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Editorial

Precision medicine in laminopathies: insights from the REDLAMINA registry

Medicina de precisión aplicada a laminopatías: enseñanzas del registro REDLAMINA

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The lamin gene (*LMNA*) is responsible for coding of isoforms of the lamin protein, which are found in virtually every differentiated cell and have a number of critical functions including structural support of the nucleus, gene regulation, and DNA repair.[1] The major isoforms, lamin A and lamin C, are generated via alternative splicing and both localize to the nucleoplasmic side of the nuclear envelope.[2] Mutations in *LMNA* have been linked to a number of clinically significant phenotypes including cardiac, neuromuscular and metabolic diseases, as well as diseases of aging.[3]

Mutations in the *LMNA* gene cause approximately 5% of dilated cardiomyopathy cases.[4,5] Dilated cardiomyopathy features progressive dilation and loss of systolic function in the left or both ventricles due to idiopathic or genetic causes. *LMNA* mutations also lead to conduction abnormalities, atrial and ventricular arrythmias, and sudden cardiac death (SCD).[6] Interestingly, arrhythmogenic complications of *LMNA* mutations usually precede systolic dysfunction, which has near complete penetrance by the seventh decade of life.[4] In particular, patients with the risk factors of left ventricular ejection fraction (LVEF) $< 45\%$, nonsustained ventricular tachycardia, male sex, atrioventricular block, and nonmissense *LMNA* mutations (ins-del/truncating or mutations affecting splicing) were identified has having a significantly higher risk for SCD.[7] Identification of these and other risk factors have influenced the indications for transplant evaluation,[8] as well as guidelines for implantable-cardioverter defibrillator (ICD) placement.[9,10]

In a recent article published in *Revista Española de Cardiología*, Barriales-Villa et al.[11] describe the clinical characteristics of inherited laminopathies in a large Spanish cohort and reassess previously reported risk criteria. The study was performed by retrospectively collecting data from the REDLAMINA registry from 1999 to 2018. Cardiac laminopathy was defined as a predominantly cardiac pathogenic phenotype in carriers including dilated cardiomyopathy, conduction disorder, atrial or ventricular arrythmia, or premature SCD. Genetic testing was performed by each institution that participated in the registry per individual protocols and the study population was then divided into missense vs nonmissense mutation groups by the authors of that study. Eighty-two patients were excluded from the registry due to lack of follow up, age < 16 at initial evaluation, noncardiac predominant phenotypes (lipodystrophy, metabolic syndrome, polyneuropathies), or variants that were classified as benign, nonpathogenic, or of unknown significance. A total of 140 patients (54 probands and 86 relatives) were included in the study.

The authors examined major arrhythmic events (MAE) defined as ICD discharge or SCD, and heart failure death defined as heart transplant or death due to heart failure as primary endpoints. They describe the clinical characteristics of men and women in the study and show statistically similar age, symptoms, and comorbidities including hypertension, diabetes, dyslipidemia, and alcoholism between the 2 groups at the initial evaluation. Interestingly, they showed that men had a statistically significant higher incidence of LVEF $< 45\%$ ($P = .033$), higher left ventricular end diastolic volume and left ventricular dilation ($P < .001$ for both) using magnetic resonance and echocardiography as quantitative assessments. There was no significant difference in late gadolinium enhancement on cardiac magnetic resonance between men and women ($P = .25$), although only 38% and 36.2% of patients were scanned respectively. Despite the differences in LVEF and dilation, there were no significant differences in the primary endpoints of MAE or heart failure death between men and women.

Examination of the classic risk factors of SCD for the primary endpoints revealed significant increases in MAE for patients with LVEF $< 45\%$ and for those with nonsustained ventricular tachycardia. There was also a significant increase in heart failure death in patients with LVEF $< 45\%$ and in carriers of missense *LMNA* variants. Remarkably, there was no significant increase in MAE or heart failure death with male sex and 1 independent risk factor. Also noted in the study was an insignificant difference in MAE between missense and nonmissense mutations.

This study broadens understanding of *LMNA* dilated cardiomyopathy in several ways. First, the authors identified 11 new pathologic variants in the REDLAMINA registry (4 missense and 7 nonmissense) in addition to 21 known variants. The data also provide an opportunity to reevaluate several current criteria for risk stratification in this specific cohort of patients. It presents conflicting new information compared with previous studies such as those by Van Rijsingen et al.[7] and Kumar et al.,[6] which reported a worse prognosis for nonmissense variants, while the current study suggests that missense mutations had worse prognosis. The authors propose that some variants from the original study by Van Rijsingen et al.[7] may have been misclassified as pathogenic due to limitations in the size and diversity of population databases at the time. In particular, one example was the missense variant p.Arg190Trp, present in 2 patients who did not meet criteria for

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ICD implantation based on the Webhi et al.[12] score who, nonetheless, both experienced SCD. Indeed, the more recent Heart Rhythm Society 2019 guidelines on the management of arrhythmogenic cardiomyopathies questioned the prognostic effect of *LMNA* missense variants and therefore these variants were not included in the risk stratification for SCD and ICD indications. The data reported by Barriales-Villa et al.[11] support the hypothesis that missense mutations can have variable penetrance, perhaps mediated through different effects on protein function leading to different clinical outcomes. The current study further suggests that not all missense mutations should be treated equally but should rather be evaluated in the context of the patient's phenotype, family history, and reported data on genotype-phenotype association for the specific variant when available.

In addition, the population in this article may suggest that sex is less of an independent predictor for SCD than previously thought.[6,7] Despite the similar rates for MAE or heart failure death between men and women, men had a statistically higher chance of ICD placement for primary prevention. Although this may reflect ongoing medical disparities between the treatment of men and women, it should be noted that men had a higher incidence of low LVEF and may thus have had additional indications for ICD besides arrhythmic events.

There are several limitations to this study. As mentioned by the authors, there are the inherent limitations of a retrospective multicenter trial, such as selection bias and differing protocols for genetic testing in each institution. Although this is one of the largest *LMNA* carrier cohorts published so far, the study population included in the analysis was relatively small for a retrospective study, which may make it more difficult to overcome these biases. In addition, up to 60 patients were excluded from the study because they had a noncardiac presentation or an *LMNA* variant that was benign or of unknown significance.

The 18 departments in the REDLAMINA registry were all associated with heart transplant centers, which likely had a high proportion of end-stage heart failure compared with the general population. This is evident by the relatively high number of heart transplants in the registry (28.2% for men and 14.5% for women). All centers in the study were also located in Spain, which may differ in terms of treatment protocols compared with other countries. Likewise, the criteria for heart transplant as a primary endpoint in the study by Barriales-Villa et al.[11] are not defined and therefore the clinical severity of the patients who received transplant is unclear. Finally, it should be noted that most patients in this cohort did not undergo formal cardiac magnetic resonance imaging and it is therefore difficult to conclude if late gadolinium enhancement is a risk factor for MAE or heart failure death.

In conclusion, this article examined a cohort of 140 patients from the REDLAMINA registry and reported 11 new pathologic variants. The authors describe the clinical characteristic of inherited laminopathies in this cohort and reassess previously reported risk criteria. Their findings differ significantly from the current known data and suggest that further investigations with large cohorts of patients need to be done to adequately risk stratify patients with this rare disorder. Despite the aforementioned limitations, this study both advances our understanding of the laminopathies and also highlights clear ongoing debates about the management of these patients.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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