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Review

Non compaction cardiomyopathy: A short review of a controversial entity☆

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ABSTRACT

Non-compaction cardiomyopathy is a heterogeneous and complex entity concerning which there are still many doubts to be resolved. While the American Heart Association includes it among genetic cardiomyopathies, the European Society of Cardiology treats it as an unclassified cardiomyopathy. It may present in a sporadic or familial form, isolated or associated with other heart diseases, affecting only the left ventricle or both and can sometimes appear as a mixed phenotype in patients with other cardiomyopathies. Different forms of clinical presentation are also associated with its different morphological manifestations, and even non-compaction of the left ventricle may be triggered by other physiological or pathological processes. The purpose of this review is an update of this entity and its controversies.

Miocardiopatía no compactada: breve revisión de una miocardiopatía con controversias

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RESUMEN

La miocardiopatía no compactada es una entidad heterogénea y compleja de la que existen todavía muchas dudas por resolver. Mientras que la American Heart Association la incluye entre las miocardiopatías de origen genético, la Sociedad Europea de Cardiología la considera como una miocardiopatía no clasificada. Puede presentarse tanto de forma esporádica como familiar, aislada o asociada con otras cardiopatías, afectar solo al ventrículo izquierdo o a ambos y puede, en ocasiones, aparecer como un fenotipo mixto en pacientes con otras miocardiopatías. A sus diferentes manifestaciones morfológicas se asocian también diferentes formas de presentación clínica e, incluso, la no compactación del ventrículo izquierdo puede estar desencadenada por otros procesos fisiológicos o patológicos. El objeto de esta revisión es una puesta al día de esta entidad y de sus controversias.

Introduction

The first description of a non-compaction cardiomyopathy (NCC), better known in the literature as "left ventricular non-compaction", dates to 1926 and was made by Grant.[1] Since then, it has been the subject of numerous studies and publications. It is a heterogeneous entity that has received different names: spongiform cardiomyopathy, left ventricular non-compactation, isolated ventricular non-compaction or hypertrabeculation syndrome, among others.[2–5] Traditionally, it is considered to be the result of an interruption of normal myocardial development between week 5 and 8 of embryogenesis.[6] It may occur sporadically, but it is often a familial presentation entity.[7] On the other hand, it has been described both isolated and associated with other congenital defects and, besides, it poses diagnostic difficulties in certain situations, such as hypertrabeculation in athletes.[8,9] In this paper we carry out a brief review of this disorder and the questions it still raises.

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Pathogenesis

It seems that the different phenotypes of cardiomyopathies share a common genetic basis. In fact, some families with a common familial pathogenic variant and autosomal dominant inheritance show intrafamilial variability in phenotypic expression (NCC or hypertrophic or even both at the same time).[10] Numerous publications have questioned whether there is a clinical overlap of different cardiomyopathies with similar genetic etiopathogenic mechanisms or if, in fact, cardiomyopathies are part of the same phenotypic spectrum.[7,10–13] The triggers or modifiers that could determine the progression towards the development of the final phenotype (NCC, hypertrophic cardiomyopathy, dilated or arrhythmogenic cardiomyopathy) are unknown, starting from the same pathogenic variant.

Different experimental studies show findings that support the embryogenic hypothesis to explain the etiopathogenesis of NCC.[13–17] During the early stages of embryonic development, the myocardium grows and forms interwoven trabeculae separated by intertrabecular spaces. Its formation serves to increase the surface area of the myocardium and facilitates myocardial feeding by diffusing the exchange from the heart lumen before the coronary circulation is established.[18] The development of coronary circulation is established between week 5 and 8 of foetal life. Progressively, in parallel, a gradual compaction of the myocardial trabeculae will begin. Parallel to the coronary artery development, this process will continue from the epicardium to the endocardium and from the base of the heart to the apex, between week 10 and week 12.[19] In a normal mature heart only residual trabeculations would remain, especially in the right ventricular myocardium. According to these embryological data, NCC could be considered a congenital alteration caused by a maturation defect in the embryonic myocardium (Fig. 1). The "non-compaction" will be more or less significant depending on the moment in which the compaction process stops.[18] And since the compaction process ends at the apex, according to this theory, this segment would always be involved in NCC. This embryogenic hypothesis of NCC and the spatiotemporal relationship of embryonic development could explain the association with coronary anomalies[20,21] or other congenital heart malformations.[22] In addition, it has been shown that NOTCH signalling in the endocardium is essential for adequate cardiac trabecular formation.[23,24]

However, there are doubts about whether NCC can be an acquired entity.[25] As we will discuss later, there are certain mechanisms that – on morphologically normal hearts – can produce an increase in trabeculations, and even reach NCC criteria in adult life. In these cases, it would be considered an acquired, secondary cardiomyopathy. But these findings seem incompatible with the embryogenic development hypothesis, based on a morphological alteration present from birth.

In summary, it could be considered that there are different ways (whether congenital or acquired) of reaching the same final morphological alteration: NCC.

Epidemiology

The real incidence and prevalence of NCC are unknown.[5] Publications based on echocardiographic studies conducted in adults during one year in a tertiary hospital report a NCC prevalence of 0.26%, and, in those studies with an ejection fraction lower than 45%, the prevalence of definitive or probable NCC increases up to 3.7%.[26] In children it represents approximately 9% of all cardiomyopathies, and it is the third most common after dilated and hypertrophic cardiomyopathy.[27] In any case, at present, both a greater knowledge of the disease (and the greater degree of suspicion) and the improvement in imaging techniques and the increase in familial studies are leading to a greater and better diagnosis of this cardiomyopathy.[5]

Signs and symptoms

Classically it has been referred to as the triad of heart failure, arrhythmias and embolic episodes. However, its presentation is very heterogeneous and covers a broad spectrum, from asymptomatic patients diagnosed by familial or other screening context to advanced heart failure and sudden death. Both its natural history and its prognosis have been analyzed in several series. Habib et al., in a cohort derived from a French registry, describe as unfavourable prognostic factors (death or transplantation), advanced functional grade, high filling pressures and hospitalizations for heart failure.[28] A previous work published by Lofiego et al. includes the presence of sustained ventricular tachycardia and left atrial growth as predictors of unfavourable prognosis.[29] More recently and as a sign of its heterogeneity, different clinical subtypes have been described[5]: a "benign" form of NCC characterized by a normal-sized ventricle with preserved systolic and diastolic function and good prognosis; a form with arrhythmias with preserved systolic function and normal ventricular size, with a more unfavourable prognosis; phenotypically mixed forms such as hypertrophic and non-compacted or dilated, hypertrophic and non-compacted together or only dilated with ventricular dysfunction in which an undulating phenotype with reversibility of dysfunction has been described. Finally, a form of biventricular involvement has been described and associated with other congenital heart diseases such as the Ebstein's anomaly, pulmonary stenosis or tricuspid atresia, among others. As we see, a wide range of forms of presentation that raises once again doubts about whether we are dealing with one or several entities.

Genetics

Since Ichida et al.[30] identified the first mutation related to NCC in the dystrobrevine gene, back in 2001, numerous genetic alterations associated with it in more than 40 genes have been documented. However, the genetic basis of the different forms of non-compaction remain a matter of debate since, although an association between genetic disorders and some forms of NCC seems undeniable, a clear causal relationship between the two has not been demonstrated to date.[31]

In favour of this causal relationship are the familial presentation and the constant association of ventricular non-compaction in the presence of specific genetic defects, such as the G4.5 gene mutation (tafazzin protein) causing Barth syndrome.[31–33]

The acquired forms of NCC (in athletes, during pregnancy, in haematological diseases), the genotype–phenotype discrepancy in different people with the same pathogenic variant and the absence of constant familial segregation (thus, a specific pathogenic variant can present diverse cardiac manifestations within the same family, different forms of cardiomyopathies, including a generation gap in dominant autosomal inheritance) are among the arguments against it. All this contrasts with a clear causal relationship of genetic defects and NCC, at least, in a homogeneous way, usually present in other cardiomyopathies.[31,32]

This internal debate and the heterogeneity of the genetic basis of NCC is evident in the different consideration that cardiology-related scientific societies give to this entity. Thus, since 2006, NCC has been accepted as an independent genetic-based cardiomyopathy by the American Heart Association.[34] However, the European Society of Cardiology[35] and the International Classification of Diseases of the World Heart Organization still consider it