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Case Report

Case Report: Biventricular Hypertrophic Obstructive Cardiomyopathy in a Patient with Noonan Syndrome

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Abstract

Background: Noonan Syndrome (NS) is a genetic condition that presents with characteristics such as short stature, distinctive facial features, and congenital heart issues. Its occurrence is estimated to be between 1 in 1,000 and 1 in 2,500 live births. The syndrome follows an autosomal dominant inheritance pattern. In around 50% of cases, NS is linked to missense mutations in the PTPN11 gene located on chromosome 12, which leads to the abnormal activation of the SHP-2 non-receptor-type protein tyrosine phosphatase.

Case summary: We are presenting a case of a 17-yearold male diagnosed with Noonan syndrome associated with a mutation in the PTPN11 gene. He was initially followed by pediatric cardiology due to a heart murmur and was diagnosed with non-obstructive Hypertrophic Cardiomyopathy (HCM) 13 years ago. A year back, he transitioned to adult cardiology, where he was found to have biventricular obstructive cardiomyopathy.

Abbreviations

NS: Noonan Syndrome; HCM: Hypertrophic Cardiomyopathy; ECG: Electrocardiogram; LVOT: Left Ventricular Outflow Tract Obstruction; RV: Right Ventricle; LV: Left Ventricle; CMR: Cardiac Magnetic Resonance; RVH: Right Ventricular Hypertrophy; SCD: Sudden Cardiac Death

Case report

We present the case of a 17-year-old male who initially visited for a cardiologic evaluation at the age of 5 due to a heart murmur. At that time, echocardiography confirmed a diagnosis of "non-obstructive hypertrophic cardiomyopathy." He underwent surgery for undescended testis at the age of 7. Since then, he has been asymptomatic, regularly attending follow-up appointments until he transitioned to adult cardiology at 15.

About three months ago, the patient began to notice episodes of rapid heart palpitations, particularly when engaging in physical activities. These sensations typically eased with rest. The palpitations appeared gradually and faded similarly, without associated chest pain or syncope. Importantly, the patient did not report other symptoms like chest pain, lightheadedness, and difficulty breathing while lying down, or swelling in the legs. There's also no known history of high blood pressure or family issues related to heart disease or sudden death.

During the examination, the patient presented as a healthy-looking young man, at rest, with a heart rate of 76 beats per minute and blood pressure of 102/60 mmHg. Notably, pectus excavatum was observed upon chest inspection. A grade 3 out of 6 harsh mid-systolic murmur was audible at the left upper sternal border, radiating toward the apex but not extending to the neck. The intensity of this murmur decreased to grade 2 out of 6 during inspiration, squatting, and passive leg elevation, but increased to grade 4 out of 6 with the Valsalva maneuver and upon standing. Normal first heart sound (S1), single second heart sound (S2), and fourth heart sound (S4) were detected during auscultation. The rest of the physical

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examination-including measures of jugular venous pressure and carotid upstroke—yielded normal findings. ECG indicated diffuse T-wave inversions (Figure 1).

The echocardiogram revealed asymmetrical septal hypertrophy with a thickness of 22 mm, accompanied by systolic anterior motion of the anterior mitral leaflet (Figure 2A). This is indicative of biventricular obstructive hypertrophic cardiomyopathy, with a peak gradient of 140 mmHg observed in the Left Ventricular Outflow Tract (LVOT). (Figure 2B), There is significant thickening of the free wall of the right ventricle, measuring 7 mm. Color Doppler imaging demonstrated turbulent flow in the mid-right ventricular cavity, with a peak gradient of 22 mmHg, (Figure 3A). Similarly, a peak gradient of 22 mmHg was also noted within the mid RV cavity (Figure 3B). The pulmonary valve appears normal, and no additional gradient was observed. Severe mitral regurgitation was also noted.

Cardiac Magnetic Resonance imaging (CMR) was performed and confirmed echocardiographic findings consistent with biventricular hypertrophic obstructive cardiomyopathy (Figure 4).

The patient declined to undergo additional evaluation. He was administered betablockers, which provided some relief from his symptoms. The legal guardians of the patient provided informed consent for publication of clinical data, and the institution where the patient was treated authorized the publication of the case.

Discussions

Noonan Syndrome (NS) is an autosomal dominant disorder characterized by short stature, typical face dysmorphology, and congenital heart defects. NS is a clinical diagnosis. Establishing a diagnosis can be very difficult, especially in adulthood. There is significant phenotypic variability, which becomes less pronounced with advancing age [1]. Several diagnostic scoring systems have been developed. The most widely accepted scoring system was developed in 1994 [2] (Table 1).

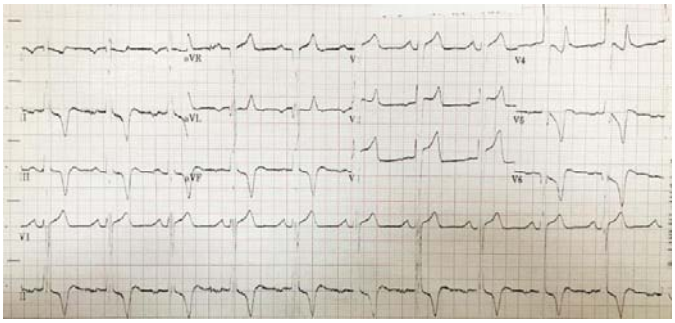

Figure 1: ECG demonstrating diffuse ST-segment changes with deep T-wave inversions.

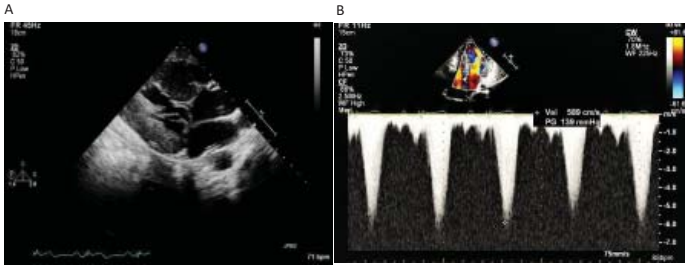

Figure 2: A. Asymmetrical Septal Hypertrophy (ASH) with Systolic Anterior Motion (SAM); B: Peak gradient across LVOT (140 mmHg).

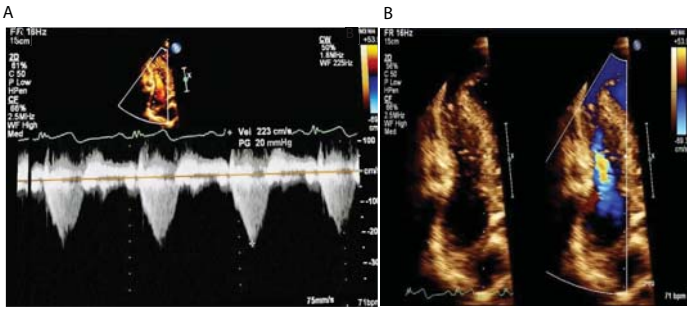

Figure 3: A: Increased right ventricular thickness with turbulent mid-cavity flow, B: Peak gradient of 22 mmHg across mid-right ventricle.

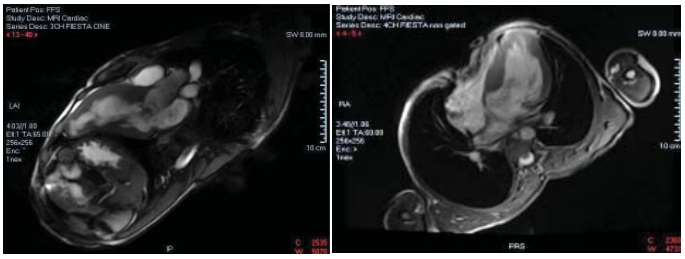

Figure 4: Cardiac Magnetic Resonance imaging (CMR) demonstrating increased Interventricular Septal (IVS) and Right Ventricular (RV) wall thickness.

Hypertrophic Cardiomyopathy (HCM) is the most common inherited cardiomyopathy worldwide with a prevalence of 0.16% to 0.29% in the general population [3]. Although the ESC definition of HCM [4] is based on Left Ventricular (LV) wall thickness criteria (≥ 15 mmin one or more myocardial segments that are not explained solely by loading conditions), Right Ventricular (RV) involvement can be noteworthy, as it is not rare and can affect the prognosis of the disease.

Noonan syndrome-HCM frequently coexists with structural cardiac malformations, whereas nonsyndromic HCM typically does not, resulting in distinct clinical courses. Long-term survival is significantly poorer in Noonan syndrome-associated HCM compared to nonsyndromic HCM [5].

Biventricular hypertrophy is relatively common and may manifest in the presence or absence of Pulmonary Valve Stenosis (PVS) [6].

RV involvement encompasses both structural hypertrophy and functional alterations. In contrast to diagnostic criteria for LV Hypertrophy (LVH), there is currently no standardized definition for RV Hypertrophy (RVH). McKenna, et al. classified RVH as mild (6-8 mm), moderate (9-12 mm) and severe (> 12 mm) 4 and Maron, et al. defined RVH as end-diastolic RV anterior, free, or apical wall thickness ≥ 5 mm and if ≥ 10 mm, it is extreme/severe RVH [6].

The incidence of RV involvement in HCM varies widely depending on diagnostic criteria and modalities used. The first

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Table 1: Scoring system for Noonan Syndrome (NS).

Feature	A=Major	B= Minor
1 Facial	Typical face dysmorphology	Suggestive face dysmorphology
2 Cardiac	Pulmonary valve stenosis, HOCM and/or ECG typical of NS	Other defects
3 Height	<P3*	<P10*
4 Chest wall	Pectus carinatum / excavatum	Broad thorax
5 Family History	First degree relative with definite NS	First degree relative with definite NS
6 Other	Mental retardation, cryptorchidism, lymphatic dysplasia	One of Mental retardation, cryptorchidism, and lymphatic dysplasia

HOCM: hypertrophic obstructive cardiomyopathy;
*P3 and P10 refer to percentile lines for height according to age, with the normal range of variation defined as P3-P97 inclusive Definitive NS: 1 "A" plus one other major sign or two minor signs; 1 "B" plus two major signs or three minor signs

observations come from postmortem and then catheterization studies. Cardiac Magnetic Resonance (CMR) studies identify RVH in 30% [7], whereas echocardiography identifies RVH in 44% of patients with HCM [4]. Severe RVH is relatively rare, with a prevalence of 1.3% in the overall HCM population [8].

Three potential sites of obstruction have been recognized: the outflow tract, apex, and mid-ventricular region. Right Ventricular Outflow Tract Obstruction (RVOTO) is defined by a pressure gradient exceeding 25 mmHg at rest [9] or 16 mmHg as reported by Shimizu, et al. [10].

Notably, RV involvement in HCM is associated with supraventricular arrhythmias in 70% and ventricular arrhythmias in 47% of patients with RVH [11].

RV Hypertrophy (RVH) serves as both a qualitative and quantitative risk factor, significantly augmenting the risk of Sudden Cardiac Death (SCD) beyond the conventional SCD risk score. Although Right Ventricular Wall Thickness (RVWT) is not currently incorporated into the SCD risk score—unlike late gadolinium enhancement of the Left Ventricle (LV)—RVH correlates with elevated SCD risk through three proposed mechanisms [10]:

a) An independent relationship with the presence of ventricular arrhythmias [12].

b) An increased percentage of myocardial fibrosis [12] and;

c) Accumulation of more than one HCM mutation [8].

Off-label trametinib therapy was associated with reversal of HCM and valvular obstruction in two patients with RIT1-associated NS. After three months of treatment, a dramatic clinical and cardiac improvement was observed, It is hypothesized that MEK inhibition may be most effective if initiated before irreversible cardiac remodeling occurs [9].

Conclusion

Noonan syndrome is a rare disease, which can be very difficult to diagnose, especially based on features other than lentigines, and identifying Noonan syndrome in young patients can be challenging. Cardiac involvement in Noonan syndrome is often progressive and may necessitate multiple medical and surgical interventions.

The detailed study of the right ventricle should be an integral part of the assessment and follow-up of patients with HCM to identify as early as possible its involvement, to clarify its modifying role in disease progression and, importantly, to implement measures to mitigate the risk of heart failure and Sudden Cardiac Death (SCD).

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