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Are We Getting Closer to Risk Stratification in Left Ventricular Noncompaction Cardiomyopathy?

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"The trouble with life isn't that there is no answer, but that there are so many answers."

-Ruth Benedict

Left ventricular noncompaction cardiomyopathy (LVNC) continues to be the focus of much discussion in the international cardiology community. Surprisingly, there is a paucity of data on the causes, diagnosis, and management, although it has an underestimated prevalence of 1:5000 individuals in the general population and in 3% to 4% of adults with heart failure.[1] Although established as an independent genetic cardiomyopathy by the American Heart Association in 2006, there is ongoing disagreement about diagnostic criteria and the clinical implications of LVNC.[2] To further complicate the debate, there are an increasing number of reports of LVNC cohorts with varying and often conflicting results. To offer a more comprehensive understanding of the heterogeneous LVNC phenotypes, we have described distinct subtypes that may have different morbidity and mortality profiles (Figure).[3] Delineation of the specific subtype informs both surveillance and treatment. Although the benign form results in longevity similar to that of the general population, the other subtypes may result in heart failure, life-threatening arrhythmias, and thromboembolic disease, which may require medical therapy, device therapy, and/or cardiac transplantation.[3]

LVNC is a genetically heterogeneous disease and traditionally thought of as monogenic, with autosomal dominant, autosomal recessive, and X-linked forms having been reported.[4–6] The genes implicated encode components of the sarcomere, Z-disc, cytoskeleton, and mitochondria.[4,7,8] LVNC has also been reported in association with clinical syndromes and neuromuscular disorders.[9–11] However, genotype-phenotype correlations have been challenging and are the topic of ongoing investigation. The challenge lies in the fact that mutations in LVNC-associated genes, such as those encoding for sarcomeric proteins, may also result in completely different cardiomyopathy phenotypes. Mutations in the β-myosin heavy chain gene (*MYH7*), for example, have been reported in association with LVNC, hypertrophic cardiomyopathy, dilated cardiomyopathy, and restrictive cardiomyopathy.[4,12,13] Prior single-center and multicenter reports have described positive genetic status with clinical phenotype and outcomes. A recent retrospective study analyzed 327 unrelated pediatric (n=52) and adult (n=275) patients with LVNC whose disease was categorized as follows: (1) genetic (mutation positive), (2) probably genetic (mutation negative, family history positive), and (3) sporadic (mutation negative, family history negative).[14] Mutations in the sarcomeric genes *MYH7* and myosin binding protein C (*MYBPC3*) were common, as were mutations in the titin (*TTN*) gene, which encodes for the protein titin. Titin is needed for sarcomere assembly and force transmission and is increasingly implicated in genetically triggered cardiomyopathies.[15–18] These three genes accounted for 71% of the mutations. LV systolic dysfunction was more common in those that were mutation positive, with the highest risk being in patients with multiple mutations and *TTN* mutations. Patients who were mutation positive were significantly more likely to have major adverse cardiovascular events, including cardiac death, LV assist device placement, heart transplantation, aborted sudden cardiac death, ischemic stroke, or appropriate implantable cardioverter-defibrillator shock. Interestingly, patients with *MYH7* mutations had a low risk of experiencing the clinical end points.

We also have reported data about novel genetic triggers of LVNC and genotype-phenotype correlations.[19] Our cohort consisted of 190 patients from 174 families with either LV hypertrabeculation or LVNC, which was diagnosed by cardiac magnetic resonance imaging. LV hypertrabeculation was defined as patients having noncompacted myocardium but not meeting the previously reported noncompacted/compacted ratio of 2.3:1.[20] Whole-exome sequencing was

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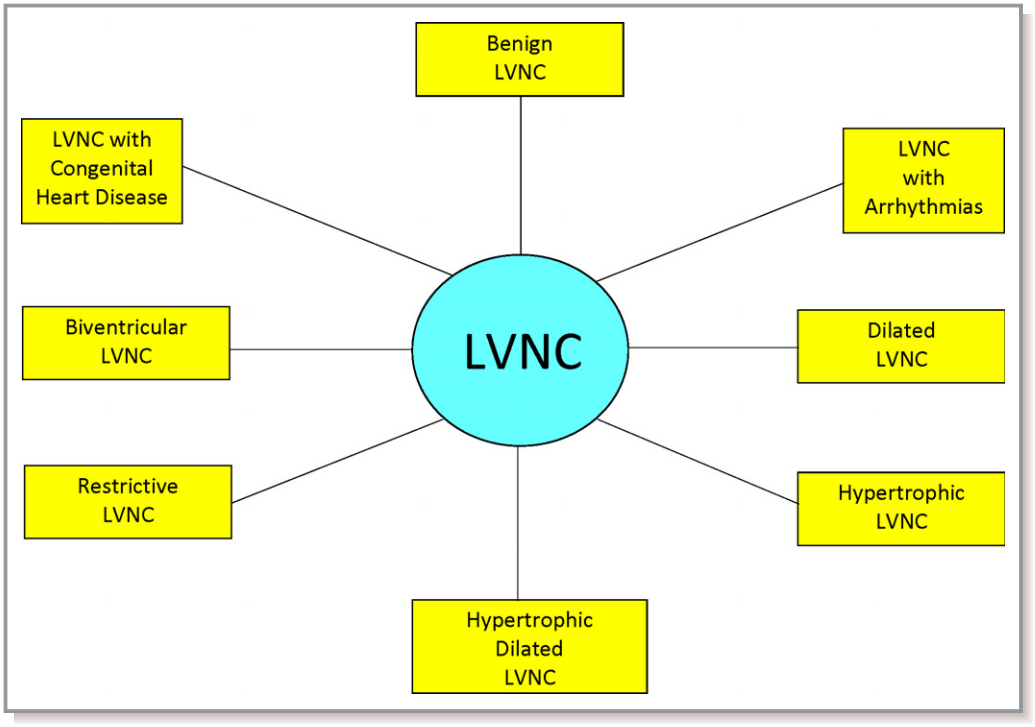

Figure. Subtypes of left ventricular noncompaction cardiomyopathy (LVNC).

performed on the entire cohort and revealed 138 variants of interest in 102 unrelated patients in 54 previously identified LVNC or other known cardiomyopathy genes. We identified 0, 1, and ≥2 variants of interest in 72, 72, and 28 probands, respectively. We found that increasing the number of variants of interest correlated with different phenotypic markers, including worsening LV ejection fraction, number of affected myocardial segments, and increasing noncompacted/compacted ratio. Patients with variants of interest in sarcomeric genes had more frequent findings of trabeculations in the interventricular septum and late gadolinium enhancement, which likely indicated fibrosis in those areas of the myocardium. One subject who experienced cardiac arrest secondary to ventricular tachycardia and end-stage heart failure had 2 variants in the cardiac sodium channel (*SCN5A*) and an additional variant in the α-1 chain of tropomyosin (*TPM1*).

In this issue of the *Journal of the American Heart Association* (*JAHA*), Pu et al report their single-center genotype-phenotype correlations in Chinese patients with LVNC.[21] The authors evaluated 100 unrelated subjects (72% men) with confirmed LVNC by either previously reported diagnostic echocardiographic or cardiac magnetic resonance imaging criteria.[20,22] The cohort consisted of 83 adults (aged ≥18 years) and 17 pediatric patients. Targeted sequencing of 72 cardiomyopathy-related genes was performed. The pathogenicity of identified variants was performed on the basis of existing recommendations, and only those that were classified as pathogenic or likely pathogenic (G+) were used in the analyses.[23] Outcomes were defined as a composite primary end point of death and heart transplantation, and secondary end points consisted of all-cause death, heart transplantation, and cardiovascular death.

A total of 42 pathogenic variants were identified in 38 patients, with 29 of these occurring in sarcomeric genes. Variants in the *TTN* gene were the most common in both groups, with *MYH7* being the second most common. A total of 8 nonsarcomeric genes were identified, including desmoplakin (*DSP*), dystrophin (*DMD*), lysosomal-associated membrane protein-2 (*LAMP2*), and *SCN5A*, with *DSP* being the most common. During a 4.2-year follow-up period, the G+ group met the primary end points more than the G− group. Thirty-two patients met the primary end point, with 27 deaths (27%) and 5 heart transplantations (5%). The 32 deaths were all secondary to cardiovascular causes. All 6 subjects with *DSP* variants had ventricular arrhythmias. Five of these subjects were treated with amiodarone, 2 received an implantable cardioverter-defibrillator, 1 required heart transplantation, and 1 died secondary to heart failure. Of the 17 subjects in the pediatric subgroup, 4 (23.5%) reached the primary end point, with half being G+.

There were no statistically significant differences in the proportion of G+ subjects and the proportion of variants in sarcomeric genes between children and adults. The proportion of variants in sarcomeric genes was different in children versus adults but did not reach statistical significance (42.9%

and 72.2%, respectively; P=0.190). This was likely secondary to the study being underpowered. In children, nonsarcomeric gene involvement was more common than in adults (57.1% versus 27.8%, respectively). LV ejection fraction was lower in G+ adults, and atrial fibrillation was more common than in G− subjects at baseline. There were 6 adults that were carriers of multiple variants. Although comparison of subjects with a single variant versus those with multiple variants revealed a higher number of events in the multiple variant group, this did not reach statistical significance. Perhaps most importantly, G+ status in adults was associated with higher risk of heart transplantation and death, independent of patient age, sex, or LV systolic function at baseline.

The report by Pu et al[21] reinforces some of the prior findings reported in LVNC but is inconsistent with other studies. Two prior studies performed genotype-phenotype correlations and showed no difference in major cardiac events, regardless of pathogenic variant status in adults.[14,24] Interestingly, in the study by van Waning et al, mutations were more common in children and were associated with poor outcome.[14] However, these reports studied fewer genes and had different clinical end points. Much of the data in this report are in agreement with other studies.[19,25] The finding that *TTN* was the most commonly reported gene is consistent with our previously reported results, as is the involvement of other sarcomeric genes.[19] The impact of LVNC on patient morbidity and mortality in the current report in both children and adults is also consistent with prior reports and underscores the importance of correctly making the diagnosis.[26,27] Once the diagnosis is made, appropriate surveillance must be used. LVNC is not a static disease, and it is not clinically possible to predict the clinical changes that may occur over time. Current approaches to monitoring include noninvasive testing to assess for myocardial function, chamber size, and wall thickness as well as arrhythmia assessment, which may include the use of Holter monitoring and stress testing.[3] As mentioned, 27 patients experienced death and 5 underwent heart transplantation. Of the 27 deaths, 20 were secondary to heart failure. These patients have the dilated form of LVNC and are managed similarly to those patients with dilated cardiomyopathy in the absence of LVNC. Pu et al[21] documented ventricular arrhythmias in 6 patients of the patients with pathogenic variants in *DSP*, which has been repeatedly associated with arrhythmogenic cardiomyopathy. This further supports the concept that we have reported on subtypes of LVNC, one of which is the arrhythmogenic phenotype and may affect the timing and nature of arrhythmia surveillance. The findings of truncating variants in the *LAMP2* gene are of particular interest because mutations in *LAMP2* are responsible for Danon disease. Although the authors did not report extracardiac findings in this study, Danon disease results in cardiomyopathy (usually hypertrophic cardiomyopathy in men), skeletal myopathy, and intellectual disability, which would require a more comprehensive management approach.

There are multiple limitations to the study. The sample size is small, from a single center, and there is an underrepresentation of pediatric patients. However, the findings are additive to existing data on multiple levels. This is the largest report on a Chinese cohort reporting genotypic and phenotypic data. The findings of pathogenic variants in 38% of the patients are similar to the reported yield of commercially based genetic testing of patients of European decent. Wang et al evaluated 102 Japanese patients with LVNC who underwent next-generation sequencing and found pathogenic variants in 38% of the cohort as well.[25] They also found that patients with pathogenic variants had an earlier age of onset of decreased LV ejection fraction and more severely depressed systolic function in those carrying pathogenic variants. Survival analysis in this study revealed a poorer prognosis in those with pathogenic variants, especially those with multiple variants. This reinforces the fact that LVNC occurs across the globe with similar genetic drivers regardless of ethnicity. Multiple novel mutations were found in the current study in *TTN*, *DSP*, *MYBPC3*, *LAMP2*, and *DMD* genes and the NAD(P) transhydrogenase gene (*NNT*), not previously reported in largely European cohorts. This expands on the growing number of mutations reported in association with LVNC and offers greater opportunity for genotype-phenotype correlations.

Although there are an increasing number of reports describing genotype-phenotype correlations, the utility of genetic testing in patients with LVNC in real-world clinical practice must be carefully considered and may be influenced by the specific subtype. A recent report suggests that genetic testing in patients with isolated LVNC may not be warranted because the yield of a positive test result may be low.[28] However, the yield is higher when performed in patients with a different phenotype, such as the dilated cardiomyopathy form of LVNC or the hypertrophic cardiomyopathy form of LVNC subtype. This may simply represent a lack of interrogation of causative genes and/or delineate that some cases of LVNC may exhibit oligogenic inheritance. The report by Pu et al[21] is additive to the literature and expands on our growing knowledge of genetic triggers, resulting in the LVNC phenotype. As additional insights are gained into LVNC, we may move closer to developing more formal risk stratification tools that would not only incorporate myocardial and arrhythmia data points but genetic/genomic data as well. This would be of great benefit to the clinicians caring for patients with LVNC. Many providers are unfamiliar with this type of cardiomyopathy and are unaware of the potential morbidity and mortality that may be associated with the diagnosis. With the increasing uptake of genetic testing in the cardiology community, cheaper whole-exome and whole-genome sequencing, and deep phenotyping, longitudinal outcome

data can be collected that will help us to better understand the importance of the genomic underpinnings of LVNC and further delineate genotype-phenotype correlations.

Disclosures

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