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EDITORIAL

A silent interweaving: interatrial block and laminopathy

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This editorial refers to 'Interatrial block as first clinical presentation of atrial cardiomyopathy related to a novel LMNA variant: a case report', by M. Iavarone *et al*. https://doi.org/10.1093/EHJCRE/ytad532.

Variants in the lamin (LMNA) gene, responsible for encoding nuclear Lamin proteins A and C, constitute a frequent cause of familial dilated cardiomyopathy (DCM) after titin (TTN)-truncating variants. Lamin A and C are structural proteins, which play a crucial role in maintaining the nuclear integrity and stability, as well as in regulating nuclear function.[1] LMNA missense and non-missense (including insertions, deletions, variants affecting splicing or truncating variants) collectively contribute to 5–8% of genetic cases of DCM.[2,3] LMNA variants are typically inherited following an autosomal-dominant pattern, and LMNA cardiomyopathy has a high cardiac penetrance with a rate of up to 86% among individuals who test positive for the genotype.[4] Although initially LMNA variants were only related to neuromuscular disorders, in 1999, the first association between LMNA variants and DCM has been described.[5] LMNA variants in the rod domain of the protein have been mainly related to DCM, whereas variants in the tail or head domain have been related to muscular dystrophy.[5]

Cardiac clinical presentation of LMNA variant ranges from a DCM-like cardiac phenotype to arrhythmogenic cardiomyopathy with conduction alterations; atrial and/or ventricular arrhythmia, which might occur also in presence of normal left ventricular ejection fraction (LVEF); or to inflammatory cardiomyopathy resembling cardiac sarcoidosis.[6] As such, the presence of LMNA variants bears a relevantly increased risk for sudden cardiac death (SCD) also in asymptomatic carriers with no morphologic evidence of cardiomyopathy.[6]

In this clinical case report, Iavarone and colleagues[7] present the case of an otherwise healthy young lady with a positive familial history for DCM who is diagnosed with a partial interatrial block in the setting of a pre-participation sport examination.

According to the newly published guidelines on cardiomyopathies, also asymptomatic LMNA carriers should be risk-stratified with cardiac magnetic resonance imaging (MRI) to better evaluate their risk of SCD.[8] In the case presented by Iavarone and colleagues[7], echocardiography was used instead of MRI to raise the suspicion of diagnosis. Echocardiography, indeed, is a clinically daily available, cost-effective tool and the use of strain analyses represents a relatively new and powerful examination. In this young lady, both atrial and ventricular strain analyses on echocardiography were altered in the presence of an otherwise normal LVEF. Of note, the finding of an altered left atrial (LA) contractile strain function has previously been reported in patients with LMNA variants who developed atrial fibrillation and may arise before the onset of overt left ventricular (LV) dysfunction and LV dilation.[9] Furthermore, the presence of interatrial block has been associated with an increased risk for malignant arrhythmias and SCD in patients with DCM.[10]

This case report highlights the importance of both findings—i.e. interatrial block and LA strain dysfunction indicating atrial cardiomyopathy—as a clinical diagnostic tool in an otherwise asymptomatic patient.

Sudden cardiac death is often the first clinical manifestation of laminopathies. To assess the risk of life-threatening ventricular arrhythmia at 5 years, risk prediction scores (such as lmna-risk-vta.fr) have been developed. Risk stratification is mainly based upon the presence of atrioventricular block, ventricular arrhythmia, LVEF, and type of LMNA variant. Given the natural history of LMNA cardiomyopathies, it is essential to thoroughly evaluate all LMNA variants that are pathogenic or likely pathogenic. Of note, in a Norwegian epidemiological study, heart transplantation was necessary for almost 20% of patients with LMNA-related cardiomyopathy.[11]

Accordingly, the young lady underwent 24 h electrocardiographic monitoring, showing a combination of atrioventricular block, ventricular premature beats, and atrial fibrillation episodes. These findings altogether led to performance of genetic testing, which showed a novel likely pathogenic LMNA gene frameshift variant (c.1367, p.Asn456Thrfs*24), in which a threonine replaces the aspargine in position 456 leading to a premature stop codon after 24 amino acids and, eventually, resulting in a truncated, likely non-functional protein.

Truncating variants are virtually all pathogenic or likely pathogenic and usually associated with early onset of LMNA-related cardiomyopathy.[11,12] This clinical case sheds the light on the importance of genetics-guided management in an otherwise young and yet asymptomatic patient.

Clinicians should be aware of the importance of performing regular cardiac screenings in the presence of a positive familial history of cardiomyopathy and considering any electrocardiographic and echocardiographic anomalies—including those indicating atrial cardiomyopathy—prompting further genetic analyses.

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Data availability

No data are related to this manuscript.

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