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EDITORIAL COMMENT

Left ventricular noncompaction and Fabry disease: An unlikely association

Não-compactação do ventrículo esquerdo e doença de Fabry: uma associação improvável

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Left ventricular noncompaction (LVNC) describes a ventricular wall anatomy characterized by prominent left ventricular (LV) trabeculae, forming a thin compacted layer, and deep intertrabecular recesses that are continuous with the LV cavity and separated from the epicardial coronary arteries.[1] In the normal heart, trabeculae actively provide mechanical leverage by contracting during early systolic ejection.[2] Trabeculae are formed during early embryonic development. The origin of LVNC is attributed to an arrest in compaction of the endomyocardial layer of the heart during early embryogenesis.

The diagnostic criteria for LVNC are based on ratios between thickness, mass or volume of noncompacted and compacted left ventricle. The number of noncompacted segments provides information on the extension of LVNC. However, this approach is highly investigator-dependent; diagnosis is based on two-dimensional planes using semi-quantitative or qualitative criteria and specificity is low.[3] Grothoff et al. demonstrated that, on cardiovascular magnetic resonance imaging (CMRI), trabeculation in segments 4-6 indicates a high probability of LVNC and distinguishes LVNC from other cardiomyopathies and normal hearts.[4] Alternative CMRI-based methods include assessment of the global trabeculation index.[5]

Some authors suggest that the established diagnostic criteria are too sensitive and that LVNC is over-diagnosed.[6] LVNC can be an incidental finding in screening studies, such as for athletes,[7] and is not associated with deterioration in LV volumes or function during long-term follow-up in the asymptomatic population.[8] When faced with isolated LVNC morphology, cardiologists must decide whether what they are observing is a cardiomyopathy or a variant LV wall anatomy. In most cases, especially in adult patients, the key element in the diagnostic decision is not the LVNC itself, but the associated LV dilation and/or dysfunction, hypertrophy, right ventricular involvement, arrhythmias and conduction disturbances. The genetic basis of LVNC is an issue of ongoing research, severely limited by the enrollment criteria, which reflect the current heterogeneous diagnostic definitions of LVNC.[1]

The weakness of a diagnosis based solely on proportions or ratios is demonstrated by using Fabry disease (FD) as an example. The hearts of patients with FD may exhibit prominent papillary muscles and trabeculae[9] which may reach LVNC criteria,[10,11] which are fulfilled for trabecular thickness rather than for a thin compacted layer. Similarly, in patients with Danon disease with LVNC,[12] the criteria for diagnosis of LVNC seem to be met due to the prominent trabeculae with a thickened compacted layer.

The occurrence of hypertrabeculation and left ventricular noncompaction (LVNC) is increasingly reported in large echocardiographic series.[8] LVNC can be regarded as an isolated entity or as one of the traits that may recur in cardiac and noncardiac diseases.[1] On the basis of current

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definitions and terminology, LVNC can occur in various settings, including as an isolated finding, or associated with LV dilatation and dysfunction or with cardiomyopathies or congenital heart disease, or acquired and potentially reversible, as has been reported in athletes.[1,7] However, the association of Fabry disease (FD) with LVNC has been reported in a few cases.[10,11] It is possible that unidentified mutations in genes other than *GLA* (responsible for FD) may coexist, which would explain the association found.

FD is a progressive multisystemic X-linked genetic sphingolipidosis caused by deficient activity of lysosomal alpha-galactosidase A (α-Gal A).[13] Accumulation of α-Gal A substrates in various cells and organs produces the clinical phenotype in FD.[14] FD can mimic other myocardial diseases, including sarcomeric hypertrophic cardiomyopathy (HCM) and amyloid cardiomyopathy. Cardiac imaging, in particular echocardiography and CMRI, plays an important role in detecting this peculiar disease.[15] Although increased left ventricular (LV) wall thickness has traditionally been the hallmark feature of FD, several other structural and functional abnormalities have been uncovered by conventional and novel echocardiographic techniques. Among patients with increased LV wall thickness due to various etiologies, those with FD tend to have more prominent papillary muscles, in both thickness and hyperechogenicity. Systolic function is generally preserved, but can be reduced in advanced disease, usually associated with extensive fibrosis.[16] CMRI is an excellent method to reveal the presence of fibrosis in FD, which is commonly located in the posterolateral basal and mid-level or subepicardial layers.[13] Magnetic resonance noncontrast myocardial T1 mapping may show glycosphingolipid deposits before the onset of left ventricular hypertrophy (LVH), and is also a useful method for differentiating FD from other causes of LVH.[17]

FD is a multisystemic disease, and depending on the affected organs it can result in neurological, ocular, skin, renal or cardiac manifestations. Therefore, cardiologists, neurologists, dermatologists, nephrologists and ophthalmologists should all be aware of the possibility of FD, depending on the patient's clinical presentation. In a cardiological setting, a diagnosis of FD should be considered systematically in cases of unexplained LVH, particularly when it is concentric, symmetric, homogeneous or non-obstructive.[18] LVH is a key feature in FD and is reported in up to 50% of male patients and one-third of female patients.[19]

LVH in FD typically combines concentric thickening without LV obstruction and normal LV ejection fraction. However, asymmetric septal or apical hypertrophy has also been described, along with subaortic obstruction, which may mimic the phenotypical and clinical features of sarcomeric HCM.[20] Right ventricular hypertrophy with preserved systolic function, impaired left atrial function and moderate aortic dilatation may also be observed, and LV hypertrabeculation and noncompaction have been described.[16,21] LV function may deteriorate with time, leading to a restrictive cardiomyopathy pattern. Other echocardiographic features include prominent papillary muscles[22] and a binary appearance of the LV endocardial border,[16] although the diagnostic value of these findings is controversial.

Specific therapy should be initiated at the earliest stage, before cardiac fibrosis develops, when the first structural or functional cardiac abnormalities are detected. Options include enzyme replacement therapy (ERT) or chaperone therapy. ERT with recombinant human α-Gal (rh-α-Gal) has been available to treat FD since 2001 and may improve ventricular morphology and function.[13,23]

In 2003, Stöllberger et al. showed that LVNC does not appear to be a manifestation of cardiac FD.[11] They studied 26 patients with LVNC diagnosed by echocardiographic criteria and ruled out FD by assessment of clinical systemic manifestations and blood tests for α-Gal A. The most common detection method is the measurement of α-Gal A activity by dried blood spot (DBS) analysis. Although decreased α-Gal A activity in DBS can confirm the diagnosis of FD in homozygous males, this is not the most reliable diagnostic method in heterozygous females, since enzyme activity may be within the normal range in around 40% of this patient group. Therefore, women with high clinical suspicion should undergo genotyping to confirm the diagnosis. Endomyocardial biopsy is the gold standard for diagnosis of cardiac involvement in doubtful cases. Caution should be exercised in clinical assessment because certain drugs such as amiodarone, chloroquine, and tamoxifen have a storage pattern mimicking FD.[13]

There are three cases in the literature documenting an association of LVNC and FD in the same patient, all three of them female.[10,24] In this issue of the *Journal*, Azevedo et al. report a multicenter study screening for FD in 78 patients with LVNC.[25] The diagnosis of LVNC was established by echocardiography in 91.0% of the patients and that of FD by α-Gal A activity measured in DBS samples by fluorometry. Molecular analysis of the *GLA* gene was performed in males with reduced α-Gal A activity. Screening of these 78 patients with LVNC did not identify any additional patients with FD. This supports the hypothesis that although LVNC may occur in patients with FD, this does not represent more than a coincidence of findings.

This article, therefore, strengthens the evidence that there is no pathophysiological link between these two conditions and that LV noncompaction is unlikely to be a phenotypical expression of FD.

In clinical practice, for the management of secondary cardiomyopathies such as FD, echocardiographic study has an important role in screening and diagnosis and in assessment of cardiac function and hemodynamics. Since ERT is usually a major component of treatment for FD, early diagnosis is essential for effective treatment. Based on recent evidence, caution should be exercised when using the current diagnostic criteria of LVNC as a basis for the decision to start specific therapy for FD.

Conflicts of interest

The author has no conflicts of interest to declare.

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