Long-Term Arrhythmic and Nonarrhythmic Outcomes of Lamin A/C Mutation Carriers.

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Abstract

BACKGROUND: Mutations in LMNA are variably expressed and may cause cardiomyopathy, atrioventricular block (AVB), or atrial arrhythmias (AAs) and ventricular arrhythmias (VA). Detailed natural history studies of LMNA-associated arrhythmic and nonarrhythmic outcomes are limited, and the prognostic significance of the index cardiac phenotype remains uncertain.

OBJECTIVES: This study sought to describe the arrhythmic and nonarrhythmic outcomes of LMNA mutation carriers and to assess the prognostic significance of the index cardiac phenotype.

METHODS: The incidence of AVB, AA, sustained VA, left ventricular systolic dysfunction (LVD) (= left ventricular ejection fraction ≤50%), and end-stage heart failure (HF) was retrospectively determined in 122 consecutive LMNA mutation carriers followed at 5 referral centers for a median of 7 years from first clinical contact. Predictors of VA and end-stage HF or death were determined.

RESULTS: The prevalence of clinical manifestations increased broadly from index evaluation to median follow-up: AVB, 46% to 57%; AA, 39% to 63%; VA, 16% to 34%; and LVD, 44% to 57%. Implantable cardioverter-defibrillators were placed in 59% of patients for new LVD or AVB. End-stage HF developed in 19% of patients, and 13% died. In patients without LVD at presentation, 24% developed new LVD, and 7% developed end-stage HF. Male sex (p = 0.01), nonmissense mutations (p = 0.03), and LVD at index evaluation (p = 0.004) were associated with development of VA, whereas LVD was associated with end-stage HF or death (p < 0.001). Mode of presentation (with isolated or combination of clinical features) did not predict sustained VA or end-stage HF or death.

CONCLUSIONS: LMNA-related heart disease was associated with a high incidence of phenotypic progression and adverse arrhythmic and nonarrhythmic events over long-term follow-up. The index
cardiac phenotype did not predict adverse events. Genetic diagnosis and subsequent follow-up, including anticipatory planning for therapies to prevent sudden death and manage HF, is warranted.

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**KEYWORDS:** atrial fibrillation; cardiomyopathy; complete atrioventricular block; genetics; heart failure; ventricular tachycardia

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