Biventricular Hypertrophic Cardiomyopathy With Right Ventricular Outflow Tract Obstruction Associated With Noonan Syndrome in an Adult

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This report describes an adult patient with Noonan syndrome accompanied by biventricular hypertrophic cardiomyopathy causing isolated right ventricular outflow tract obstruction. Biventricular hypertrophic cardiomyopathy causing right- and/or left-side outflow tract obstruction, as well as valvular pulmonary stenosis, is relatively common in infants with Noonan syndrome. However, this condition without a dysplastic pulmonary valve, or indeed any polyvalvular dysplasia, is rare in adults with Noonan syndrome. Treatment with a -adrenergic receptor blocking agent improved the patient’s symptoms. Because neither the etiologic and prognostic relationship nor the genetic linkage between hypertrophic cardiomyopathy associated with Noonan syndrome and non-syndromic hypertrophic cardiomyopathy is clearly defined, clinicopathological findings and further follow-up may provide important evidence for the pathogenesis of hypertrophic cardiomyopathy.

Key Words: Biventricular hypertrophic cardiomyopathy; Echocardiography; Noonan syndrome

Noonan syndrome is one of the most common non-chromosomal syndromes frequently accompanied by cardiovascular malformations [1]. The major cardiovascular defects are valvular pulmonary stenosis, commonly due to a dysplastic valve [2,3] and hypertrophic cardiomyopathy (HCM), which predominantly affects the interventricular septum and left ventricle [4-9]. We report an adult case of Noonan syndrome with biventricular HCM accompanied by isolated right ventricular outflow tract (RVOT) obstruction without valvular abnormalities. To the best of our knowledge, these conditions are regarded as rather uncommon manifestations of cardiac defects in adults with Noonan syndrome.

Case Report

A 42-year-old man with dyspnea and palpitation on exertion was referred from his local hospital for further cardiac examination in April 2000. Heart murmur and electrocardiographic abnormalities were first noticed when he was 10 years of age, and he had experienced mild dyspnea on exertion since that time. On admission, blood pressure was 118/68 mmHg and pulse was regular at 72 beats/min. Neither mental retardation nor sexual infantilism was observed. He was of short stature (152 cm; < mean –3.0 SD), had a short neck, a shield-like chest with widely spaced nipples, cubitus valgus (Fig 1A), and the characteristic facial traits of ocular hypertelorism and low-set posteriorly rotated ears (Fig 1B). A grade 3 systolic ejection murmur was heard at the mid-left sternal border and S4 was heard at the apex. An electrocardiogram showed left axis deviation, P waves with high peaks in the inferior limb leads, and deep S waves over the precordial leads. Chest X-ray showed cardiomegaly with normal pulmonary vascularity. Laboratory tests revealed prolongation of the activated partial thromboplastin time (46.2 s; normal value, 24–37 s) and a somewhat deficient clotting factor 11 (61.2%; normal value, 75–137%) but without any hepatic dysfunction. The lymphocyte karyotype showed a normal male pattern.

Transthoracic echocardiography (Fig 2) revealed biventricular hypertrophy with asymmetric septal hypertrophy. The hypertrophied septum bulged out into the outflow portion of the right ventricle, thus reducing the size of the right ventricular cavity and resulting in outflow obstruction. Transesophageal echocardiography (Fig 3) demonstrated far more pronounced hypertrophy in the interventricular septum than in the free wall of each ventricle and marked narrowing of the RVOT. The pulmonary valve was normal. Magnetic resonance imaging clearly demonstrated marked biventricular hypertrophy including that of the left ventricular free wall (Fig 4). Cardiac catheterization showed a pulmonary capillary wedge pressure of 11 mmHg, pulmonary arterial pressure of 22/12 (16) mmHg, RVOT pressure of 22/6 mmHg, right ventricle apex pressure of 70/6 mmHg, right atrial pressure of 6 mmHg, systemic arterial pressure of 110/70 (90) mmHg, and cardiac index of 1.44 L·min⁻¹·m⁻². A systolic pressure gradient of 48 mmHg was seen across the right ventricular outflow tract (Fig 5), despite the absence of a left ventricular-aortic pressure gradient. Oximetric studies showed no intracardiac shunt. Right ventriculography demonstrated narrowing of the infundibulum by the grossly hypertrophied interventricular septum,
but no evidence of valvular pulmonary stenosis or a dysplastic pulmonary valve. Endomyocardial biopsy specimens from the right ventricular side of the septum demonstrated bizarre myocyte hypertrophy with disorganization of the muscle bundle (Fig 6). On the basis of the characteristic somatic stigmata and the cardiovascular involvement, a diagnosis was made of Noonan syndrome accompanied by biventricular HCM with RVOT obstruction. There was no evidence of Noonan phenotype or cardiac defects in the patient’s offspring. Treatment with atenolol (25 mg/day) reduced the RVOT pressure gradient at rest, assessed by Doppler echocardiography, to 33 mmHg and improved his symptoms.

**Discussion**

Noonan syndrome, first described by Noonan and Ehmke in 1963, is a relatively common non-chromosomal syndrome with a Turner-like phenotype and frequent cardiovascular features. The patient presented here had typical somatic stigmata of Noonan syndrome, including short stature, short neck, shield-like chest with widely spaced nipples, and abnormalities of the extremities (cubitus valgus). The characteristic facial appearance included ocular hypertelorism and low-set posteriorly rotated ears. The cardiovascular involvement was evident with biventricular hypertrophy and RVOT obstruction. Endomyocardial biopsy revealed bizarre myocyte hypertrophy with disorganization of the muscle bundle. Treatment with atenolol reduced the RVOT pressure gradient and improved symptoms.

**Fig 1.** General features (A) and facial stigmata (B) characteristic of Noonan syndrome. The patient is of short stature, has a short neck and a shield-like chest with widely spaced nipples, and displays cubitus valgus (A) and the characteristic facial appearance of ocular hypertelorism and low-set posteriorly rotated ears with a thick helix (B).

**Fig 2.** Parasternal long-axis (A) and short-axis (B) views by transthoracic echocardiography. Asymmetric septal hypertrophy with biventricular hypertrophy (A) and bulging of the hypertrophied septum into the right ventricular outflow tract (arrow heads) (B) are seen. IVS, interventricular septum; RVOT, right ventricular outflow tract; LVOT, left ventricular outflow tract.

**Fig 3.** Four-chamber (A) and right ventricular outflow (B) views by transesophageal echocardiography. Hypertrophy of the interventricular septum is far more pronounced than that of the free walls of the bilateral ventricles (A). The right ventricular outflow tract has narrowed to a slit (B). The pulmonary valve is normal. RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; RVIT, right ventricular inflow tract; PV, pulmonary valve. Other abbreviations as shown in Fig 2.

**Fig 4.** Cross-sectional magnetic resonance image demonstrating marked biventricular hypertrophy accompanied by asymmetrical septal hypertrophy.
The most common cardiac malformation is valvular pulmonary stenosis with dysplasia of the valve cusps. HCM is the second most commonly associated cardiac abnormality and tends to affect predominantly the interventricular septum and left ventricle. In the case presented here, bulging of the hypertrophied septum into the right ventricular outflow tract caused RVOT obstruction, which manifested itself as right-side hypertrophic obstructive cardiomyopathy. Because the hypertrophied muscle bundles were positioned infundibular, this case was thought to be different from double-chambered right ventricle. The definition of septal hypertrophy in Noonan syndrome is complicated by the frequent association of valvular pulmonary stenosis, which may result in asymmetrical septal hypertrophy and thus mimic HCM. In this case, the marked hypertrophy was thought to be the primary manifestation of HCM, but not the secondary hypertrophy, because both the ventricular free walls, as well as the interventricular septum, were distinctly hypertrophied without evidence of valvular stenosis. Moreover, the histopathology of the endomyocardial biopsy specimens was consistent with HCM. More pronounced involvement of the interventricular septum on the left-side outflow tract could even have caused biventricular outflow tract obstruction. Although several cases of biventricular HCM with right- and/or left-side outflow obstruction have been reported in infants with Noonan syndrome, relatively few cases have been reported in adults. Although no mention was made whether their patients showed the Noonan phenotype, Maron et al reported RVOT obstruction to be relatively common in infants and young children with HCM, but rare in older patients with HCM. This difference between infants and adults can be explained as follows. First, the RVOT obstruction might be alleviated with growth and aging, which would result in an increase in size of the RVOT. Second, biventricular outflow tract obstruction could produce lethal hemodynamic changes in infants with HCM, thus predisposing them to premature death and accounting for the rare occurrence of marked obstruction to right ventricular outflow in adults with this disease. In fact, of the 20 infants with HCM causing right- and/or left-side outflow tract obstruction studied by Maron et al, 9 died with signs of progressive congestive heart failure within the first year of life. Burch et al reported a histopathological similarity between HCM associated with Noonan syndrome and classic (non-syndromic) HCM, but they also stressed the dissimilarity between the 2 conditions in terms of the hypertrophied region, having found that hypertrophy associated with Noonan syndrome tended to be confined to the upper anterior septum. McKenna et al reported that 44% of adult patients with classic HCM also had mild to moderate right-side ventricular hypertrophy. However, such severe hypertrophy involving the right ventricle as seen in the present case has rarely been found in patients with classic HCM. Moreover, apical hypertrophy, which is occasionally recognized in classic HCM, has not been reported in HCM associated with Noonan syndrome.

The natural history of HCM in Noonan syndrome is markedly variable. Whereas some patients have symptoms of heart failure in infancy and deteriorate rapidly, others remain asymptomatic and stable for many years or, at least, become symptomatic only in late childhood. Hirsch et al reported fatal outcomes for 2 infants with Noonan syndrome in whom biventricular hypertrophic obstructive cardiomyopathy progressed rapidly. Shimizu et al described a rare case of HCM associated with Noonan syndrome that progressed to dilated cardiomyopathy. The gene for familial Noonan syndrome is located on chromosome 12q, but the gene...
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responsible for cardiac defects accompanying this syndrome has not yet been identified. However, the locations of several genes associated with HCM have been reported.

Linkage analysis of HCM associated with Noonan syndrome and classic HCM could thus provide important evidence as to whether these 2 conditions share a common etiology and prognosis.

Another noteworthy finding in the present case was the minor defect in the coagulation system. A variety of bleeding problems, including factor 11 deficiency, von Willebrand disease, thrombocytopenia, and platelet dysfunction, has been identified in patients with Noonan syndrome. The potential occurrence of bleeding diathesis should thus be taken into consideration, especially when surgery is required.

Sharland et al reported the mean age at diagnosis of Noonan syndrome to be 9.0 years. In the present case, the correct diagnosis was missed and may have resulted in a delay of appropriate clinical management. Early and correct diagnosis of this common condition can be beneficial with respect to clinical management and genetic counseling because of the high incidence of associated cardiac defects and the occasional familial occurrence of Noonan syndrome.

Acknowledgments

We wish to thank Satoshi Yasukochi, MD (Department of Pediatric Cardiology, Nagano Children's Hospital) for his valuable and helpful suggestions.

References