

EDITORIAL COMMENT

Improving Diagnosis and Management of Dilated Cardiomyopathy With Advanced Cardiac Imaging and Early Genetic Testing



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The multiple etiologies for dilated cardiomyopathy (DCM) can make diagnosis and treatment extremely challenging. Furthermore, optimal evidence-based management may be delayed if the underlying pathobiology is not initially identified. Over one-third of DCM cases have a genetic cause or result from a genetic predisposition.¹ However, this is often unrecognized and underdiagnosed in clinical practice. It is estimated that genetic testing can reveal pathogenic variants causing DCM in approximately 20% of adult patients with unexplained complicated myocarditis.² Studies in women with peripartum cardiomyopathy suggest that up to 15% of these women carry a pathogenic or likely pathogenic variant.³ Moreover, recent data suggest that as many as one-third of patients with isolated cardiac sarcoidosis on positron emission tomography (PET) scan may have an underlying genetic DCM.⁴ Identifying the genetic causes and specific pathophysiological mechanisms are vital to individualizing treatment and improving outcomes in patients with genetic DCM.

Advances in cardiac imaging techniques using echocardiography, nuclear imaging, and cardiac magnetic resonance (CMR) can noninvasively phenotype heart failure patients. Three-dimensional volumetric analysis augmented by machine learning algorithms, tissue tracking to derive myocardial

mechanics, and tissue characterization for the evaluation of fibrosis, extracellular deposition, edema, and inflammation are among the many imaging tools available for phenotyping DCM patients.⁵ Leveraging advanced cardiac imaging capabilities may identify patients that could benefit from panel-based genetic testing and allow for a better understanding of the complex genotype-phenotype relationships in genetic DCM.

In this issue of *JACC: Case Reports*, Ahmed et al⁶ demonstrates how advanced cardiac imaging, genetic testing, and multidisciplinary team management play a crucial role in the diagnosis and management of genetic DCM. The authors include 4 cases that highlight the overlap in presenting signs and symptoms of different genetic DCMs, describe the diagnostic ambiguity of DCM, and illustrate the use of an imaging-guided pathway for diagnosis and treatment. In each of the case examples, CMR was followed by cardiac PET imaging. The ability to detect the presence, extent, and distribution of myocardial fibrosis with late gadolinium enhancement (LGE) makes CMR an essential tool in diagnosing and phenotyping DCMs. The 2023 European Society of Cardiology guidelines for the management of cardiomyopathies give a Class I recommendation for CMR at the initial evaluation in patients with cardiomyopathy.⁷ Additionally, parametric mapping techniques with CMR have expanded our ability to characterize abnormal myocardium beyond fibrosis patterns. Native T1 mapping and extracellular volume expansion or deposition provide diagnostic insights about infiltrative diseases, such as cardiac amyloidosis, and can assess the response to therapy.⁸ In inflammatory conditions, such as acute myocarditis, T1

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mapping, T2 mapping for myocardial edema, and extracellular volume quantification provide superior diagnostic accuracy compared with the Lake Louise Criteria and LGE.⁹ The first case described the intersection of viral-induced myocardial inflammation and genetic predisposition, highlighting the synergistic role of advanced imaging and genetic testing in making a conclusive diagnosis and appropriately guiding management.

Nuclear imaging using ¹⁸F-fluorodeoxyglucose (FDG) cardiac PET can also identify inflammation and is particularly helpful in the diagnosis and management of suspected cardiac sarcoidosis, as demonstrated in several of the case presentations.¹⁰ However, a negative PET does not exclude the diagnosis. Moreover, diseases like cardiac amyloidosis have been shown to have FDG avidity in the myocardium, further confounding interpretation and management decisions based on PET findings alone.¹¹ This also underscores that reliance on diagnostic imaging alone, without genetic insights, may be insufficient for correctly diagnosing and treating patients with DCM, as highlighted in the second case of *LMNA*-related DCM, which was masquerading as cardiac sarcoidosis on imaging. In fact, recent reports have noted similar findings of FDG uptake on PET, and myocardial fibrosis and LGE on CMR in patients with pathogenic *LMNA* variants who were initially thought to have isolated cardiac sarcoidosis.¹² It is worth noting that patients with *LMNA* cardiomyopathy often present with early conduction issues and atrial and/or ventricular arrhythmias before showing evidence of DCM; hence, the presentation can be very similar to cardiac sarcoidosis.¹³ To ensure the early identification of a genetic cause in patients with overlapping signs of isolated cardiac sarcoidosis and

LMNA cardiomyopathy, a proposed approach would be to pursue genetic testing before starting long-term immunosuppression. Though inflammation is thought to be part of the pathogenesis of arrhythmogenic cardiomyopathy due to *LMNA*, there is a paucity of data exploring the role of immunosuppression in these cases.

Genetic DCM also includes other arrhythmogenic cardiomyopathies, as seen in the third case, and emphasizes the importance of early genetic testing, especially in patients with nonischemic cardiomyopathies and a family history of sudden cardiac death or arrhythmias. Early genetic testing can also, as illustrated in the fourth case, obviate the need for additional invasive diagnostic procedures and the associated risk. Taken together, these cases suggest that advanced cardiac imaging and early implementation of genetic testing as part of the initial diagnostic workup can improve the diagnostic yield and management of patients with genetic DCM. Additionally, the multidisciplinary team approach implemented in these cases was crucial in managing the complex interplay of genetic, inflammatory, and arrhythmic factors that characterize genetic DCM, allowing for more personalized and effective treatment strategies.

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