CONTRASTING ASPECTS IN NONCOMPACTION CARDIOMYOPATHY

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Abstract

Left ventricle noncompaction or noncompaction cardiomyopathy is a rare cause of cardiomyopathy, presumed to be the consequence of the cessation of the embryological phenomenon of progressive compaction of the ventricular myocardium (which normally occurs between the 5th and 8th week) with the persistence, to varying degrees, of prominent trabeculae and deep intertrabecular spaces. Placed as an unclassified cardiomyopathy, this pathology is of interest due to different contrasting aspects observed in its evolution over time. The article reviews the etiopathogenic hypotheses, the diagnostic criteria according to the imagery used, the clinical forms of presentation and certain general principles of treatment. To illustrate the imagery used in this heart disease, the article has attached images of a case of noncompaction cardiomyopathy in a 26-year-old patient with left ventricular ejection fraction of 17% (measured by cardiac magnetic resonance imaging). Finally, the idea of the need for multicenter studies to establish whether this cardiomyopathy is an independent disease or a distinct phenotype which is not necessarily pathological is supported.

Keywords: noncompaction cardiomyopathy, ventricular trabeculations, stratified myocardium.

Rezumat

Noncompactarea de ventricul stâng sau cardiomiopatia de noncompactare este o cauză rară de cardiomiopatie, presupusă a fi consecința încetării fenomenului embriologic de compactare progresivă a miocardului ventricular (care are loc în mod normal între săptămâna a V-a și a VIII-a) cu persistența, în grade diferite, a trabeculațiilor proeminente și a spațiilor intertrabeculare profunde. Clasată ca și cardiomiopatie neclasificată, această patologie prezintă interes datorită diferitelor aspecte contrastante observate în evoluția sa de-a lungul timpului. Articolul revizuieste ipotezele etiopatogenice, criteriile de diagnostic în funcție de metodele de imagistică utilizate, formele clinice de prezentare și anumite principii generale de tratament. Pentru a ilustra imagistica utilizată în această afecțiune cardiacă, sunt atașate imagini ale unui caz de cardiomiopatie de noncompactare la un pacient de 26 de ani, cu o fracție de ejeecție a ventriculului stâng de 17% (măsurată prin rezonanță magnetică cardiacă). În final este susținută ideea necesității studiilor multicentrice pentru a stabili dacă această cardiomiopatie este o boală independentă sau un fenotip distinct care nu este neapărat patologic.

Cuvinte cheie: cardiomiopatie de noncompactare, trabeculații ventriculare, miocard stratificat.

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Introduction

Left ventricle noncompaction or noncompaction cardiomyopathy is a heterogeneous morphological disorder caused by the action of various genetic or non-genetic factors on the normal structure of the primitive heart resulting in a special myocardial phenotype. In a recent article published in January 2020, Davinder et al. mentions that the disease can also be found under the name: spongy myocardial pattern, spongiform cardiomyopathy, left ventricular hypertrabeculation, persistence of isolated myocardial sinusoids or zaspopathy (a form of progressive muscular dystrophy)⁽¹⁾.

The main characteristic of this type of cardiac pathology is an increased trabecular mass of the left ventricular in contrast to a thin compact epicardial layer. Prominent ventricular trabeculations, intertrabecular recesses and a myocardium composed of two layers: the compacted layer and the noncompacted layer can be visualized with imaging techniques that confirm the diagnosis. The predominant locations of the noncompacted segments are the apex, posterior and lateral wall⁽²⁾. Many authors have questioned the category in which noncompaction of the left ventricle should be placed - some consider it an independent disease referring to cardiomyopathy, others reclassify it as a distinct phenotype that is not necessarily pathological.

Etiology

From a genetic point of view, sporadic and familial forms are described, caused by pathogenic mutations in genes encoding sarcomeric proteins, with a predominant autosomal transmission⁽²⁾. In a study published by Bennet et al., which followed 34 patients diagnosed with noncompaction of isolated left ventricle, only 6 patients had a family history. They identified several genes involved in the genesis of this pathology: Fbcp1a / Notch pathway, G4.5 gene / TAZ protein, 14-3-3 deletion, ZASP protein, TNNT2 protein, MYH7 protein, TPM1 protein, MYBPC3 protein, ACTC1 protein, concluding that routine genetic testing is not recommended⁽³⁾.

Contrary to these results, van Waning et al. notes in his study a significant genetic heterogeneity and genetic mutations frequently encountered in other myocardial disorders. In 45% of the cases studied in children, they found a genetic cause, while in adults they recorded a percentage of 30%. Therefore, they opted for routine genetic testing in order to subsequently establish a genotype-phenotype relationship⁽⁴⁾.

There are two etiopathogenic hypotheses - the embryological origin closely related to the genesis process of the intramiocardial capillary network and the non-embryological origin. Until the end of the first trimester of intrauterine life, a series of trabeculae emerge

in the structure of the primitive heart as protuberances of the endocardial layer. Their role is to increase the surface / volume heart ratio and also to increase muscle mass before the appearance of the coronary arteries.

Until the 4th month of gestation, the involution of these trabeculae occurs, being compressed and transformed into a capillary network, the myocardium becoming compacted in his majority^(5,6). When this sequence of events is disturbed, the phenotype of noncompaction cardiomyopathy appears, characterized by a thickened myocardium, about twice as large as the compacted layer, with excessive and deep trabeculae and deep intertrabecular cavities⁽⁷⁾. The clinical consequences of these changes are heart failure syndrome, the risk of arrhythmia and stroke. Contrary to this embryological theory of noncompaction, an article by Jensen et al published in 2017 reports that excessive trabecularity in this cardiomyopathy does not have the same identity as normal embryonic trabecularity, claiming that etiopathogenesis is, probably, a malformation⁽⁸⁾.

Epidemiology

The incidence of left ventricle noncompaction is uncertain, ranging from 0.05% to 0.24%, depending on the studied population⁽⁹⁾. The prevalence in a study that included 104 pediatric patients with primary cardiomyopathy was about 9%⁽¹⁰⁾, while among adults, the incidence reported a value of 0.05%⁽¹¹⁾.

Another study conducted on 2742 individuals recruited to the Multi-Ethnic Study of Atherosclerosis (MESA) concluded minor differences during 9,5 years in left ventricular ejection fraction, ventricular volumes, or adverse cardiovascular outcomes, so the noncompaction of left ventricular seemed to be a common morphological finding⁽¹²⁾.

The low percentages in prevalence are explained by the fact that left ventricle noncompaction remains asymptomatic for a long time and by the fact that it is frequently underdiagnosed by ultrasound. Using current diagnostic criteria, a higher prevalence of this disease has been reported in healthy black people, intensely trained athletes or among patients with heart failure^(13,14).

Thus, the question is whether this cardiomyopathy is a phenotype of a physiological myocardium or of a pathological one. The pathological character is supported by the presence of genetic mutations or non-genetic factors such as volume or pressure overload, while the physiological character may be supported by the presence of a reversible left ventricular myocardium remodeling with prominent trabeculations in athletes or pregnant women.

The age at presentation is very variable, from prenatal diagnosis to patients over 80 years of age, the average being 40 to 50 years in adults and 5 to 7 years in children. Men are more often affected than women^(15,16).

Pathophysiological mechanisms

Pathophysiological consequences of left ventricle noncompaction are the result of modified coronary microcirculation through its compression by the thickened myocardium, generating myocardial fibrosis and impaired cardiac systolic function.

Also, trabeculations affects ventricular filling pattern by their protruding into the left ventricular lumen, causing reduced ventricular compliance.

Arrhythmias, a prothrombotic condition caused by blood stagnation in the intertrabecular recesses and dilation of heart chambers eventually lead to heart failure and risk of sudden cardiac death^(2,17,18).

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Forms of clinical presentation

The clinical presentation can be in a variety of ways, from the asymptomatic stage to the end-stage of heart failure, often associated with a high risk of fatal arrhythmias, sudden cardiac death or thromboembolic events^(19, 20). Diagnosis of noncompaction cardiomyopathy may be found incidentally by an echocardiography in a family screening or may be suspected due to conduction disturbances or potentially fatal arrhythmias such as ventricular tachycardia. Therefore, dyspnea, palpitations, chest pain or syncope may be common symptoms in patients with this disease. In pediatric populations neuromuscular disorders and dysmorphism have been noticed⁽²¹⁾.

Diagnosis

Diagnosis of noncompaction cardiomyopathy is a non-invasive one, based on clinical criteria and highlighted by the study of left ventricular morphology by different methods: electrocardiography, echocardiography, computed tomography, cardiac magnetic resonance imaging or left ventriculography. Electrocardiography does not show abnormalities specific to this entity, the most common changes being intraventricular conduction disorders, left ventricular hypertrophy, repolarization disorders and Wolf

- Parkinson - White syndrome. Holter-ECG is a useful investigation highlighting cardiac arrhythmias that require pacing or implantable defibrillator^(21,22,23).

From an echocardiographical point of view, diagnosis of noncompaction cardiomyopathy must be considered in the presence of a stratified myocardium composed of a single thinner epicardial layer and a thick endocardial layer with prominent trabeculae and deep intraventricular recesses (Figure 1 and Figure 2)⁽²²⁾. Three diagnostic criteria are described in the literature as follows: Chin, Jenni and Stöllberger criteria. The first two use the ratio between compacted and non-compacted layer, the main difference being the moment of the cardiac cycle at which measurements are made (end of systole / end of diastole), and the third criteria - Stöllberger, requires the presence of four or more trabeculations protruding from the apical wall of the left ventricle to the papillary muscles^(23,24,25). A study published in 2008 by Kohli et al, analyzes the accuracy of echocardiography by comparing the three sets of criteria described above, concluding the superiority of Chin criteria, but at the cost of a high percentage of false-positive diagnosis.

This result highlights a limitation of echocardiographic criteria, especially when it is applied to certain categories of patients, such as healthy black individuals, pregnant

women or athletes, who are often overdiagnosed. It is necessary to use advanced techniques in the future, especially in the apical region or in patients with a limited acoustic window, such as three-dimensional echocardiography, contrast agents to better define myocardial layers, transesophageal echocardiography, tissue Doppler or myocardial strain study^(26,27,28). These methods facilitate differential diagnosis with other types of cardiomyopathies and allow discovery of subclinical systolic dysfunction in patients with preserved ejection fraction.

Cardiac magnetic resonance imaging is a complementary technique to cardiac ultrasound, confirming the diagnosis of noncompaction cardiomyopathy by better visualization of the myocardial layers (Figure 3 and Figure 4). The possibility of visualizing the cardiac apex, the cardiac morphology, the comparative kinetics between the two myocardial layers, as well as the late gadolinium enhancement in the evaluation of myocardial fibrosis are only some of the advantages of this method. The most used diagnostic criteria in magnetic resonance are the Peterson criteria, which establish the diagnosis if the ratio of uncompact / compacted layers is greater than 2.3 and the Jacquier criteria which suggest the diagnosis if the trabecular mass of the left ventricle represents more than 20% of the global myocardium mass measured at the end of the diastole^(29,30).

Cardiac computed tomography is an alternative to magnetic resonance imaging, being used when the latter is contraindicated, allowing visualization of coronary arteries and large vessels. High doses of irradiation and reactions to the contrast substance are some of the disadvantages of this method^(31,32,33). Computed tomography diagnostic criteria are not specified in the literature due to lack of

studies. Contrasting left ventriculography is indicated in patients with left ventricular systolic dysfunction who also have ischemic coronary heart disease and require coronary angiography, and there are no clear diagnostic criteria so far⁽³⁴⁾.

Classification

Noncompaction cardiomyopathy was originally considered a primary genetic cardiomyopathy by the American Heart Association, a classification supported by numerous published studies that supported the genetic cause of failure of intrauterine compaction. The subsequent emergence of acquired forms of cardiomyopathy without compaction in highly trained athletes and pregnant women, in response to an overload of volume and pressure, led the European Cardiovascular Society to propose this pathology as unclassified cardiomyopathy⁽³⁵⁾. In a 2015 Lancet article, Towbin and colleagues argue that left ventricular noncompaction should not be viewed as a single entity but should be divided into several subtypes to facilitate treatment⁽²¹⁾. Thus, at least eight different phenotypes of noncompaction cardiomyopathy are described, as follows:

- Benign noncompaction cardiomyopathy - characterized by normal-sized left ventricle with preserved systolic-diastolic function, also considered a variant of normal^(36,37).
- Noncompaction cardiomyopathy associated with arrhythmias: preserved systolic function, left ventricular size and wall thickness within normal limits. The presence of arrhythmias is an independent factor of mortality, increasing the risk of sudden death⁽³⁸⁾.

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- Dilated noncompaction cardiomyopathy: characterized by left ventricular dilation and left ventricular dysfunction.
- Hypertrophic noncompaction cardiomyopathy: phenotype characterized by thickening, dilation and dysfunction of the left ventricle that has an increased risk of mortality.
- Restrictive non-compaction cardiomyopathy: it is very rare, characterized by a phenotype similar to restrictive cardiomyopathy that presents a risk of sudden death by associated arrhythmias or by heart failure with preserved ejection fraction.
- Right or biventricular noncompaction cardiomyopathy: characterized by excessive trabeculation of both cardiac cavities.
- Noncompaction cardiomyopathy associated with congenital heart diseases such as Ebstein's disease, aortic bicuspid, ventricular septal defect (DSV), transposition of large vessels - prognosis depending on the type of congenital heart disease⁽²¹⁾.

Considering these subtypes, we notice an important overlap with the other types of cardiomyopathies, making differential diagnosis more difficult, being described the so-called overlap phenotype. In most cases,

the left ventricle non-compaction is a component of an underlying cardiomyopathy, the so-called pure noncompaction cardiomyopathy being very rare. There is no gold standard for the diagnosis of noncompaction, so family history, clinical examination and imaging support are defining in this pathology. The presence of a thrombus in the cardiac apex, of some structural abnormalities (rupture of cords) or changes in physiological situations - pregnancy, sports - are criteria for differential diagnosis. The evaluation of papillary muscles is very important, as they are endocardial structures, they will not have a normal appearance, being affected by the noncompaction process^(39,40).

Treatment

Management of noncompaction cardiomyopathy depends on the subtype diagnosed, each phenotype having a different approach. The hereditary nature of this pathology obliges the attending physician to recommend ultrasound screening of first-degree relatives. Treatment is established according to the presentation of the patient and the degree of left ventricular dysfunction:

- Anticoagulation - there is currently no consensus on the use of anticoagulants to prevent embolic complications, some authors recommend the use of routine anticoagulant treatment in all

Figure 1 and Figure 2. Noncompaction dilated cardiomyopathy in a 26-year-old patient with LVEF = 17% (measured by cardiac MRI)

2D short axis cardiac ultrasound and 4 chambers with trabeculae and spongy appearance

Source: Non-invasive Cardiovascular Laboratory - Dr. Carol Davila Central Emergency

University Military Hospital Bucharest, Romania

Figure 3 and Figure 4. Appearance of cardiac MRI with short axis sections and 4 chambers that objectifies a ratio between non-compacted myocardium / normal myocardium of minimum 2.4 and maximum 3.2 at the apical level.

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patients diagnosed with noncompaction cardiomyopathy, others recommend anticoagulation only at a low ejection fraction less than 40% or in those with intracavitary thrombus. If atrial fibrillation is associated, anticoagulation will be performed using the CHA2DS2-VASC score^(17,18).

- Primary prevention of sudden cardiac death: patients with noncompaction cardiomyopathy present an increased risk of sudden death even if the ejection fraction is normal. Patients with severe systolic dysfunction are considered at risk, but also those whose systolic function is preserved, if they meet one of the criteria: history of syncope, unsupported ventricular tachycardia or family history of sudden cardiac death⁽⁴¹⁾.
- The treatment of heart failure and atrial fibrillation is indicated to patients according to the current guidelines (beta-blocker, angiotensin converting enzyme inhibitor, diuretic, etc.).

Prognosis

The long-term prognosis for this disease is dictated by the degree of left ventricular dysfunction. Studies have shown that progressive heart failure, malignant ventricular arrhythmias or thromboembolic

complications are the most common causes of death. It was also pointed out the existence of groups of patients with a higher risk of an unfavorable prognosis: patients with heart failure at presentation, young age at presentation, reduced ejection fraction, the presence of arrhythmias, especially malignant tumors and patients with comorbidities of neuromuscular disease^(42,43,44). Unlike previous studies which have reported a very high risk of mortality and morbidity, the prognosis of patients has improved by improving the treatment of heart failure and by detecting early pathological changes⁽⁴⁴⁾.

Conclusions and future perspectives

In conclusion, as future perspectives, genetic test may be useful in differentiating a phenotype with trabecular myocardial pattern due to a myocardial remodeling that resulted from a noncompaction cardiomyopathy. We also need additional data from multicenter studies to establish a gold standard for diagnosis, as the different diagnostic criteria presented above show varying sensitivity, both with the disease itself and in relation to each other.

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