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EDITORIAL COMMENT

Winter Is Coming

The Slippery Slope of Defining Disease and the Implications for Hypertrophic Cardiomyopathy*

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The widespread availability of routine cardiovascular genetic testing for hypertrophic cardiomyopathy (HCM) has led to greater identification of genetically affected family members who do not exhibit left ventricular hypertrophy (LVH).[1-4] These "genotype-positive (+) LVH-negative (−)" (G+LVH−) individuals have an increased risk for the future development of clinical HCM (with LVH), but the time to when hypertrophy develops can be variable.[5,6] Therefore, given the substantial number of gene carriers in HCM families throughout the world, understanding the clinical relevance of this patient subset is becoming increasingly important.

Over the past 2 decades, the systematic application of cardiovascular magnetic resonance (CMR), with its high spatial resolution imaging, has expanded our appreciation for the diverse phenotypic expression of HCM, including G+LVH− individuals. A variety of morphologic or structural abnormalities have been identified in these patients, including alterations in systolic and diastolic function, mitral valve leaflet abnormalities, myocardial crypts, abnormal LV muscle bundles, and fibrosis.[1,7-9] These imaging-based observations have suggested that despite the absence of LVH, the hearts of G+ LVH− individuals may not be completely normal.[7] For these reasons, several unresolved clinical dilemmas have arisen with respect to this unique patient subgroup, including practical management considerations such as eligibility for competitive sports or consideration for prophylactic implantable cardioverter-defibrillator therapy.

In this issue of *JACC: Case Reports*, the case report by Chan et al[10] underscores several of these unanswered questions involving HCM gene carriers. In this example, a young asymptomatic competitive athlete with a family history of HCM was identified through family gene testing to have the same pathogenic sarcomere mutation as other affected relatives. Extensive cardiovascular workup with echocardiography and cardiovascular magnetic resonance (CMR) demonstrated the absence of LVH, placing this individual in a category of G+LVH−. However, several structural abnormalities were observed, predominantly with CMR, including multiple myocardial crypts, elongated anterior leaflet of the mitral valve, abnormal LV muscle bundles, and a focal myocardial scar at the insertion area of the right ventricular free wall and posterior ventricular septum.

The authors submit that these morphologic abnormalities provide evidence of a limited HCM phenotypic expression of HCM and therefore consider these individuals as having "subclinical" HCM—a patient group distinct from HCM gene carriers without evidence of structural changes to the heart (ie, true "phenotype negative"). The authors also suggest that subclinical HCM should be formally recognized in expert consensus guidelines because the evidence for a subtle phenotype could affect management consideration and risk assessment, including safety with engaging in vigorous physical activities and therefore eligibility for competitive sports.

To try and make sense of the potential implications of this unique group of patients, it is necessary to take a step back and consider what we know today about the clinical significance of G+LVH− patients. First, as expected, the likelihood of the development of HCM is increased but is potentially less than was

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previously considered. In 1 large international multicenter cohort of >200 patients prospectively followed up for >6 years, conversion to the HCM phenotype was uncommon, including almost 20% who achieved a relatively advanced age of >50 years without evidence of LVH.[5] Indeed, these longitudinal data suggest that in fact many gene carriers may never experience clinical HCM throughout their entire lifetimes.[5,6] In addition, risk factors that can be used to identify gene carriers more likely to develop HCM are not well defined.[5,6] For these reasons, screening to detect future conversion to LVH is recommended for all HCM gene carriers, with electrocardiography and cardiac imaging every 1 to 2 years in children and adolescents and every 3 to 5 years in adults performed until midlife.[1]

Furthermore, there is no conclusive evidence that G+LVH− patients are at increased risk for adverse disease-related events, including sudden death or heart failure symptoms.[1-6] Indeed, their risk is considered to be no different from that of the general population.[5] Therefore, the clinical significance of subclinical structural abnormalities is unclear, but inasmuch as they do not appear to increase the risk of arrhythmia or represent a mechanism for the generation of limiting symptoms, treatment decisions should not be based on these findings alone.[1,7] This is an important point that should serve as a major source of reassurance for G+LVH− individuals.

For these reasons, the recent 2020 American Heart Association (AHA)/American College of Cardiology (ACC) HCM consensus guidelines considered it reasonable for G+LVH− individuals to participate in vigorous competitive sports and offered no specific role for implantable cardioverter defibrillators for the primary prevention of sudden death.[1] That is also consistent with the outcome in this case report by Chan et al,[10] in which during the follow-up period the HCM gene carrier athlete remained asymptomatic and was not restricted from continuing to compete in competitive sports while continuing to undergo the recommended longitudinal surveillance testing imaging for potential conversion to a clinical HCM phenotype.[10]

What, then, is the current clinical relevance of subclinical structural or functional abnormalities in an HCM family member? These morphologic alterations have been associated with an increased likelihood that an HCM family member may carry a disease-causing sarcomere mutation (as was demonstrated in this case report).[8] Therefore, if 1 or more of these abnormalities are identified in an HCM family member during routine imaging screening, this should prompt close surveillance with serial imaging for the development of LVH and potentially genetic testing (if not already performed) to aid in confirming the presence of a pathogenic sarcomere mutation.[7-9] The results of genetic testing in this situation could therefore help define whether a family member is at risk (or not) for the development of clinical HCM in the future.

The report by Chan et al[10] also raises several other broader potential implications, including how we define patients as having cardiac disease. As our imaging capabilities become more sophisticated we continue to expand our appreciation of what may be "seen" in individuals who may be at risk but do not yet meet the clinical definition of disease, ie, an illness that affects a person and prevents the body (or mind) from performing normally. On the basis of the totality of evidence today, individuals with subclinical HCM do not fulfill this definition; therefore, considering such patients as having a chronic genetic heart disease represents a slippery slope that could have additional profound consequences, including negative psychological impact as well as implications for access to insurance and other benefits. Of course, as the authors correctly point out, we are still early in our understanding of the natural history of G+LVH− individuals, and therefore we will undoubtedly benefit from insights derived from longer-term outcome studies in order to best inform management recommendations. For now, the current AHA/ACC HCM guidelines provide a thoughtful and measured approach to the evaluation and follow-up of G+LVH− individuals.

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