few case reports available that describe polyvalvular disease in patients with NS. However, in a

Figure 1 (A) Parasternal short axis view showing prolapse of pulmonary valve and (B) parasternal right ventricular outflow view showing prolapse of pulmonary valve leaflet with mild regurgitation.

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Figure 2 (A) Parasternal long axis view showing billowing mitral leaflets and (B) parasternal short axis view showing scalloping of P1 and P2 segments of mitral leaflets.

majority of the cases, the patients died.^{10–12} In this case-report, we report a case of a young man who was phenotypically diagnosed with NS and was examined thoroughly for cardiac abnormalities due to suggestive symptoms. On systematic cardiac examination, we found polyvalvular disease—prolapse of all four cardiac valves. Unlike the reported cases, the patient had uneventful survival until the age of 22 years. The patient is currently being treated medically with regular follow-up.

CASE PRESENTATION

A 22-year-old man presented to our clinic with exertional dyspnoea of New York Heart Association (NYHA) class-I for the past 6 months. He was born of a non-consanguineous marriage and was first in birth order. The second sibling died of congenital heart disease with heart failure (certified by a paediatrician) at the age of 1 month. However, other details were not available. The other siblings were surviving uneventfully so far.

The patient had normal growth except for delay in mentation. He had poor scholastic performance as well. He had characteristic dysmorphic features, which included triangular facies, ptosis, epicanthal folds, low set ears, low hair line, webbed neck, widely spaced nipples and syndactyly of toes. His height (168 cm) was appropriate for his age. He had underdeveloped and undescended testes for which he underwent bilateral orchidectomy in childhood, but the secondary sexual characters developed normally. Genotyping showed normal male (XY) karyotype.

INVESTIGATIONS

On the basis of characteristic features, we suspected NS in this patient. As there is high incidence of cardiac abnormalities in NS and the symptoms of the patient were also suggestive of a cardiac problem, we carried out systemic cardiac examination of the patient.

Figure 3 M-mode across mitral leaflets showing prolapse of mitral leaflets (arrows).

Figure 4 Parasternal long axis view showing elongated chordae with mild regurgitation; (B) parasternal short axis view showing two regurgitant jets arising from P1 and P2 segments of posterior segment of mitral leaflets and (C) apical four-chamber view showing mild mitral regurgitation.

On auscultation, we found systolic murmur of grade 2/6 in the second left intercostal space. Transthoracic echocardiography (TTE) was performed to evaluate the patient for cardiac defects, which showed a concordant atrioventricular and ventriculoarterial connection. There was no transposition of great arteries but abnormalities of all the valves were observed. There was a prolapse of pulmonary valve with mild regurgitation

(figure 1). However, pulmonary stenosis or pulmonary hypertension was not observed. We found myxomatous mitral valves with prolapse (figures 2 and 3), which resulted in mild mitral regurgitation (figure 4). TTE in parasternal long-axis and short-axis view revealed prolapse of right coronary cusp of the aortic valve (figure 5). There was a mild regurgitation of tricuspid valve due to prolapse of septal leaflet of the tricuspid valve

Figure 5 (A) Parasternal long axis view showing prolapse of right coronary cusp of aortic valve and (B) parasternal short axis view showing prolapse of right coronary cusp of aortic valve.

(figure 6). Left ventricular function was normal. However, there was no evidence of hypertrophic cardiomyopathy or enlargement of cardiac chambers. The ECG, coagulation profile, renal function test, liver function test and ultrasound of abdomen were found to be normal.

We evaluated (phenotypically) first degree relatives of the patient for the presence of NS but none of them was found to have NS.

TREATMENT

Since there was no severe regurgitation, we decided on medical management of the patient with regular follow-up. The patient is currently managed in accordance with the guidelines for valvular heart disease.

DISCUSSION

NS was first described by Noonan and Ehmke based on characteristic phenotypic features associated with pulmonary stenosis.¹ The diagnosis of NS is suspected based on the characteristic phenotypic features, but due to variable expressivity of phenotype, NS may remain undiagnosed in many cases.

Several scoring systems have been developed to aid the diagnostic process. However, the scoring system developed by Van der Burgt has been used widely for diagnosis of NS.¹³ The scoring system includes major as well as minor criteria (table 1). Definitive NS criteria include major criterion (1A) plus one other major sign (2A to 6A) or two minor signs (2B to 6B); minor criterion (1B) plus two major signs (2A to 6A) or three minor signs (2B to 6B). Our patient had one major (1A) and four minor criteria, that is, suggestive facies (triangular face, ptosis, epicanthal folds, low set ears and low hair line), prolapse of all cardiac valves and broad thorax as well as mild developmental delay with cryptorchidism (B1, B2, B4 and B6, respectively), making a diagnosis of definitive NS as per the criteria. In our patient, genetic diagnosis was not possible due to financial constraints. As the patient had cardiac abnormality along with NS and one other sibling of the patient died due to heart failure, we phenotypically evaluated first degree relatives of the patient for NS. However, none of them was found to have NS.

It has been found that a majority of patients with NS (~80%) have cardiac abnormalities.⁶ The most commonly

described valvular abnormality in NS is dysplasia of the pulmonary valve often associated with pulmonary stenosis. The malformations of other cardiac valves in NS, particularly the mitral and aortic valves, have also been reported.⁶⁻⁹ There have also been rare cases of all the cardiac valves being affected in patients with NS.

Bonnet *et al*¹¹ had retrospectively studied atrioventricular valve dysplasia in 22 new-born infants. They found dysplasia of all four cardiac valves along with left ventricular hypertrophy in one patient who was phenotypically diagnosed with NS and, as a consequence of dysplasia of the mitral and tricuspid valves, there was trivial tricuspid regurgitation and mitral regurgitation (follow-up was not available). Apart from the above reported case, the pathological reports of four infants who were phenotypically diagnosed with NS were published by Sreeram *et al*¹² in 1994. The authors described cases of four infants who presented abnormal physical signs related to the cardiovascular system in the first year of life. Initially, all the patients were diagnosed with dysplastic pulmonary valve and hypertrophic cardiomyopathy. However, the postmortem reports revealed dysplasia of the pulmonary valve (in four patients), mitral valve (in four patients), tricuspid valve (in four patients) and aortic valve (in three patients), along with hypertrophic cardiomyopathy (in four patients). Feit *et al*¹⁰ had also reported an unusual case of an infant who was diagnosed phenotypically with NS. The infant was diagnosed with large atrial septal defect, mild hypertrophy of left ventricle as well as thickening of all cardiac valves during cardiac evaluation at birth. The mitral valve was cleft along with having mild regurgitation. The patient developed congestive cardiac failure and died after 4 weeks of life.

In the above mentioned case reports, the patients were infants. The infants died as a result of cardiac abnormalities in the case reports by Sreeram *et al*¹² and Feit *et al*,¹⁰ and the outcome was unknown in the case report by Bonnet *et al*,¹¹ whereas in our case, the patient remained asymptomatic until 22 years of age and presented with prolapse of all the cardiac valves. In our case, there was no evidence of hypertrophic cardiomyopathy. We decided to manage the patient according to ACC/AHA guidelines for valvular heart disease with regular follow-up because there was only mild regurgitation.¹⁴

Figure 6 (A) Apical four-chamber view showing billowing of tricuspid valve leaflets with two regurgitant jets and (B) parasternal right ventricular outflow view showing billowing of tricuspid valve leaflets with mild tricuspid regurgitation.

Table 1 Scoring system of Noonan syndrome developed by Van der Burgt

	Feature	A=Major	B=Minor
1	Facial	Typical face dysmorphism	Suggestive facies
2	Cardiac	Pulmonary valve stenosis, hypertrophic cardiomyopathy and/or ECG typical of Noonan syndrome	Other cardiac defect
3	Height	<3rd centile	<10th centile
4	Chest wall	Pectus carinatum/excavatum	Broad thorax
5	Family history	First degree relative with definite Noonan syndrome	First degree relative suggestive of Noonan syndrome
6	Other	All of the below 1. Mental retardation 2. Cryptorchidism 3. Lymphatic dysplasia	Any of the below 1. Mental retardation 2. Cryptorchidism 3. Lymphatic dysplasia

Learning points

- ▶ Noonan Syndrome remains undiagnosed in many cases until it presents with clinical abnormalities such as congenital heart defects, learning disabilities, cryptorchidism in men, bleeding diathesis and lymphatic abnormalities. Clinical evidence of Noonan syndrome by evaluation of phenotype (dysmorphic facies) in neonatal care or in paediatric follow-up would prove helpful in early recognition of clinical abnormalities.
- ▶ All patients with Noonan syndrome should be carefully examined for cardiac abnormalities as these can manifest at any stage of their lives.
- ▶ Although prolapse of all cardiac valves is extremely rare in Noonan syndrome, it can be detected as late as after 22 years of uneventful survival.

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Competing interests None.

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