Original Article

Association of Noonan Syndrome, Noncompaction of the Myocardium, Hypertrophic Cardiomyopathy, and Long QT Syndrome: A Case Series

Anna Luisa de Melo Lula Lins Pimentel,[1] Érika Alves da Silva,[1] Marcelo Dantas Tavares de Melo,[1] Vera Maria Cury Salemi[2]

Universidade Federal da Paraíba,[1] João Pessoa, PB – Brazil
Hospital Sírio Libanês,[2] São Paulo, SP – Brazil

Abstract

Background: The Noonan syndrome (NS) is a rare genetic disorder characterized by manifestations such as short stature, a webbed neck, micrognathia, and hypertelorism. Although NS predisposes to cardiac disorders such as hypertrophic cardiomyopathy (HCM), it has only rarely been associated with noncompaction cardiomyopathy (NCCM), an embryonic anomaly defined by excessive trabeculation and formation of deep myocardial recesses. The clinical presentation of NCCM ranges from asymptomatic to severe thromboembolic events. This study aims to describe cardiovascular changes and outcomes in patients with NS and NCCM followed at the cardiology department of a Brazilian hospital.

Methods: Observational, longitudinal, prospective follow-up of three adult patients with the NS phenotype. All underwent echocardiography and cardiac magnetic resonance imaging (CMR). Data such as age, sex, family history, symptom onset, and outcomes of interest, such as thromboembolic events, heart transplantation (HTx), and death, were analyzed.

Results: All three patients followed (one male-female sibling pair and one unrelated male) had NCCM with ventricular dysfunction. The female patient also had the long QT syndrome (LQTS). All developed apical thrombi, in the left ventricle in two cases. The female patient underwent successful HTx, while the two males died after decompensation of heart failure (HF) progressing to cardiogenic shock.

Conclusion: This case series highlights the need for early diagnosis and family screening of patients with NS to optimize treatment and improve prognosis. There is no prior record in the literature of the association of all conditions described herein in the same patient.

Keywords: Noonan Syndrome; Isolated Noncompaction of the Ventricular Myocardium; Long QT Syndrome.

Introduction

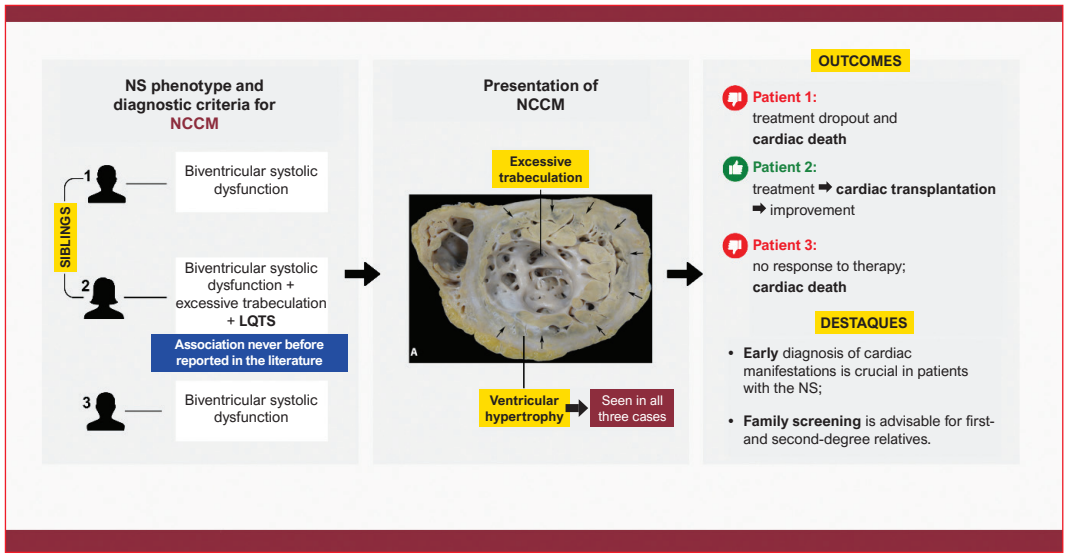
The Noonan syndrome (NS) is a rare, predominantly autosomal genetic condition characterized by distinct phenotypic features, including short stature, a webbed neck, hypertelorism, micrognathia, low-set ears, and pectus carinatum.[1,2] NS is frequently associated with heart diseases, such as hypertrophic cardiomyopathy (HCM), arrhythmias, and conduction disorders, having been described only once—in 2016—in association with noncompaction cardiomyopathy (NCCM).[2,3] NCCM, also known as noncompaction of the myocardium, is a complex embryonic disorder characterized by excessive trabeculation of the myocardium, resulting in formation of deep ventricular recesses that fill with blood. The clinical picture of NCCM can range from asymptomatic to severe thromboembolic complications.[4] The diagnostic criteria for this cardiomyopathy are not yet fully established. The use of echocardiography and cardiac magnetic resonance imaging (CMR) for diagnosis is widespread, especially using the Zurich criteria (described by Jenni in 2001) and the Petersen criteria.[4-6]

The prevalence of cardiac disease in adults with NS is not well studied, but the syndrome is known to affect multiple organs, which means clinicians must be aware of and have a high index of suspicion for serious events arising from the most prevalent causes.[2] The present report describes three clinical cases (including one sibling pair) of patients simultaneously affected by the NS, HCM, and NCCM, all followed at the outpatient cardiology clinic of a Brazilian public hospital. One of the patients also had long QT syndrome (LQTS), a condition that compromises ventricular repolarization; the association of NS, NCCM, and LQTS is heretofore undescribed in the literature.[7] Furthermore, the

Mailing Address: Marcelo Tavares •
Universidade Federal da Paraíba. Cidade Universitária, sn, Conj. Pres. Castelo Branco III. Postal code: 58051-900. João Pessoa, PB – Brazil
E-mail: marcelo_dtm@yahoo.com.br
Manuscript received October 25, 2024; revised October 28, 2024; accepted October 28, 2024
Editor responsible for the review: Marcelo Tavares

DOI: https://doi.org/10.36660/abcimg.20240107i

Central Illustration: Association of Noonan Syndrome, Noncompaction of the Myocardium, Hypertrophic Cardiomyopathy, and Long QT Syndrome: A Case Series



Arq Bras Cardiol: Imagem cardiovasc. 2025;38(1):e20240107

NS: Noonan syndrome; NCCM: noncompaction cardiomyopathy; HCM: hypertrophic cardiomyopathy; LQTS: long QT syndrome.

outcomes of each case were analyzed to highlight similarities and differences, considering the rarity and heterogeneity of this association. Given the growing need to elucidate the interactions between genotype and phenotype in NS, this report also highlights the importance of early diagnosis of cardiac anomalies, which is essential to improving the prognosis and quality of life of these patients. We chose to provide a detailed description of each individual patient, due to their particular features.

Methods

This observational, longitudinal, prospective study was based on the follow-up of three adult patients with the NS treated at Quaternary Hospital.

In addition to a detailed review of systems and physical examination to collect clinical data, patients also underwent diagnostic testing to assess cardiovascular function and possible complications, including plain chest radiography, electrocardiography, 24-hour Holter monitoring, transthoracic echocardiography, and CMR — the latter two being the preferred imaging methods for assessing myocardial noncompaction. In echocardiography, the most commonly used initial method, a suspected diagnosis of NCCM is assessed by criteria such as Jenni's, which compares the proportion between compacted (C) and noncompacted (NC) layers of the myocardium, with measurements taken during systole, in which a NC/C ratio > 2 is considered diagnostic.[5] CMR provides improves spatial definition, aiding in visualization of trabeculae and possible thrombi, especially apical ones. In CMR, the Petersen criterion defines as diagnostic an NC:C myocardium ratio > 2.3.[6] Diagnosis of the LQTS was established by electrocardiography and 24-hour Holter monitoring. For diagnostic confirmation, all imaging findings and test results were reassessed by a second, experienced specialist.

Parameters of interest included age, sex, past medical history, family history, age at onset of cardiac symptoms, current medications, imaging findings and laboratory test results, and the following endpoints: development or decompensation of heart failure (HF), thromboembolic events, cardiac events, heart transplantation (HTx), and death.

The study was approved by the institutional Research Ethics Committee with decision no. 0103/09. All three participants provided written informed consent in accordance with the provisions of Brazilian National Health Council Resolution 466/2012.

Results

Case presentation

Case 01:

A 26-year-old male was diagnosed with dilated cardiomyopathy (DCM) of unknown etiology. Symptoms had developed 5 years before with lower-extremity edema, palpitations, and progressive dyspnea. He denied chest pain, syncope, or paroxysmal nocturnal dyspnea. However, he had a history of pulmonary thromboembolism (PE) and was positive for the NS phenotype (webbed neck, hypertelorism, micrognathia, low-set ears, and right-sided cryptorchidism).

The family history included a sister with heart disease of unclear etiology and the same NS phenotype. Their parents were healthy and non-consanguineous; there were no other cases in the family. He also denied a history of hypertension, diabetes mellitus (DM), dyslipidemia, or problem alcohol use, and did not use tobacco or take illicit drugs. Medications for the past 6 months included warfarin, carvedilol, losartan, spironolactone, and furosemide.

At the first clinic visit, the patient was in no acute distress, afebrile, with pink and moist mucous membranes and no dyspnea at rest. Cardiovascular examination revealed visible jugular venous distension when supine, a regular rhythm with no third heart sound, and a grade II/IV systolic murmur in the mitral area. The heart rate (HR) was 60 beats per minute and the blood pressure (BP) 100/80 mmHg. The respiratory rate was normal, and the lungs were clear to auscultation. The extremities were warm and well-perfused, with grade II/IV lower-limb edema.

Plain radiography of the chest showed an enlarged heart shadow, and the initial electrocardiogram was notable for evidence of biventricular hypertrophy and first-degree atrioventricular block; 24-hour Holter monitoring recorded several runs of nonsustained ventricular tachycardia (NSVT). Echocardiography revealed marked biventricular systolic dysfunction, pulmonary hypertension, mild mitral and moderate tricuspid regurgitation, and a filling defect consistent with an apical thrombus in the right ventricle (RV). CMR confirmed biventricular systolic impairment (LVEF: 0.25; RVEF: 0.21) and increased myocardial thickness, as well as positive criteria for NCCM (NC/C ratio: 2.7) (Figure 1).

The patient experienced initial improvement in symptoms but was then lost to follow-up for 2 years. When next seen, he was in fair condition, pale, with poor peripheral perfusion, anasarca, palpitations, and dyspnea at rest, and was hospitalized for acute decompensated HF. Cardiovascular examination revealed jugular venous distension in the seated position and muffled heart sounds (regular S1/S2 rhythm). The HR was 88 beats per minute and the BP 90/60 mmHg. The respiratory rate was 30 breaths per minute; bibasilar crackles were heard on lung auscultation. Laboratory tests were notable for evidence of acute kidney injury and leukocytosis. During hospitalization, PE was once again suspected but ruled out by CT angiography. Within 36 hours, cardiogenic shock developed despite high-dose vasopressors, standard measures for septic shock, and intra-aortic balloon pump placement. He died in cardiac arrest with pulseless electrical activity.

Postmortem examination confirmed the Noonan phenotype and myocardial involvement consistent with NCCM. Extensive intramural fibrosis in the ventricular myocardium and thrombi in the right atrium were found (Figure 2). Changes secondary to congestive HF were seen in the lungs (passive pulmonary congestion, dilatation of the pulmonary artery), liver (chronic passive congestion, centrilobular hepatic necrosis), and spleen (chronic passive congestion), in addition to anasarca (ascites, pleural effusion, and pericardial effusion). Multiple thromboembolic phenomena were also identified, including organizing thrombi in the right atrium and posterior wall of the right atrium, healed cortical infarcts in both kidneys, multiple splenic infarcts, and widespread petechiae, as well as diffuse alveolar damage and massive hemorrhage in both lungs.

Case 02:

A 33-year-old female presented for HCM screening after the death of her brother (Case 01). She reported sporadic palpitations as her only symptom. There was an established history of infertility and the NS phenotype (Figure 3). The family history was as for Case 01. She denied hypertension, DM, dyslipidemia, and use of alcohol, tobacco, or other substances. She took no medications. At the first visit, the patient was in no acute distress, afebrile, with pink and moist mucous membranes and no dyspnea at rest. Cardiovascular examination was unremarkable except for a grade I/IV systolic murmur in the mitral area; the rhythm was regular with no third heart sound and there was no appreciable jugular venous distension. The HR was 72 beats per minute and the BP 110/80 mmHg. The respiratory rate was normal, the lungs were clear to auscultation, and the extremities were warm and well-perfused, with no peripheral edema.

A plain radiograph of the chest showed an enlarged cardiac shadow and evidence of pulmonary congestion (Figure 4). The initial electrocardiogram showed regular sinus rhythm with evidence of biatrial enlargement, RV hypertrophy, and septal hypertrophy (Figure 5); 24-hour Holter monitoring showed prolongation of the QT interval, as well as a single episode of NSVT. CMR was notable for significant ventricular hypertrophy (septal thickness 17 mm and lateral wall thickness 16 mm) and excessive trabeculation of the anterior, lateral, and inferior walls—findings consistent with NCCM (NC/C ratio: 2.4). There was also prominent dilatation of the pulmonary trunk, vena cava, and hepatic veins, as well as an apical thrombus in the left ventricle (Figure 6).

The patient was started on warfarin, carvedilol, and enalapril and reported improvement of palpitations. Seven months later, she suddenly developed pain in the left leg with associated malaise and right-sided paresthesias (including the face). She presented to the emergency department and was diagnosed with a transient ischemic attack involving multiple cerebral segments. Neuroimaging was consistent with subtotal occlusion of the proximal segment of the left middle cerebral artery (Figure 7). Chemical thrombolysis was performed uneventfully, and she recovered with no residual motor or cognitive deficits. During the same hospitalization, arteriography of the left lower extremity confirmed acute arterial occlusion in the left femoral artery, which was treated by surgical thrombectomy. After discharge, the patient experienced several further episodes of acute decompensated HF, NSVT, and QT prolongation, ultimately requiring placement of an implantable cardioverter/defibrillator. Despite optimization of medical therapy, over the following year she required frequent hospitalization for decompensated HF; HTx was indicated and performed successfully. As of the time of writing, she remains stable under close outpatient follow-up.

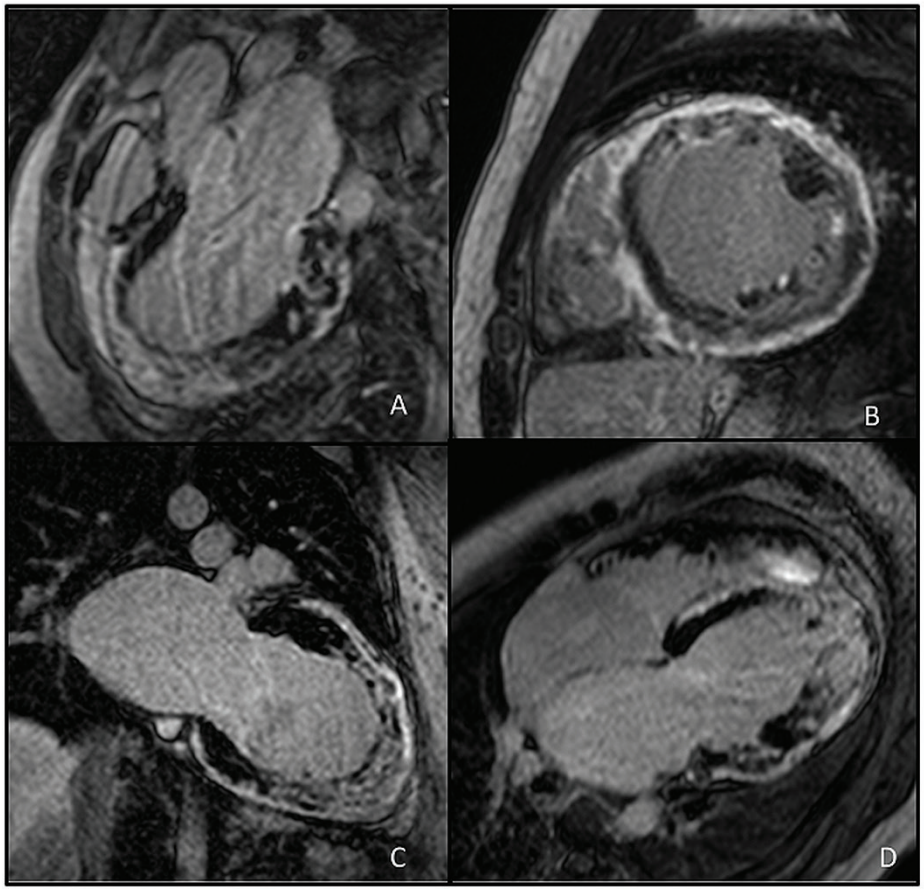


Figure 1 – *Late gadolinium enhancement CMR of Patient 1 showing diffuse delayed hyperenhancement of prominent left ventricular trabeculations, suggesting fibrosis. This patient showed overlap of findings consistent with HCM and NCCM.*

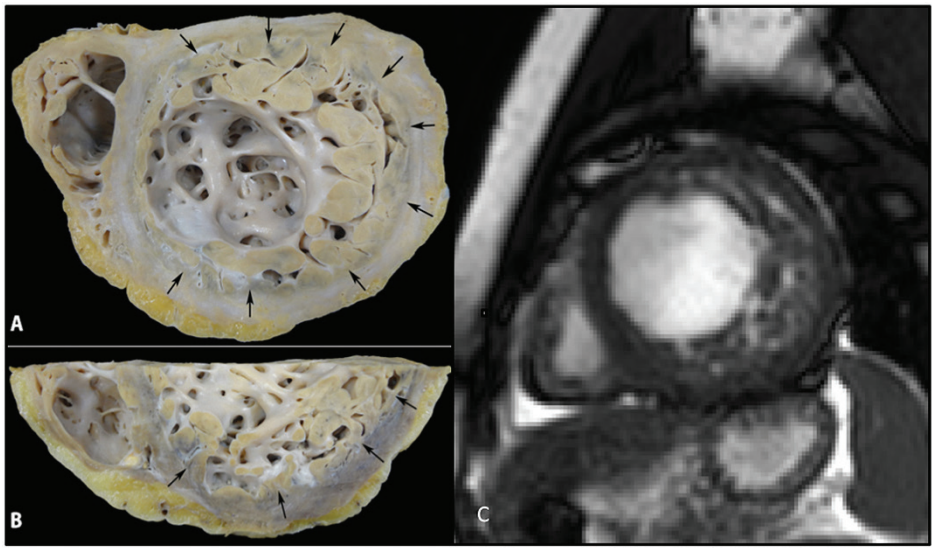


Figure 2 – *Axial (A) and coronal (B) sections through the cardiac ventricles of Patient 1 showing apical views of the left ventricular cavity with polypoid, anastomosing trabeculations (arrows) of the subendocardial layer. Short-axis cine CMR images (C) of the same patient, showing overlap between HCM and NCCM findings.*

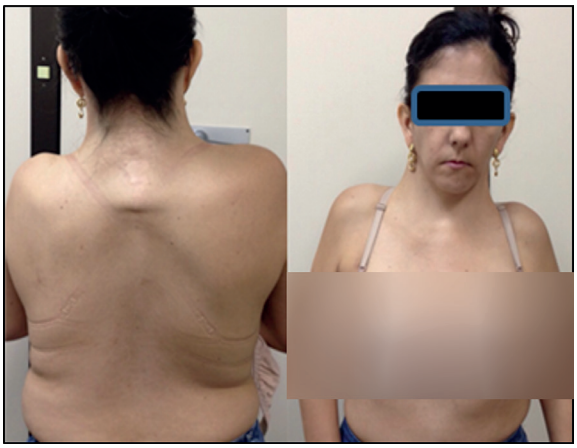


Figure 3 – *Photographs of Patient 2 (A and B). Note the webbed neck, low-set ears, pectus carinatum, scoliosis, and micrognathia.*

Case 03:

A 24-year-old male presented with a history of cardiomyopathy of unknown etiology, diagnosed at 3 years of age. He had been well until age 20, when he experienced a sudden deterioration of functional class requiring successive hospitalizations for acute decompensated HF. Physical examination was notable for the NS phenotype (short stature, webbed neck, hypertelorism, micrognathia, and low-set ears). There were no other cases in the family. Both parents were healthy and non-consanguineous. There was no psychomotor retardation. The patient denied hypertension, DM, dyslipidemia, and use of alcohol, tobacco, or other substances. Medications included bisoprolol, ivabradine, captopril, furosemide, spironolactone, hydrochlorothiazide, and warfarin. He was referred to our hospital for admission due to acute HF decompensation with dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, and right upper quadrant pain. He reported no palpitations, chest pain, or syncope.

At the first visit, the patient was afebrile and well-hydrated but appeared acutely ill, with grade II/IV pallor and dyspnea at rest. Cardiovascular examination was notable for a grade I/IV systolic murmur in the mitral area, a regular rhythm with no third heart sound, and visible jugular venous distension while seated. The HR was 72 beats per minute and the BP 80/50 mmHg. He was tachypneic (RR 29 breaths per minute) and pulmonary auscultation revealed bibasilar crackles. The extremities were cold, clammy, and poorly perfused, with marked (grade III/IV) lower-limb edema.

Plain chest radiographs showed an enlarged cardiac shadow. The initial electrocardiogram showed evidence of biatrial and RV enlargement; 24-hour Holter monitoring recorded runs of NSVT. Transthoracic echocardiography showed increased myocardial thickness consistent with HCM, significant biventricular systolic dysfunction, marked LV diastolic dysfunction with a restrictive pattern (Figure 8), pulmonary hypertension, and a filling defect suggestive of apical thrombus in the LV. CMR confirmed biventricular systolic impairment (LVEF: 0.24; RVEF: 0.28) and increased myocardial thickness, as well as positive criteria for NCCM (NC/C ratio: 3.4). Late gadolinium enhancement was seen in the mesocardial layer mid-apically and in the epicardial layer circumferentially.

The patient had a stormy course complicated by bronchopneumonia, cardiac tamponade due to pericardial effusion requiring drainage, acute kidney injury, and mixed cardiogenic-septic shock, dying on the 62nd hospital day.

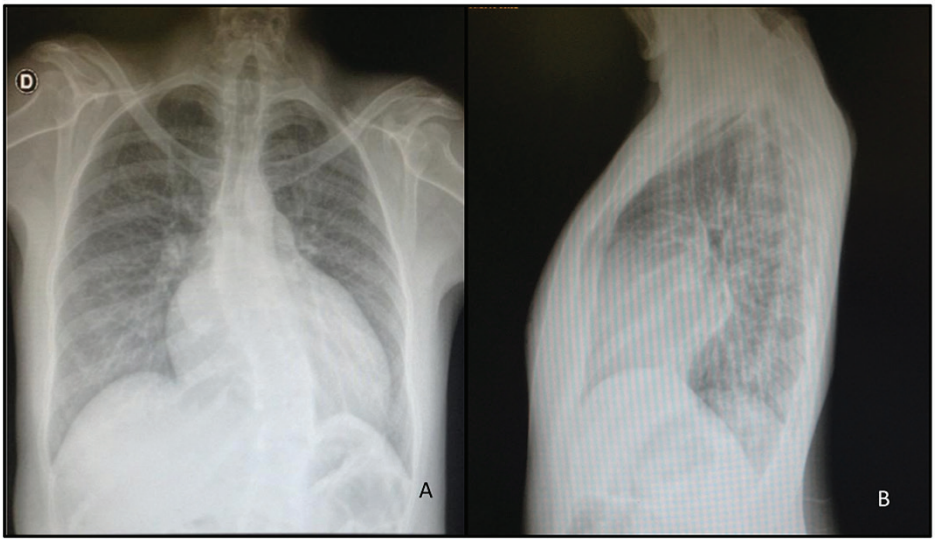


Figure 4 – *Patient 2 - PA (A) and lateral (B) chest radiographs showing pectus carinatum, scoliosis, cardiomegaly, and evidence of pulmonary congestion.*

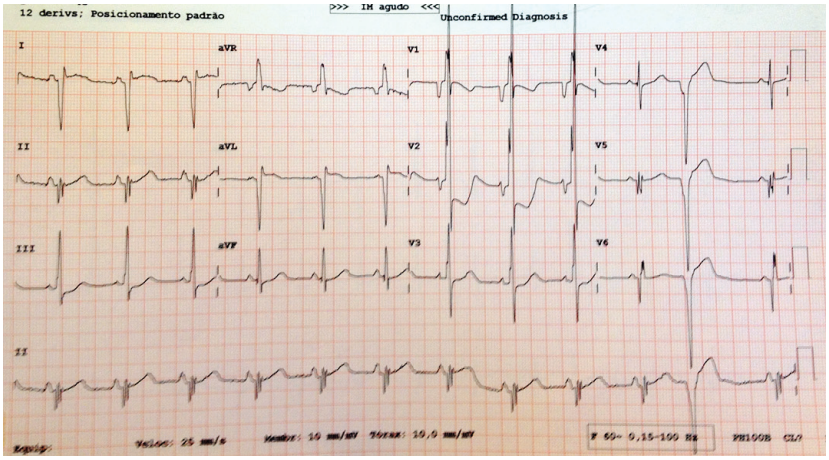


Figure 5 – *Patient 2 - 12-lead ECG showing sinus rhythm, evidence of biatrial and right ventricular enlargement, and severe septal hypertrophy.*

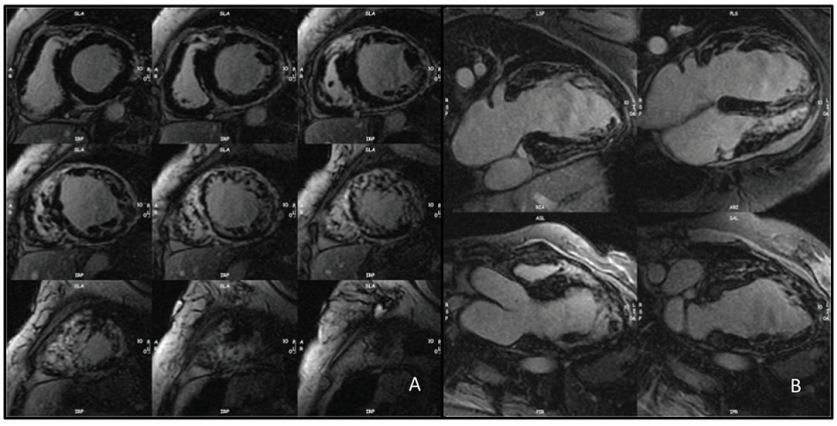


Figure 6 – *Patient 2 - CMR showing severe ventricular hypertrophy, excessive trabeculation of the anterior, lateral, and inferior myocardial walls (NC/C ratio: 2.4), and an enlarged left ventricle with significant systolic dysfunction (LVEF: 0.20). A non-ischemic delayed enhancement pattern is visible. There is also an apical thrombus in the left ventricle.*

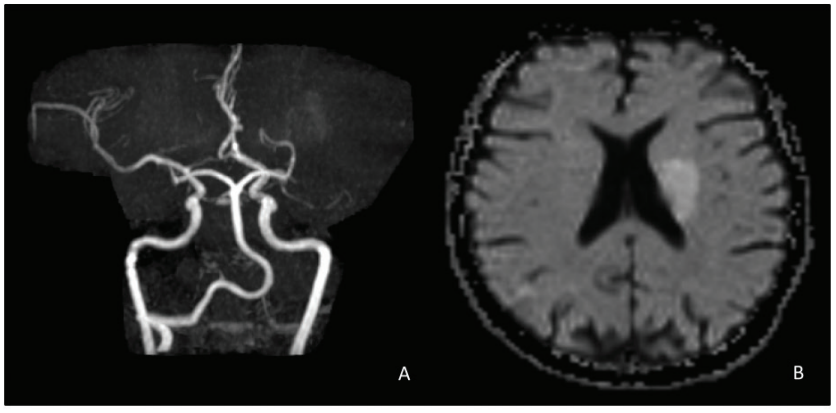


Figure 7 – *Brain MRI: ischemic stroke secondary to involvement of multiple cerebral vascular territories. Imaging is consistent with subtotal occlusion of the proximal segment of the left middle cerebral artery (A). The periventricular region, internal capsule, part of the caudate nucleus, posterior putamen, and subinsular region on the left are all involved (B).*

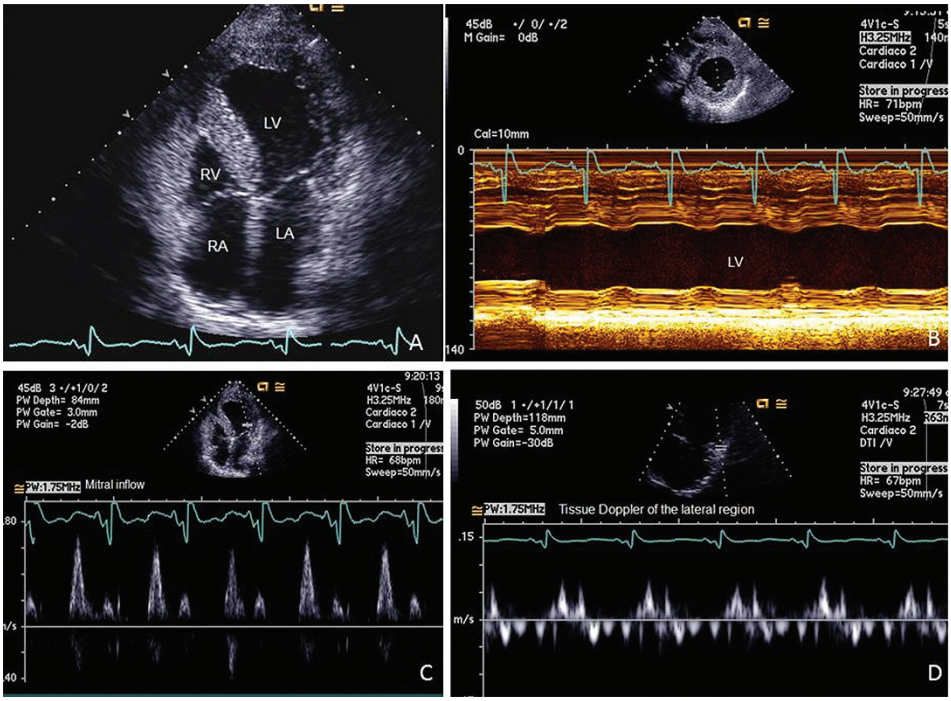


Figure 8 – *Two-dimensional and M-mode transthoracic echocardiography showing biventricular hypertrophy, LV trabeculation (A and B), and a restrictive diastolic dysfunction pattern (C and D).*

Analysis of common findings

All patients had the NS phenotype and met diagnostic criteria for NCCM. Of the 3 patients, 1 was female and 2 were male (66.6%), with a mean (SD) age of 27.6 (3.8) years. The female patient and the first male patient were siblings, while the other male patient had no family history of NS or cardiomyopathy; none of the patients had consanguineous parents. All had an established diagnosis of cardiomyopathy, with the second male patient having been diagnosed at 3 years of age. The presenting symptoms were dyspnea (n=2), palpitations (n=2), lower-limb edema (n=2), paroxysmal nocturnal dyspnea (n=1), and anasarca (n=1). All patients denied hypertension, DM, dyslipidemia, and use of alcohol, tobacco, or illicit substances. Physical examination was notable for a regular rhythm with no third heart sound, systolic murmur in the mitral area, and jugular venous distension while seated in all three patients, as well as muffled heart sounds in one.

Plain chest radiographs showed an enlarged cardiac shadow in 100% of cases (n=3). Electrocardiography revealed biventricular enlargement and first-degree atrioventricular block (n=1), normal sinus rhythm with evidence of biatrial enlargement (n=1), and biatrial enlargement with no prominent sinus rhythm (n=1), right ventricular hypertrophy (n=2), and septal hypertrophy (n=1). All patients had runs of NSVT on 24-hour Holter monitoring; the female patient also had prolongation of the QT interval. Echocardiography was performed in only two patients, revealing significant biventricular systolic dysfunction (n=2), LV dysfunction with a restrictive pattern (n=1), pulmonary hypertension (n=2), mitral regurgitation (n=1), and tricuspid regurgitation (n=1). All patients had evidence of apical thrombi, two confirmed by echocardiography and the third by CMR; two were in the left ventricle and one in the RV.

CMR showed increased myocardial thickness in 100% of cases (n=3), with a mean NC/C myocardium ratio of 2.8 (SD = 0.4). One patient showed excessive trabeculation of the anterior, lateral, and inferior walls.

All patients presented with HF (n=3) and acute decompensation. Pulmonary congestion was present in two cases, as was pericardial effusion. Optimized medical therapy was attempted in all patients; one discontinued treatment and was lost to follow-up and two had an inadequate response to treatment. Thromboembolic events occurred in 66.6% of cases (n=2), in the form of PE (n=1) and transient ischemic attack (n=1). The outcomes were implantable cardioverter/defibrillator placement with subsequent HTx in one case and death in cardiogenic shock in the two others. The patient who underwent HTx has since experienced significant improvement in her condition.

Discussion

NS is an autosomal dominant genetic disorder with a wide range of phenotypic presentations, including short stature, webbed neck, facial dysmorphism, delayed puberty, and skeletal and cardiovascular anomalies. Its incidence ranges from 1 in 1000 to 1 in 2500 live

births, being the second leading genetic cause of heart defects.[1,2,8] Although its clinical manifestations are not yet fully understood, cardiovascular changes are common, with pulmonary artery stenosis being most prevalent, which highlights the importance of cardiology follow-up throughout adulthood.[2,8,9] Outcomes similar to those of our series were found in a cohort studied by Shaw et. al., with 112 individuals followed for 12 years; 19% of them developed HCM, with one undergoing HTx, and three deaths due to myocardial infarction secondary to HCM.[10] The association of NS with NCCM is exceedingly rare, having been reported only by Nakamura et al. in a rat model in 2007 and by Sun et al. in a 12-year-old child in 2016.[3,11] Heart disease is the worst prognostic factor in patients with NS and, therefore, that most associated with mortality, as demonstrated in the three cases described herein, where the two male patients died in cardiogenic shock and the female patient ultimately required HTx.[2]

The American Heart Association considers NCCM a genetic disorder, with great genotypic and phenotypic variability.[12] Candidate genes have already been identified, such as *MYH7*, *TNNT2*, *TNNI3*, and *ACTC*, with those associated with defects in the genesis of sarcomere proteins being most common.[13-16] NCCM is characterized by the arrest of myocardial compaction during embryogenesis, leading to varying degrees of trabeculation, creating deep recesses that predispose to the formation of thrombi and consequent thromboembolic events. CMR performed alongside echocardiography is currently the method of choice for diagnosis.[5, 6, 17] Imaging shows thickening of the LV myocardial wall with two distinct layers: a thin, compact epicardial layer (C) and a thick, NC endocardial layer (NC) filled with blood from the ventricular cavity. Using the Petersen criterion, a ratio of NC to compacted myocardium (NC/C) > 2.3 confirms the diagnosis.[6] NCCM usually progresses to microcirculatory dysfunction and ventricular systolic dysfunction. It may be associated with other genetic conditions such as Ebstein's anomaly, bicuspid valve, HCM, septal defects, and neuromuscular disorders, such as the Barth and Becker syndromes.[1,2,18] Other family members can be involved at rates ranging from 18 to 50% in the literature, which highlights the importance of family screening.[13, 18]

HCM is the most prevalent cardiomyopathy (1:500 live births). It is inherited in an autosomal dominant pattern and leads to thickening of the myocardial walls, although function is often initially preserved.[19] Recent research has demonstrated similar genetic anomalies in sarcomeres and beta-myosin heavy chain in patients with HCM and NCCM, such as the L620P mutation in *MYH7*, suggesting there may be genetic overlap in the different presentations of these two cardiomyopathies—which appears to be in agreement with the cases reported herein.[13-16] Some cases of comorbid HCM and NCCM have been described in the same individual or separately in different members of the same family, such as children of patients with NCCM who have HCM or NCCM/HCM overlap and vice versa.[15, 20]

LQTS affects ventricular repolarization, leading to serious arrhythmias such as *torsades de pointes* and ventricular fibrillation; it is associated with a high risk of sudden death. Although it may be caused by drug interactions or genetic mutations – such as the *KCNQ1* mutation –, it has only rarely been reported in association with NCCM, making genetic screening essential for diagnosis and intervention.[7, 21] As of the time of writing, the co-occurrence of NS, NCCM, and LQTS had not been reported.

The symptoms reported by the patients in our series were similar to those found in the literature on NCCM, such as dyspnea, chest pain, and clinical manifestations of HF.[18] Areas of delayed enhancement on imaging have been suggested as a criterion for preventive implantable cardioverter/defibrillator placement,[17] as was required by one of our patients. The literature shows that mortality and heart transplantation rates in isolated noncompaction of the myocardium are similar to those found in idiopathic cardiomyopathy. However, our patient presented with NCCM in association with NS and other cardiac dysfunction, with additional complications and a worse prognosis. The simultaneous co-occurrence of all of these conditions has not been previously reported in the literature.

Conclusion

This paper describes three cases (including one sibling pair) of NS and NCCM with significant ventricular dysfunction and other associated conditions. The association of all conditions reported herein in the same patient has not been previously described in the literature. We highlight the importance of early screening for heart disease in patients with NS. Family screening should be recommended for all first- and second-degree relatives. Early diagnosis and treatment can improve prognosis in these cases.

Author Contributions

Conception and design of the research: Tavares M, Salemi VMC; acquisition of data: Pimentel ALL, Tavares M; analysis and interpretation of the data: Pimentel ALL, Tavares M, Silva EA, Salemi VMC; obtaining financing: Salemi VMC; writing of the manuscript: Pimentel ALL, Tavares M, Silva EA; critical revision of the manuscript for intellectual content: Pimentel ALL, Silva EA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of Doctoral submitted by Marcelo Dantas Tavares de Melo, from Incor - USP.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Análise de Projetos de Pesquisa-CAPPesq da Diretoria Clínica do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo under the protocol number 0103/09. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Mendez HM, Opitz JM. Noonan Syndrome: A Review. Am J Med Genet. 1985;21(3):493-506. doi: 10.1002/ajmg.1320210312.
2. Smpokou P, Tworog-Dube E, Kucherlapati RS, Roberts AE. Medical Complications, Clinical Findings, and Educational Outcomes in Adults with Noonan Syndrome. Am J Med Genet A. 2012;158A(12):3106-11. doi: 10.1002/ajmg.a.35639.
3. Sun XL, Zhao JX, Chen XJ, Zeng Z, Chen YC, Zhang Q. A Unique Case of a 12-Year-Old Boy with Noonan Syndrome Combined with Noncompaction of the Ventricular Myocardium. Int Heart J. 2016;57(2):258-61. doi: 10.1536/ihj.15-343.
4. Gerecke BJ, Engberding R. Noncompaction Cardiomyopathy-History and Current Knowledge for Clinical Practice. J Clin Med. 2021;10(11):2457. doi: 10.3390/jcm10112457.
5. Jenni R, Oechslin E, Schneider J, Jost CA, Kaufmann PA. Echocardiographic and Pathoanatomical Characteristics of Isolated Left Ventricular Non-Compaction: A Step Towards Classification as a Distinct Cardiomyopathy. Heart. 2001;86(6):666-71. doi: 10.1136/heart.86.6.666.
6. Petersen SE, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Anderson RH, et al. Left Ventricular Non-Compaction: Insights from Cardiovascular Magnetic Resonance Imaging. J Am Coll Cardiol. 2005;46(1):101-5. doi: 10.1016/j.jacc.2005.03.045.
7. Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, et al. The Long QT Syndrome. Prospective Longitudinal Study of 328 Families. Circulation. 1991;84(3):1136-44. doi: 10.1161/01.cir.84.3.1136.
8. Prendiville TW, Gauvreau K, Tworog-Dube E, Patkin L, Kucherlapati RS, Roberts AE, et al. Cardiovascular Disease in Noonan Syndrome. Arch Dis Child. 2014;99(7):629-34. doi: 10.1136/archdischild-2013-305047.
9. van der Burgt I. Noonan Syndrome. Orphanet J Rare Dis. 2007;2:4. doi: 10.1186/1750-1172-2-4.
10. 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(2):128-32. doi: 10.1136/adc.2006.104547.
11. Nakamura T, Colbert M, Krenz M, Molkentin JD, Hahn HS, Dorn GW 2nd, et al. Mediating ERK 1/2 Signaling Rescues Congenital Heart Defects in a Mouse Model of Noonan Syndrome. J Clin Invest. 2007;117(8):2123-32. doi: 10.1172/JCI30756.
12. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary Definitions and Classification of the Cardiomyopathies: An American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113(14):1807-16. doi: 10.1161/CIRCULATIONAHA.106.174287.
13. Oechslin E, Jenni R. Left Ventricular Non-compaction Revisited: A Distinct Phenotype with Genetic Heterogeneity? Eur Heart J. 2011;32(12):1446-56. doi: 10.1093/eurheartj/ehq508.
14. Klaassen S, Probst S, Oechslin E, Gerull B, Krings G, Schuler P, et al. Mutations in Sarcomere Protein Genes in Left Ventricular Noncompaction. Circulation. 2008;117(22):2893-901. doi: 10.1161/CIRCULATIONAHA.107.746164.
15. Laaroussi L, Halima AN, Boukhris M, Addad F, Kachboura S. Left Ventricular Non-compaction Associated with Hypertrophic Cardiomyopathy in the Same Patient. Kardiol Pol. 2017;75(4):397. doi: 10.5603/KP.2017.0064.
16. Lorca R, Martín M, Gómez J, Santamarta E, Morís C, Reguero JJ, et al. Hypertrophic Cardiomyopathy and Left Ventricular Non-compaction: Different Manifestations of the Same Cardiomyopathy Spectrum? Int J Cardiol. 2015;190:26-8. doi: 10.1016/j.ijcard.2015.04.138.
17. Zuccarino F, Vollmer I, Sanchez G, Navallas M, Pugliese F, Gayete A. Left Ventricular Noncompaction: Imaging Findings and Diagnostic Criteria. AJR Am J Roentgenol. 2015;204(5):W519-30. doi: 10.2214/AJR.13.12326.
18. Rosa LV, Salemi VMC, Alexandre LM, Mady C. Miocardiopatia não compactada: uma visão atual. Arq Bras Cardiol. 2011;97(1):13-9. doi: 10.1590/S0066-782X2011000900021.
19. Iio C, Ogimoto A, Nagai T, Suzuki J, Inoue K, Nishimura K, et al. Association between Genetic Variation in the SCN10A Gene and Cardiac Conduction Abnormalities in Patients with Hypertrophic Cardiomyopathy. Int Heart J. 2015;56(4):421-7. doi: 10.1536/ihj.14-411.
20. Hoedemaekers YM, Caliskan K, Michels M, Frohn-Mulder I, van der Smagt JJ, Phefferkorn JE, et al. The Importance of Genetic Counseling, DNA Diagnostics, and Cardiologic Family Screening in Left Ventricular Noncompaction Cardiomyopathy. Circ Cardiovasc Genet. 2010;3(3):232-9. doi: 10.1161/CIRCGENETICS.109.903898.
21. Nakashima K, Kusakawa I, Yamamoto T, Hirabayashi S, Hosoya R, Shimizu W, et al. A Left Ventricular Noncompaction in a Patient with Long QT Syndrome Caused by a KCNQ1 Mutation: A Case Report. Heart Vessels. 2013;28(1):126-9. doi: 10.1007/s00380-012-0235-8.