Non-Compacted Cardiomyopathy in Children and Adolescents: From the Challenge of Echocardiographic Diagnosis to Clinical Follow-Up

Miocardiomatía Não Compactada em Crianças e Adolescentes: do Desafio do Diagnóstico Ecocardiográfico ao Acompanhamento Clínico

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Abstract

Background: Non-compacted cardiomyopathy (NCCM) is characterized by hypertrabeculations and deep recesses in the left ventricle, with a heterogeneous clinical presentation, ranging from asymptomatic patients to those with heart failure (HF), thromboembolic events and arrhythmias with risk of sudden death. As it is rare and does not have well-defined diagnostic criteria, its natural history in pediatrics is poorly understood. This study describes the clinical presentation and clinical course of patients with NCCM.

Methodology: Observational, longitudinal, prospective study of pediatric patients seen at a pediatric cardiology referral center from metropolitan region II in the state of Rio de Janeiro, with NCCM phenotype on echocardiogram (ECHO) during a 2-year follow-up, from the ChARisMa registry.

Results: 6 patients aged 4 to 14, with NCCM, were analyzed. Mean age 7.5 years (SD: 3.93), 3 males (50%). The patients presented HF (n=2), cardiac murmur (n=1), cardiac arrhythmia (n=1), were asymptomatic (n=1) or were under investigation for a genetic syndrome (n=1). Phenotypes on ECHO: NCCM/dilated cardiomyopathy (n=1) and NCCM/restrictive cardiomyopathy (n=1), isolated phenotype of NCCM (n=4). Cardiac magnetic resonance imaging was performed and confirmed the diagnosis (n=4). The outcomes observed were thromboembolism, indication for heart transplantation, and sustained ventricular tachycardia.

Conclusions: This case series provides relevant data for pediatric NCCM as it shows its heterogeneous clinical presentation and potentially fatal complications. More prospective studies are needed for an accurate diagnosis and to allow its clinical course, therapeutic response and prognosis to be better known.

Keywords: Cardiomyopathy; Heart failure; Children; Pediatrics.

Resumo

Fundamentos: Miocardiomatía não compactada (MCNC) caracteriza-se por hipertrabeculações e recessos profundos no ventrículo esquerdo, com apresentação clínica heterogênea, desde pacientes assintomáticos a insuficiência cardíaca (IC), eventos tromboembólicos arritmias com risco de morte súbita. Por ser rara e não apresentar critérios diagnósticos bem definidos, sua história natural na pediatria é pouco conhecida. Este estudo descreve a apresentação e evolução clínica de pacientes portadores de MCNC.

Metodologia: Estudo observacional, longitudinal, prospectivo, de pacientes pediátricos atendidos em um centro de referência em cardiologia pediátrica provenientes da região metropolitana II do Estado do Rio de Janeiro, com fenótipo de MCNC ao ecocardiograma (ECO) no período de 2 anos de acompanhamento, provenientes do Registro ChARisMa.

Resultados: Analisados seis pacientes com MCNC, de 4 a 14 anos de idade, média de idade de 7,5 anos (DP: 3,93), 3 do sexo masculino (50%). Apresentando-se com IC (n=2), sopro cardíaco (n=1), arritmia cardíaca (n=1), assintomático (n=1) ou em investigação de síndrome genética (n=1). Fenótipos ao ECO: MCNC/Miocardiomatía dilatada (n=1) e MCNC/Miocardiomatía restritiva (n=1), fenótipo isolado de MCNC (n=4). A ressonância magnética cardíaca foi realizada, confirmando o diagnóstico (n=4). Os desfechos observados foram tromboembolismo, indicação de transplante cardíaco e taquicardia ventricular sustentada.

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Conclusões: Esta série de casos proporciona dados relevantes da MCNC pediátrica, mostrando a heterogeneidade da apresentação clínica, bem como a ocorrência de complicações potencialmente fatais. São necessários mais estudos prospectivos para que seu diagnóstico seja corretamente realizado e sua evolução clínica, resposta terapêutica e prognóstico sejam mais bem conhecidos.

Palavras-chave: Cardiomiopatias; Insuficiência cardíaca; Criança; Pediatria.

Introduction

Cardiomyopathies are a group of rare diseases in childhood that, once diagnosed, are associated with high morbidity and mortality rates¹. With an estimated incidence of 0.12 per 100,000 children under ten years of age, non-compaction cardiomyopathy (NCM) is the third most common pediatric CM, followed by dilated CM (DCM) and hypertrophic CM (HCM)^{2,3,4}.

Also called left ventricular (LV) non-compaction, NCM was first described in 1932 in a necropsy study of a newborn. In 1986, the first echocardiographic report characterized it as spongy myocardium, and only in 2006 was it classified as a primary genetic CM by the American Heart Association (AHA). However, it remains a familial CM not classified by the European Society of Cardiology (ESC)^{2,5-8}. NCM is morphologically characterized by a myocardium with trabeculations and deep recesses that communicate with the ventricular cavity. It occurs more frequently in the LV but can affect the right ventricle and the interventricular septum as an isolated or mixed phenotype (association with other cardiomyopathies, congenital heart disease, and neuromuscular diseases)^{1-3,9,10}. Its pathophysiology is still not completely understood, but an embryogenetic failure in the myocardial layer compaction leads to hypertrabeculation and the characteristic spongy appearance. Different genetic changes controlling the sarcomeric, cytoskeletal, and mitochondrial functions have been described in NCM patients¹⁻³.

NCM can occur at any age, with a very heterogeneous clinical presentation ranging from asymptomatic patients to heart failure (HF), thromboembolic events, arrhythmias, and sudden death^{2,6,9}. Different echocardiographic and magnetic resonance diagnostic criteria have been proposed by different authors, hindering an accurate diagnosis^{2,8,10}.

Given its rarity, heterogeneous etiology and clinical presentation, and absence of universal diagnostic criteria, NCM is not well known by pediatricians and causes a diagnostic challenge for pediatric cardiologists and echocardiographers. This study aims to describe the clinicodemographic characteristics and presentation phenotype of pediatric NCM patients treated at a reference center in pediatric cardiology.

Methods

This was an observational longitudinal prospective study of pediatric patients seen at a pediatric cardiology referral center with NCM phenotype on echocardiography (ECHO). These patients were part of the ChARisMA Study (**C**hildren and **A**dolescent **R**egistry in **M**yocarditis and **C**ardiomyopathy), which consists of a registry of patients with different myocarditis and CM phenotypes diagnosed before the age of 19 years from the Metropolitan Region II of the State of Rio de Janeiro,

which covers seven municipalities: Itaboraí, Maricá, Niterói, Rio Bonito, São Gonçalo, Silva Jardim, and Tanguá.

The echocardiographic criterion for diagnosing the patients was the one described by Jenni, including a compaction–non-compaction layer ratio > 2 measured at the end of systole, with color Doppler showing the presence of blood filling from the ventricular cavity in the deep recesses, presence of several trabeculations, and absence of structural cardiac malformations¹¹. All ECHO images were reviewed by a second experienced examiner. Cardiac magnetic resonance imaging (CMRI) was used to confirm the echocardiographic diagnosis of NCM.

The patients underwent the most recent CM classification endorsed by the World Heart Federation, the MOGE(S) classification, which stands for **M**orphofunctional, **O**rgan involvement, **G**enetic or familial, **E**tiology, and **S**tage, and was developed to describe the multiple characteristics of cardiomyopathies¹². The variables studied were age at diagnosis, sex, phenotype on ECHO, clinical presentation, and family history. The outcomes analyzed were development of thromboembolic events, arrhythmias, HF development or worsening, heart transplantation, and death.

This study was approved by the local REC (CAAE: 93874218.2.0000.5243), and guardians and participants signed an informed consent and assent form as described in resolution 466/2012.

Results

From March 2019 to September 2021, 32 patients were included in the ChARisMA registry, six of whom had an echocardiographic diagnosis of NCM, representing 18.75% of the cases. These patients are still being followed up.

Of the six NCM patients, three were male (50%) and three were female. The age at diagnosis was 4–14 years (mean, 7.5 years; median, 7; and standard deviation, 3.93). At the time of diagnosis, two patients had HF, both with a mixed phenotype on ECHO, one with NCM and DCM, and the other with NCM and restrictive CM (RCM). The other cases (n = 4) presented an isolated NCM phenotype on ECHO (Figure 1). The main characteristics of this case series are shown in Table 1.

All patients underwent the MOGE(S) classification (Table 2), which describes the phenotype, family history, etiology, and clinical condition of the patient by HF functional class and staging.

Diagnosis was based on HF symptoms (n = 2) and physical examination changes such as heart murmur and cardiac arrhythmia – ventricular extrasystole (n = 2), one patient underwent familial screening with the phenotype confirmed on ECHO, and the other was confirmed in the context of the possible associated malformations on genetic syndrome investigation. CMRI performed in four cases confirmed the ECHO diagnosis.

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Figure 1 – Two-dimensional echocardiogram of a patient with non-compaction cardiomyopathy. The arrows show the non-compaction layer with excess trabeculations and the characteristic deep recesses at the left ventricular apex and free wall.

Table 1 - Clinical characteristics and progression of NCM patients.

ID	Sex	Age at diagnosis (years)	Reason for diagnosis	Functional class (NYHA)	Phenotype on ECHO	24-hour Holter	CMRI	Observations throughout follow-up	Patient condition at the end of follow-up
1	M	5	Heart murmur to be clarified	I	NCM	No changes	Yes	Absent	Asymptomatic, functional class I (NYHA)
2	M	9	Family screening (case 1's brother)	I	NCM	---	No	Absent	Asymptomatic, functional class I (NYHA)
3	F	9	Heart failure	III	NCM/RCM	NSSVT NSVT	Yes	Pulmonary thromboembolism, functional class IV (NYHA), included in the heart transplant list	Death
4	F	14	Heart failure	II	NCM/RCM	Without changes	No	Absent	Functional class II (NYHA), medicated with carvedilol
5	F	4	Irregular rhythm (ventricular extrasystole on ECG)	I	NCM	VT	Yes	Sustained ventricular tachycardia	Controlled arrhythmia after ablation and use of amiodarone.
6	M	4	Screening for malformations associated with genetic syndrome to be clarified	I	NCM	Without changes	Yes	Genetic diagnosis of 22q13 microdeletion confirmed (Phelan-McDermid Syndrome)	Functional class I (NYHA), hypotonia, global developmental delay

CMRI, cardiac magnetic resonance imaging; ECG, electrocardiogram; ECHO, echocardiogram; F, feminine; ID, identification; M, male; NSSVT, non-sustained supraventricular tachycardia; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; VT, sustained ventricular tachycardia.

The outcomes included arrhythmia on 24-hour Holter monitoring: non-sustained supraventricular tachycardia and non-sustained ventricular tachycardia and sustained ventricular tachycardia (Figure 2). In addition to pulmonary thromboembolism (PTE) in the case of a mixed NCM/RCM phenotype that progressed with HF worsening, the patient died after a 27-month follow-up despite drug optimization and referral for heart transplantation.

Discussion

As a rare disease, little is known about the clinical progression, prognosis, and treatment of pediatric NCM^{2,3}. Its classification as a distinct CM remains controversial, being defined as genetic primary CM by the AHA in 2006 but still

Table 2 - The MOGES classification (Morphofunctional, Organ involvement, Genetic or familial, Etiology, Stage).

Id	MOGES
1	$M_{NC} O_H G_{Undet} E_0 S_{B-I}$
2	$M_{NC} O_H G_{Undet} E_0 S_{B-I}$
3	$M_{R+NC} O_{H+C+Lu} G_{Undet} E_0 S_{D-IV}$
4	$M_{D+NC} O_H G_N E_0 S_{C-II}$
5	$M_{NC} O_H G_N E_0 S_{B-I}$
6	$M_{NC} O_{H+N+K} G_{22q13deletion} E_0 S_{B-I}$

E_{0^*} , without genetic testing; G_N , negative family history; G_{Undet} , genetic heritage undetermined; ID, patient identification; M_{NC} , non-compaction cardiomyopathy; M_{R+NC} , restrictive and non-compaction cardiomyopathy; O_H , heart involvement; O_{H+C+Lu} , heart, skin, and lung involvement; O_{H+N+K} , heart, neurological, and kidney involvement; S, New York Heart Association functional classification (I-IV) and American College of Cardiology/American Heart Association staging (A-D).

These criteria are based on the relationship between the compaction and non-compaction layers; however, they differ regarding the time of the cardiac cycle in which the measurement must be performed⁸. The criterion proposed by Jenni¹¹ consists of a ratio greater than two at the end of systole, being the most frequently used in studies available in the literature^{2,28,29}. Neme et al. highlights the importance of techniques such as real-time 3D ECHO and speckle tracking in understanding this CM³⁰. CMRI contributes to the diagnosis, especially when the ECHO is uncertain and the ratio between the compaction and non-compaction layers greater than 2.3 has a sensitivity of 86% and a specificity of 99% (Petersen criterion)^{2,21}. In addition to confirming the diagnosis, imaging studies are essential for phenotype categorization (mixed or isolated) and the determination of systolic and diastolic function, providing the physician with necessary information on its clinical progression and treatment³¹.

In the present case series, two patients could not undergo CMRI, and only the Jenni's ECHO criterion was used¹¹ associated with the family history and clinical presentation. These patients had a positive family history or HF signs and symptoms, and hypertrabeculation was characterized as NCM, not just as a physiological condition. As imaging methods do not determine the NCM pathognomonic sign, the Rotterdam criteria were proposed to differentiate pathological NCM trabeculations from the physiological trabeculations found in athletes, Afro-descendants, and long-term hypertensive patients. This criterion consists of clinical evaluation combined with ECG, ECHO/CMRI, family history, and genetic evaluation².

The most frequent NCM phenotype in children is the non-isolated form, which presents concomitantly with other CM or congenital heart disease (mixed phenotype) or associated with genetic syndrome, neuromuscular disease, or inborn error of metabolism^{2,3}. The North American and Australian registries showed that the most common phenotype was mixed, with NCM/DCM of 58.7–93%, followed by NCM/HCM (11%). The association with RCM is very rare^{4,14}. An anatomopathological study by Marques et al.¹⁰ showed that ventricular septal defect is the congenital heart disease most commonly associated with NCM. On the other hand, this case series presented a predominance of the isolated form, corroborating the study by Jurko et al.²¹.

No specific drug or surgical therapy strategy has been successfully introduced for NCM. However, the use of a beta-blocker or an angiotensin-converting enzyme inhibitor can lead to favorable LV remodeling^{2,16,20}. A case report by Redondo et al. described an important improvement in refractory HF after use of the phosphodiesterase-5 inhibitor (sildenafil) in a six-year-old boy³². Patients with a mixed phenotype or associated systemic condition should undergo targeted therapy^{3,13,28,33}.

Once NCM is diagnosed, patients should be closely monitored for possible complications and ventricular function deterioration. Imaging tests such as ECHO and CMRI, ECG, 24-hour Holter monitoring, and exercise stress testing should be performed whenever possible to rule out exercise-induced arrhythmia^{2,3}. Arrhythmias should be treated according to the established clinical protocols². One of the cases presented here progressed with sustained ventricular tachycardia for which the patient underwent ablation and remains free from new episodes of arrhythmia during the follow-up period.

Effort is needed to determine whether anticoagulation or prophylactic antiplatelet therapy is justified and beneficial in children^{2,3}. If cardiac function deteriorates despite optimized drug therapy, the viable option is heart transplantation. In North America, 4% of pediatric patients listed for heart transplantation are diagnosed with isolated NCM².

A study by Lofiego et al. of a cohort of adult patients demonstrated that disease presentation at diagnosis can determine the prognosis³⁴. Asymptomatic patients have a better prognosis than those with HF or VT, even children with an isolated NCM phenotype have better clinical progression^{1,3,13,14,16}. This also occurred in this case series, in which patients with mixed phenotypes (NCM/DCM and NCM/RCM) still required HF treatment in addition to presenting complications such as PTE, indication for heart transplantation, and death.

In the study by BRESCHIA et al.¹⁶, being less than 12 months of

age at diagnosis, LV systolic dysfunction, and ventricular arrhythmia were considered risk factors for death or heart transplantation. A systematic review by van Waning et al.³⁵ reported that children have a more severe presentation than adults.

Childhood cardiomyopathies have an important and heterogeneous genetic substrate in their etiology derived from multiple mutations in several genes. Variants in the same gene can cause different phenotypes and systemic changes that commonly affect organs other than the heart. More than 40 monogenetic and chromosomal defects have been described in the NCM population, with different inheritance patterns (autosomal dominant, autosomal recessive, and X-linked). NCM is a common finding in Barth syndrome, an autosomal recessive X-linked disease with mutation in the tafazzin (TAZ) gene on chromosome Xq28; it is also found in inborn errors of metabolism such as glycogen storage disease type 1, decarboxylase deficiency, and cobalamin C deficiency and associated with aneuploidies (Turner syndrome or trisomy 13, 18, and 21), copy number variations (22q11 and 1p36 deletion), neuromuscular disease (Duchenne and Becker dystrophy), mitochondrial diseases, and other genetic syndromes (Soto, Marfan, and RASopathies)^{2,3,28}.

Due to the genetic characteristic of NCM, family screening must always be performed using ECHO, with a possible early phenotypic diagnosis in asymptomatic patients. About 25–50% of patients with NCM have a positive family history^{2,14,15,28,29,35,36}. Genetic studies should also be encouraged despite the difficult access and numerous ethical issues involved in the genetic diagnosis of asymptomatic patients². According to a study published by van Waning, genetic causes have a worse prognosis in pediatric than adult patients, and NCM more commonly has a genetic cause when diagnosed in children, especially those younger than one year of age³⁷. Although genetic investigations were not conducted in all cases analyzed, family screening identified one case of NCM (brother) and one of a 22q11 microdeletion.

The use of the MOGE(S) classification in the studied cases proved useful in gathering fundamental characteristics requiring addressing in patients with cardiomyopathies, such as a morphofunctional phenotype, involvement of other organs and systems, family history, genetic changes, and clinical status through HF functional and staging classification, providing better understanding of the disease^{1,12,38,39}.

Conclusions

This case series provides relevant data on pediatric NCM, showing heterogeneous clinical presentation and the occurrence of potentially fatal complications. A limiting factor of the study is its small number of patients. More prospective studies are needed to ensure that NCM is correctly diagnosed and its clinical progression, therapeutic response, and prognosis are better known.

Authors' contributions

Research conception and design, critical review of the manuscript for important intellectual content: Torbey AFM, Souza ALAAG, Mosque ET; Data collection: Torbey AFM,

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Conflict of interest

The authors have declared that they have no conflict of interest.

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