

Non-Compaction Cardiomyopathy: A Genetically and Clinically Heterogeneous Disorder

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Commonly known as non-compaction cardiomyopathy (NCC), the isolated left ventricular non-compaction or spongiform cardiomyopathy is an unclassified cardiomyopathy whose etiology lies in the arrest of the compaction process during endomyocardial embryogenesis, which occurs between weeks 5 and 8 of fetal life; it is characterized by the loss of sinusoidal intertrabecular spaces in the embryonic myocardium, which gradually become capillaries within the coronary circulation. Its predominant characteristic includes prominent trabeculations typically located in the apical and lateral segments of the left ventricle, with deep intertrabecular recesses.

NCC is a familial cardiomyopathy, predominantly of autosomal dominant heredity, and only 50% of the relatives affected can be identified. (1, 2) In contrast, NCC observed in patients with G4.5 gen mutations – associated with mitochondrial function– shows sex-link heredity. This type of mutation occurs in patients with Barth syndrome, characterized by non-compaction, neonatal heart failure, neutropenia, and myopathy. (3-5)

The NCC is genetically heterogeneous and is associated with at least five genes (G4.5/TAZ, alpha-dystrobrevin, Cypher/ZASP, lamin A/C and TPM1), and a genetic locus (11p15).

Because of this genetic heterogeneity, screening of families through genetic studies –of limited availability in our country– is a very costly strategy with limited diagnostic results. (3) However, in the future, it is possible that genetic tests can improve risk stratification in NCC patients, identifying those who have the potential to progress to ventricular dysfunction.

At present, imaging studies are a more effective diagnostic strategy for family screening, despite its limitations. Echocardiographic diagnosis of NCC is controversial, with little correlation among the three echocardiographic definitions of NCC. (6) Paradoxically, that study concluded that the current echocardiographic criteria are too sensitive, which results in overdiagnosis of NCC by this method, but there could be an unidentified large number of patients with dilated cardiomyopathy and underlying NCC. (6)

The difficulties of the method were illustrated with the exclusion of a Ghanaian striker of the Bundesliga, whose contract with his team was cancelled because he was misdiagnosed NCC (false tendon), resulting in his deportation and withdrawal of his playing license.

Back in his country of origin, repeated echocardiographies and cardiac magnetic resonance (CMR) imaging confirmed his non-compaction; after some time, he played normally during the World Cup in South Africa. (7) In this issue of the Revista, Deviggiano et al (8) present a series of 20 patients with NCC, diagnosed by CMR. Consistent with these antecedents, the previous echocardiography detected the NCC in only 28% of the cases.

CMR is currently the reference standard method for assessing ventricular volumes and mass, and unlike echocardiography, has no window limitations, so it can assess the apical segments with high accuracy. This method represents an accurate, reproducible and non-ionizing strategy, which allows not only the follow-up of patients with NCC but also the screening of relatives of affected individuals. However, the high spatial resolution of the method may occasionally identify hypertrabeculation in healthy individuals. (7) Therefore, the question one should ask oneself in the finding of myocardial non-compaction is whether hypertrabeculation considered as NCC is undoubtedly attributed to a specific genetic disorder, to a particular phenotypic expression manifesting in different conditions, or simply to an anatomic variant.

Regarding the natural history, although the first publications associated this condition with a bad prognosis and high likelihood of progression to heart failure, thromboembolic events and arrhythmias, it was later demonstrated that there is a large number of asymptomatic patients who are diagnosed with NCC by echocardiographic studies, CMR, or cardiac multi-detector row computed tomography. (2, 9, 10)

In line with previous communications, the work by Deviggiano et al shows great variability in the clinical evolution of the disease, in which half the patients were asymptomatic and a 10% had a family history of sudden death. This variability in the history of NCC could be explained by genetic heterogeneity, from isolated forms to complex immunodeficiencies. Myopathies with myocardial involvement –like the Barth syndrome, Emery-Dreifuss muscular dystrophy, and myotubular myopathy, as well as isolated myocardial non-compaction– may lead to endomyocardial fibrosis, and that would explain the late onset of left ventricular dysfunction in patients with NCC. (4, 5) Similarly, endocardial fibrosis and calcifications are commonly

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found in NCC patients with deficit of mannose-binding lectin, although it remains unknown whether fibrosis is associated with this type of complement immunodeficiency, or whether fibrosis is associated with myocardial hypertrabeculation. (11)

Once patients are symptomatic, and with the development of chamber dilatation and/or systolic dysfunction, they have a disfavorable outcome. An echocardiography with a 6-year follow-up of 17 asymptomatic patients with NCC showed a mortality rate of 47%, and need for transplantation in 12% of the cases. (12) Another study that included 34 symptomatic patients with systolic dysfunction showed a similar trend after a 44-month follow-up, including a mortality rate of 35%, need for transplantation in 12% of the cases, and 12% for implantable cardioverter-defibrillator. (13)

It should be pointed out that neurological assessment is recommended in patients with NCC, as most of them have neuromuscular disorders –either specific or of unknown etiology. (14)

From a technical –but also important– point of view, I would like to explain that in order to avoid overdiagnosis of NCC, the relationship between non-compacted (NC) and compacted (C) myocardium must be measured in the sector with more trabeculations, preferably at the lateral level, provided the location is not too apical, not only because apical segments are typically trabeculated but also because compacted myocardium in that region is usually very thin, and this favors the diagnosis of NCC even in healthy individuals, when the NC/C myocardium ratio is used.

If we consider that the mean compact myocardial thickness was only 3.6 mm in the work by Deviggiano et al, the presence of trabeculae of only 8.3 mm would suggest a diagnosis of NCC.

In fact, in the germinal work by Petersen, 91% of the healthy volunteers had NC myocardium in apical segments, 100% had NC myocardium in segment 17 (apex), and 78% in mid-ventricular segments.

(15) That work reported a larger number of segments involved and a NC/C ratio greater than 60% in patients diagnosed with NCC than in healthy volunteers and patients with other cardiomyopathies.

Unlike the commonly accepted strategy of measuring the long axis, Deviggiano et al measured the short axis in order to quantify the trabeculated left ventricular mass, as recently described by Jacquier et al. (16) The association between left ventricular diastolic diameter (LVDD) and trabecular mass is expected even in healthy individuals, while no association was found between LVDD and NC/C ratio. Late enhancement was detected in 28% of the patients, possibly due to endocardial fibrosis, although the pattern is not described. It would be interesting to assess these patients prospectively so as to determine whether they are most likely to progress to systolic dysfunction.

Out of Deviggiano's work and other works that preceded it, it appears that unfortunately, there are still

no imaging parameters to discriminate patients most likely to progress to ventricular dysfunction. Therefore, it is essential to conduct large-scale prospective studies that allow us to know the natural history of asymptomatic patients with NCC.

Little is known about NCC, a clinically heterogenic genetic entity that may not be considered a disease in itself, but a phenotypic manifestation observed in a wide spectrum of conditions with a different prognosis.

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