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Case Report

Left Ventricular Noncompaction in Noonan Syndrome

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Abstract

Noonan Syndrome (NS) is a relatively common genetic disorder with complete penetrance and variable expressivity. More than 80% of NS patients have cardiovascular abnormalities, including malformations and cardiomyopathy. However, the occurrence of left ventricular non compaction (LVNC) in a series of NS patients has not been studied. We present a case series of 6 patients from five families with NS and LVNC. Causative NS mutations were identified in 40% of unrelated patients. LVNC was present as an isolated finding, associated with cardiovascular malformation (CVM), and/or associated with hypertrophic cardiomyopathy (HCM). This is the first series of LVNC in NS reported. Awareness of NS in LVNC is important for management and family based cardiac screening recommendations.

Keywords

Cardiomyopathy; Noncompaction; Cardiac malformation; Mutation; RASopathy

Abbreviations: CVM: Cardiovascular Malformation; HCM: Hypertrophic Cardiomyopathy; NS: Noonan Syndrome; LVNC: Left Ventricular Noncompaction

Introduction

Noonan Syndrome (NS) is a relatively common genetic disorder with an incidence of approximately 1 in 1000-2500 live births and an autosomal dominant inheritance pattern with complete penetrance and variable expressivity [1]. Pathogenic variants are currently identifiable in approximately two-thirds of patients, with a high *de novo* rate. Clinical diagnosis is based upon classic physical features, including characteristic dysmorphic facial features, short stature, chest deformities, and cardiovascular malformation (CVM) [2]. More than 80% of patients with NS have cardiovascular abnormalities, most commonly CVMs, but approximately 20-30% have hypertrophic cardiomyopathy (HCM) [3-6].

NS is one of the RASopathies, a group of disorders that also includes Costello syndrome, Cardio-facio-cutaneous syndrome, Noonan syndrome with multiple lentigines (formerly LEOPARD), and Noonan syndrome-like disorders, all of which are characterized by dysregulation of the RAS-MAPK signaling pathway. Approximately 50% of those who have NS have a variant in *PTPN11*, with variants in

SOS1, *RAF1*, and *KRAS*, among other RASopathy genes, accounting for a smaller subset of cases [1,7]. *RAF1* variants have also recently been associated with dilated cardiomyopathy in individuals without physical features of NS [8]. While clear cardiovascular genotype-phenotype correlations remain elusive, *PTPN11* variants are identified more often with pulmonary valve stenosis and less often with HCM, and HCM is observed in up to 85% of NS patients with *RAF1* variants [1,6]. HCM in NS typically presents early in life and is associated with worse outcomes when compared with HCM without NS [9]. Because of their genetic risk of developing HCM, patients with NS require life-long cardiac surveillance.

Left ventricular noncompaction (LVNC) is a type of cardiomyopathy associated with heart failure, arrhythmias and embolic events that can present in isolation or in combination with CVMs or cardiomyopathies, including HCM [10]. LVNC is a myocardial developmental disorder characterized by excessive and prominent left ventricular trabeculations and a thin compact layer [11,12]. The definition and classification of LVNC is complex and controversial [13], and an understanding of the genetic basis of LVNC is incomplete, but evidence to date demonstrates clear genetic heterogeneity. Mutations in cardiomyopathy genes, specifically those that encode sarcomeric proteins, account for a small proportion of isolated LVNC cases, and, in some of these cases, both LVNC and HCM coexist [14,15]. The presence of LVNC in NS has been reported in an isolated case from a series of syndromic patients with LVNC [16] but has not been systematically evaluated in a cohort of NS patients.

Herein, we describe a case series of 6 patients with NS and LVNC, the first such report. There are multiple presentations of LVNC, including isolated LVNC, LVNC associated with CVM and LVNC associated with HCM. Awareness of LVNC as a potential cardiac finding in patients with NS will inform diagnosis, management and surveillance strategies.

Case Series

Patients with RASopathies were identified through the Cardiovascular Genetics service at Cincinnati Children's Hospital Medical Center (CCHMC) from August 2010 through December 2013. All patients had a clinical diagnosis of a RASopathy, most commonly NS, with or without genetic testing. Individuals who underwent genetic testing had clinical testing performed using a 10 gene panel that included: *BRAF, HRAS, KRAS, MEK1, MEK2, NRAS, PTPN11, RAF1, SHOC2,* and *SOS1* or a 12 gene panel that included the additional genes *CBL* and *SPRED1*. No subjects had genetic testing for cardiomyopathy. This retrospective review was approved by the Institutional Review Board at CCHMC. Patients' electronic medical records were reviewed to determine cardiac involvement. Three criteria were used to evaluate the presence of LVNC by echocardiography: 1) a non-compact to compact ratio >2:1 at end systole in the parasternal short axis; 2) numerous deep trabeculations with blood demonstrated in the recesses by color Doppler; and 3) more than three trabeculations visible in a single plane [12,17].

A total of 42 patients with RASopathies and cardiovascular abnormalities were identified. There were 9/42 (21%) with HCM and 6/42 (14%) with LVNC. There were 28/42 (67%) molecular

diagnoses, including mutations in *PTPN11* (18), *SOS1* (3), *RAF1* (2), *BRAF* (2) and *HRAS* (2). The latter two patients had a diagnosis of Costello syndrome, whereas all the remaining patients in the cohort had a diagnosis of NS. Among those with LVNC, two (33%) also had HCM and four (67%) also had CVM. Detailed cardiac phenotypes for each patient are shown in Table 1. There were no obvious differences in associated cardiac findings between cases with LVNC without HCM when compared with cases of LVNC with HCM. There was a broad age range (1 year to 46 years) and the cohort included one father-daughter dyad, with the remaining cases all unrelated and without a family history of LVNC or other cardiomyopathy. Interestingly, there was one case of isolated LVNC, and one case with left ventricular systolic dysfunction. Patient 5 and Patient 6 were on oral anticoagulation therapy due to their LVNC diagnosis. None of the patients had developed severe complications of LVNC. Dysmorphology and organ-specific observations are shown in Table 2, including cardinal findings consistent with consensus guidelines [2,18]. All patients without a molecular diagnosis of NS were given a clinical diagnosis by a physician not associated with this study prior to evaluation in cardiovascular genetics. Therefore, each patient had multiple independent assessments of their genetic syndromic diagnosis. Two of five unrelated patients (40%) had a molecular diagnosis of NS. Both cases had *PTPN11* variants, one with HCM. Among the subset of the larger cohort without LVNC, 16/36 (44%) of cases had *PTPN11* variants. Interestingly, no *RAF1* mutations were identified despite the strong association of variants in this gene with HCM.

Discussion

The clinical presentation, and hence significance, of LVNC is variable. It can present as an isolated morphological finding of unclear significance, a distinct subtype of cardiomyopathy, an associated feature of CVM, and/or in association with another type of cardiomyopathy (e.g. HCM with LVNC) [19,20]. The American Heart Association has classified LVNC as a distinct type of cardiomyopathy [8], but the European Society of Cardiology views LVNC as a form of unclassified cardiomyopathy [21]. LVNC can be independently associated with significant clinical compromise, and therefore may represent an important predictive marker of future disease. Therefore, a diagnosis of LVNC in a patient with NS is particularly important given the overall worse outcome of cardiomyopathy in this patient population.

The genetic heterogeneity of LVNC is demonstrated by its association with rare genetic syndromes such as Barth syndrome, 1p36 deletion syndrome, and Filamin A disorders. Sarcomeric gene variants have been associated with LVNC, with prior studies suggesting an incidence of 17-41% in cases with a confirmed molecular etiology [20,22,23]. These estimates, however, do not account for overlapping cardiomyopathy phenotypes, e.g. HCM and LVNC, and thus the genetic contribution to isolated LVNC is not yet completely clear [14]. Recently, variants in genes with functions unrelated to the structural components of the sarcomere have been identified as causes of nonsyndromic LVNC, for example the *NOTCH1* signaling gene *MIB1* [24]. LVNC is thought to result from arrest of ventricular compaction of myocardium that takes place during cardiogenesis [25,26]; therefore, unlike other types of cardiomyopathy, LVNC is arguably on a congenital malformation spectrum. This suggests that there are fundamental differences in the development of LVNC and other cardiomyopathies.

Because LVNC is a heritable condition with a variable presentation, family screening has been recommended upon diagnosis in addition to genetic counseling and testing [20]. However, testing with one of the current comprehensive cardiomyopathy panels does

Table 1: Cardiac findings in a Series with Noonan Syndrome and Left Ventricular Noncompaction.

Subject	Age (years)	Gender	Race	Age at Dx of LVNC	Echocardiogram	ECG	Holter/GXT
1	1	Male	Caucasian	birth	Non-obstructive HCM (birth); Polyvalvular disease; Diastolic dysfunction	Sinus rhythm; Right superior axis deviation; Right ventricular hypertrophy deviation; Prolonged QT interval	Rare PACs Rare PVCs
2	17	Female	Asian	12 years	Non-obstructive HCM (age 1); Pulmonary valve stenosis Discrete membranous subvalvar aortic stenosis; Mitral valve prolapse with mild mitral regurgitation Mild aortic root dilation (3.1 cm, z-score +2.7) s/p pulmonary valvotomy and RVOT patch (age 2)	Sinus rhythm; Left axis deviation; Right ventricular hypertrophy	Rare PACs Rare PVCs Poor chronotropic response
3	21	Male	Caucasian	20 years	Secundum ASD; Pulmonary valve stenosis; Bicuspid aortic valve; s/p ASD device closure (age 10)	Sinus rhythm; Right superior axis deviation; Right bundle branch block	Occasional EAR Sinus rhythm during exercise; Rare PACs Rare PVCs
4	9	Female	Caucasian	7 years	Structurally normal heart	Sinus rhythm with sinus arrhythmia Nonspecific T wave changes Borderline prolonged QT interval	Rare PACs
5*	46	Male	Caucasian	44 years	Structurally normal heart; Left ventricular hypertrophy (not HCM), with associated coronary artery bridge s/p ICD placement (age 46)	History of Sick Sinus Syndrome; History of non-sustained atrial tachycardia, History of non-sustained ventricular tachycardia; Sinus rhythm alternating with atrial pacing; Nonspecific T wave changes	Rare PACs Poor chronotropic response; Intermittent EAR; ST changes during exercise
6	35	Female	Caucasian	34 years	Secundum ASD; Mildly depressed LV function s/p ASD device closure (age 35)	Sinus rhythm; Nonspecific T wave changes; Borderline prolonged QT interval	Rare PACs Rare PVCs

*father of subject 4. ASD, atrial septal defect; EAR, ectopic atrial rhythm; ECG, electrocardiogram; GXT, graded exercise test; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction; PAC, premature atrial contractions; PVC, premature ventricular contractions; RVOT right ventricular outflow tract

Table 2: Molecular and Extracardiac Findings in a Series with Noonan Syndrome and Left Ventricular Noncompaction.

Subject	Age at Dx of NS	Genetic testing	Family history	Facial features	Growth/Endocrine	GI	Renal/GU	Hematologi0063	Neurologic/Cognitive	ENT	Lymphatic
1	3 weeks[a]	PTPN11[b] p.Ala461Thr	No	Downslanting palpebral fissures, small, upturned bulbous nose with flat nasal bridge, tented upper lip	<3 centile	Dysphagia as infant	Bilateral cryptorchidism; duplicated R renal collecting system	Mild VWD type 1; Excessive bleeding	Arachnoid cyst; DD	Bilateral conductive hearing loss	No
2	13 years	Normal[b]	Unknown[c]	Triangular facies, downslanting palpebral fissures, epicanthal folds, narrow vaulted palate and micrognathia, low set, posteriorly rotated ears	<3 centile; delayed puberty	No	No	Elevated PT/PTT	No	Hyperopia	No
3	6 years	PTPN11[b] p.Asn58Lys	No	Triangular facies, hypertelorism with downslanting palpebral fissures, micrognathia, low set, posteriorly rotated ears, short broad neck with low posterior hairline.	<3 centile	No	Inguinal hernia	Elevated PT/PTT; abnormal coagulation profile	Cerebellar astrocytoma; Mild DD; depression/anxiety	No	No
4	1 year	Normal[b]	Yes[e]	Hypotelorism with downslanting palpebral fissures, hooded eyelids, exotropia, posteriorly rotated ears	5-13 centile	No	No	No	Plagiocephaly; Mild DD; school IEP	Astigmatism; myopia	No
5	37 years	None[f]	Yes[g]	Triangular facies with bitemporal narrowing, hypotelorism with downslanting palpebral fissures, micrognathia, low set, posteriorly rotated ears, short webbed neck with low posterior hairline.	<3 centile; hypothyroidism	No	Single kidney	No	ID	Unknown	No
6	22 years[a]	Normal[h]	Suspected[i]	Triangular facies, midface hypoplasia, downslanting palpebral fissures, narrow vaulted palate and micrognathia, low set, posteriorly rotated ears	<3 centile; Hypothyroidism	GERD; dysphagia	No	Elevated PT/PTT	Unknown	Hearing loss Cleft palate	No

[a] Clinical diagnosis made by Dr. Jackie Noonan; [b] 10 gene Noonan panel (Patient 3 had single gene testing); [c] adopted; birth family history unknown; [d] 6th centile after growth hormone; [e] given a clinical diagnosis in first year of life without knowledge of paternal diagnosis or family history; [f] father of subject 4; no genetic testing performed due to normal results in subject 4; [g] diagnosed with additional affected family members at Mayo Clinic as a child; [h] 12 gene Noonan panel (same as 10 gene panel with additional genes *CBL* and *SPRED1*); [i] short stature, intellectual disability, and question of NS in great aunt; DD, developmental delay; GERD, gastroesophageal reflux disease; ID, intellectual disability; IEP, individualized educational plan; PT, prothrombin time; PTT, partial thromboplastin time; VWD, von Willebrand's

not include genes causing RASopathies such as NS. NS has variable expressivity and can be subtle and difficult to diagnose, especially in adulthood after many characteristic features are less obvious. Thus, it is important to consider NS in the differential of a patient who presents with LVNC for whom genetic testing is considered.

The recognition of NS in a patient with LVNC has clear management implications for the individual, given guideline recommendations for patients with NS. For example, bleeding disorders occur in some NS patients and anticoagulation is recommended for some LVNC patients; these challenges require attention, especially in the preoperative patient [27]. A geneticist can play an important role in advocating for the NS patient and ensuring that all subspecialists are aware of potential risks, such as the need to balance the risk for bleeding with the risk for clot formation. There is also the need for education and assistance with the transition of a patient with NS to adult care providers. In addition, a diagnosis of NS has implications for the family. If a *de novo* mutation were the cause of NS in the family, then cardiac screening of first-degree relatives for cardiomyopathy would not be indicated. *RAF1* mutations tend to be associated with HCM. Since there may be etiologic differences between isolated LVNC, isolated HCM, and HCM with LVNC, and because there were no *RAF1* mutations in this small series, it may be that cases of NS with LVNC are associated with either a new as yet identified genetic cause of NS or represent a new type of mutation, e.g. in a regulatory region.

Both CVM and HCM are observed in individuals with NS. Here we describe comprehensive cardiac and extracardiac findings in a subset of NS patients that have LVNC. In the larger cohort with RASopathies, 21% (9/42) had a diagnosis of HCM, which is consistent with previous reports, and 14% (6/42) had a diagnosis of LVNC. Not surprisingly, LVNC co-occurred with HCM in 2 cases (33%), but was present in 4 cases independent of HCM. To our knowledge, this is the first case series describing LVNC in NS. It remains to be determined whether NS patients with LVNC have an increased risk for the development of HCM, DCM, or heart failure. Nevertheless, as patients with NS and LVNC transition to adult care, geneticists can play important an important educational role regarding the need for lifelong cardiac surveillance.

This case series has several limitations. First, 60% of patients with NS were diagnosed clinically. This compares with a frequency of clinical diagnoses of 33% in the larger cohort without LVNC, suggesting that the groups may differ in this regard. We note that the patient described in the previous single case report of NS and LVNC also did not have positive molecular testing for NS [16], leaving the possibility that these patients belong to a distinct RASopathy subset. Second, molecular testing for an established sarcomeric gene mutation cause of LVNC was not performed. While none of these patients had a family history of LVNC (or other cardiomyopathy) in family members without NS to prompt additional cardiomyopathy testing, we cannot formally rule out a different cause or second variant resulting in LVNC in these patients. Excluding other genetic causes of LVNC, such as sarcomeric gene mutations, will be important in future investigations.

Conclusions

We report the first series of LVNC in NS. Our case series demonstrated various presentations of LVNC including: isolated LVNC, LVNC associated with CVM, and LVNC associated with HCM. Our case series points to the need for increased awareness of LVNC as a potential cardiac finding in patients with NS, and will inform management and surveillance.

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