Management of Cardiovascular Disorders in Patients with Noonan Syndrome: A Case Report

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Abstract

The Noonan syndrome is a rare disorder, one of whose major complications is cardiovascular involvement. A wide spectrum of congenital heart diseases has been observed in this syndrome. The most common cardiac disorder is pulmonary valve stenosis, which has a progressive nature. Hypertrophic cardiomyopathy is less common, but its morbidity and mortality rates are high. We herein introduce a 12-year-old boy with the typical findings of the Noonan syndrome. His symptoms began from infancy, and there was a gradual exacerbation in his respiratory and cardiac manifestations with age. The cardiac involvement included right ventricular outflow tract and pulmonary valve stenosis, hypertrophic cardiomyopathy, and subaortic valve stenosis. Due to the progressive course of the disease, surgical repair was done. Although the patient had a difficult postoperative period, his general condition improved and he was discharged. At 3 months’ follow-up, his symptoms showed improvement. Additionally, there was a reduction in the echocardiographic parameters of the outflow tract stenosis gradient as well as a significant improvement in the cardiac hemodynamic indices.

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Introduction

The Noonan syndrome is a rare disorder with diverse body organs involvement and one of the main organs that involved in this syndrome is cardiovascular system.1 The most common cardiac disorder is pulmonary valve stenosis, which has a progressive nature. Hypertrophic cardiomyopathy is less common. The Noonan syndrome is a genetic disorder that usually was observed as sporadic pattern but autosomal transmission also was seen. Because the cardiac diseases have progressive nature in Noonan syndrome development of cardiac symptoms and signs necessitate careful cardiac evaluation and prompt treatment.1,2

Case Report

A 12-year-old boy was admitted to our hospital due to shortness of breath, exertional dyspnea, and exercise intolerance. Based on his past medical history as an infant,
the 1st signs had begun when he was 4 months old by bluish discoloration of the lips, lethargy, and poor feeding. His mother declared that her child suffered from inguinal hernia but that he had no other disease. He had another sibling, who was healthy. There was no family history of congenital cardiac disease or sudden cardiac death.

Gradually as the patient grew up, his symptoms increased and mere usual childhood activities let to dyspnea and fatigue. On physical examination, short stature, failure to thrive, and chest wall deformity were noted. Additionally, he had special facial characteristics such as low-set ears, ptosis, hypertelorism, and low posterior hairline (Figure 1). Multiple lentigines were observed on his face, trunk, and extremities as well. Cardiac auscultation findings included normal 1st heart sound, single 2nd sound, and a grade 4/6 systolic murmur at the left sternal border.

Chest X-ray revealed an increased cardiothoracic ratio and a decreased pulmonary vascular marking. The laboratory test was normal except for iron deficiency anemia (hemoglobin = 10.2 g/L). Electrocardiography (ECG) yielded evidence of biventricular hypertrophy, biatrial enlargement, and ST–T change. The family showed us another ECG trace of his infantile period, which also propounded hypertrophic cardiomyopathy (HCM). Medical treatment with propranolol and captopril was recommended. The patient, however, failed to consume these drugs regularly. Echocardiographic findings included severe left and right ventricular hypertrophy, severe mitral valve regurgitation, moderate dynamic subvalvular aortic stenosis with a 56 mmHg pressure gradient, severe tricuspid regurgitation, severe subvalvular and valvar pulmonary stenosis with a 150 mmHg pressure gradient via the pulmonary valve, and reduced left ventricular (LV) systolic (LV ejection fraction = 35%) and diastolic (impaired relaxation) function (Figures 2–5).

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Figure 1. Dysmorphic facial features, characteristic of the Noonan syndrome: hypertelorism, downward slant of the palpebral fissures, inverted triangle-shaped head, and small chin.

Figure 2. 4-chamber view in echocardiography showed severe LV hypertrophy indicated hypertrophic cardiomyopathy.

Figure 3. Echocardiography in short-axis view, showing concentric hypertrophic cardiomyopathy.

Figure 4. Long-axis view in echocardiography, showing severe concentric hypertrophic cardiomyopathy with significant subaortic obstruction.
Due to severe pulmonary valve stenosis, percutaneous pulmonary balloon valvuloplasty was done 1 year before the present article was written, but there was no significant decrease in the pressure gradient via the pulmonary valve. Because the patient’s symptoms and signs were progressive and there was no proper response to drug therapy, he was considered for surgical repair. During surgery, via a right ventricular outflow tract incision, the outflow tract muscle was shaved and the pulmonary valve was repaired. Also, septomyomectomy was done in the left ventricular outflow tract (LVOT) region. After surgery, in the intensive care unit, the patient had a devastating postoperative course. A combination of low cardiac output, disseminated intravascular coagulation, and ischemic pattern due to HCM and frequent arrhythmia deteriorated his condition. His condition was further exacerbated by gastrointestinal bleeding and bleeding from the chest tube. Acidosis and electrolyte imbalance were corrected, and inotropes and broad-spectrum antibiotics were prescribed. He then developed junctional ectopic tachycardia, which was treated with intravenous amiodarone. Gradually, however, his general condition improved. At the time of his discharge, echocardiography revealed better LV systolic function (LV ejection fraction = 45%), reduced pressure gradient via the pulmonary valve (60 mmHg), and a 10 mmHg pressure gradient between the LVOT and the aortic valve. At 3 months’ follow-up, his functional class showed a significant improvement, as confirmed by the exercise test.

Our patient has a single major pediatric risk factor (maximum LV wall thickness ≥ 30 mm), which is class IIb for the implantation of the implantable cardioverter-defibrillator (ICD). Nonetheless, in the future, he may be candidated for ICD implantation and may, as such, need very careful observation.

**Discussion**

The Noonan syndrome is a rare but well-recognized genetic syndrome, and cardiovascular disorder is one of its major complications. The incidence of the Noonan syndrome is between 1,000 and 2,500 in live births. The Noonan syndrome is a heterogeneous genetic syndrome, but mutation in the PTPN11 gene on chromosome 12 has been found in approximately 50% of the patients. The syndrome usually has a sporadic pattern, but autosomal dominant transition has also been reported. Owing to multiple organ involvement, a wide spectrum of symptoms and signs may occur in this syndrome (Table 1) and most patients are referred for medical management during infancy and childhood.

Most patients with the Noonan syndrome have cardiac abnormalities, which predominantly present as congenital heart defects, cardiomyopathy, arrhythmia, or a combination of all. Pulmonary valve stenosis is the most common congenital heart defect. The pulmonary valve may be dysplastic and malformed, and it may be accompanied by subvalvular stenosis. In a study by Marino et al. on 136 patients with the Noonan syndrome, pulmonary stenosis was reported in 39% of the patients. Although HCM in the Noonan syndrome is less common, its morbidity rate is high. The association between HCM in the Noonan syndrome and sudden cardiac death and heart failure necessitates an exact evaluation. HCM presents in earlier age often during infancy, and LVOT obstruction is also common (average gradient = 32 mmHg).

In our patient, the presenting sign was cardiac involvement, beginning during infancy. A combination of pulmonary valve stenosis, a usual cardiac sign in the Noonan syndrome, and HCM rendered the management of this patient very difficult. We tried in vain to eliminate the pulmonary valve stenosis with balloon valvuloplasty, which seemed reasonable given the dysplastic valve morphology and stenosis in the subvalvular region. On the other hand, HCM with its progressive nature led to severe diastolic and systolic dysfunction, which together with right ventricular systolic and diastolic dysfunction lessened the functional class and exercise tolerance and—in short—caused an almost intolerable condition for the child. In a study by Poterucha et al., surgical myectomy in patients with the Noonan syndrome and HCM with LVOT obstruction decreased the LVOT gradient and the New York Heart Association’s class. These results are similar to those reported in patients with nonsyndromic HCM.

Although we expected the patient’s bad course in the early postoperative period, the addition of sepsis to low cardiac output state after surgery made this condition even worse.
than was expected. With appropriate treatment, the patient’s cardiac function and general condition gradually improved. The next step in the management of this patient is the decision-making for ICD insertion.¹⁶

Table 1. Clinical features of the Noonan syndrome

| Facial dysmorphism: hypertelorism, downward slant of palpebral fissures, epicanthal folds, triangular facies, small chin, low-set and/or posteriorly rotated ears, webbed neck with low posterior hairline |
|-----------------------------------------------|
| Cardiovascular: pulmonic stenosis and dysplasia, hypertrophic cardiomyopathy, secundum atrial septal defects, atrioventricular septal defects, tetralogy of Fallot |
| Skeletal: pectus excavatum and/or carinatum, cubitus valgus, scoliosis |
| Hematology: bleeding diathesis, leukemia |
| Development: delay, attention deficit/hyperactivity disorder |
| Oral/Dental: articulation difficulty, high arched palate, malocclusion Cryptorchidism |
| Skin: dystrophic nails, follicular keratosis, hyperelastic skin, multiple lentigines |

Conclusion

The cardiovascular involvement in the Noonan syndrome has a progressive and often life-threatening course. We recommend a comprehensive evaluation for cardiovascular disorders, especially pulmonary valve involvement and HCM, in children with the Noonan syndrome. Repair of cardiovascular disorders in earlier age before severe injury to the right ventricular and LV myocardium may prevent postsurgical complications and long-term hospitalization.

References

1. Allanson JE. Noonan syndrome. J Med Genet 1987;24:9-13.
2. Shaw AC, Kalidas K, Crosby AH, Jeffery S, Patton MA. The natural history of Noonan syndrome: a long-term follow-up study. Arch Dis Child 2007;92:128-132.
3. Mendez HM, Opitz JM. Noonan syndrome: a review. Am J Med Genet 1985;21:493-506.
4. Sharland M, Burch M, McKenna WM, Paton MA. A clinical study of Noonan syndrome. Arch Dis Child 1992;67:178-183.
5. Burch M, Sharland M, Shinebourne E, Smith G, Patton M, McKenna W. Cardiologic abnormalities in Noonan syndrome: phenotypic diagnosis and echocardiographic assessment of 118 patients. J Am Coll Cardiol 1993;22:1189-1192.
6. Tartaglia M, Mehler EL, Goldberg R, Zampino G, Brunner HG, Kremer H, van der Burgt I, Crosby AH, Ion A, Jeffery S, Kalidas K, Paton MA, Kucherlapati RS, Gelb BD. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nat Genet 2001;29:465-468.
7. van der Burgt I. Noonan syndrome. Orphanet J Rare Dis 2007;2:4.
8. Bhambhani V, Muenke M. Noonan syndrome. Am Fam Physician 2014;89:37-43.
9. Tartaglia M, Gelb BD, Zenker M. Noonan syndrome and clinically related disorders. Best Pract Res Clin Endocrinol Metab 2011;25:161-179.
10. Jongmans M, Sistermans EA, Rikken A, Nillesen WM, Tamminga R, Patton M, Maier EM, Tartaglia M, Noordam K, van der Burgt I. Genotypic and phenotypic characterization of Noonan syndrome: new data and review of the literature. Am J Med Genet A 2005;134A:165-170.
11. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. Lancet 2013;381:533-542.
12. Marino B, Digilio MC, Toscano A, Giannotti A, Dallapiccola B. Congenital heart diseases in children with Noonan syndrome: an expanded cardiac spectrum with high prevalence of atrioventricular canal. J Pediatr 1999;135:703-706.
13. Gelb BD, Roberts AE, Tartaglia M. Cardiomyopathies in Noonan syndrome and the other RASopathies. Prog Pediatr Cardiol 2015;39:13-19.
14. Wilkinson JD, Lowe AM, Salbert BA, Sleeper LA, Colan SD, Cox GF, Towbin JA, Connuck DM, Messee JE, Lipshultz SE. Outcomes in children with Noonan syndrome and hypertrophic cardiomyopathy: a study from the Pediatric Cardiomyopathy Registry. Am J Cardiol 2012;109:442-448.
15. Poterucha JT, Johnson JN, O’Leary PW, Connolly HM, Niaz T, Maleszewski JJ, Ackerman MJ, Cetta F, Dearani JA, Eidem BW. Surgical ventricular septal myectomy for patients with Noonan syndrome and symptomatic left ventricular outflow tract obstruction. Am J Cardiol 2015;116:1116-1121.
16. Authors/Task Force members, Elliott PM, Anastasakis A, Borger MA, Boggere M, Cecchi F, Charron P, Haugege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733-2779.