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CASE REPORT

Laminopathies: A Pandora's box of heart failure, bradyarrhythmias and sudden death☆

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KEYWORDS
Laminopathy;
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Abstract
Introduction: The *LMNA* gene encodes a group of proteins that have an important structural and functional role in the cell nucleus. Mutations in this gene have been found in 6% of all forms of dilated cardiomyopathy and in up to 33% of those with conduction system disturbances.
Aims and Methods: Using a case report as an example, we performed a review of the literature on the pathophysiological mechanisms, clinical manifestations, risk stratification and treatment options of cardiac involvement in laminopathies.
Case report: We present the case of a 46-year-old man, whose ECG showed bizarre voltage criteria for left ventricular hypertrophy and first-degree atrioventricular block, a dilated left ventricle with mildly impaired global systolic function and non-sustained ventricular tachycardia on Holter monitoring, and with a family history of sudden death. Genetic testing identified an *LMNA* mutation. No ventricular arrhythmias were induced during electrophysiological study. The patient is under close clinical and echocardiographic monitoring and an event loop recorder has been implanted.
Discussion: Phenotypically, myocardial involvement in laminopathies is indistinguishable from other forms of idiopathic dilated cardiomyopathy. Ventricular arrhythmias are common, but the best method for sudden death risk stratification has yet to be established. The few studies that have been performed, with a very limited number of patients, show that factors associated with an unfavorable prognosis are ejection fraction <45%, non-sustained ventricular tachycardia, male gender and any form of atrioventricular block. Given the lack of evidence, indications for an implantable cardioverter-defibrillator for primary prevention in this context are the same as conventional indications for other forms of idiopathic dilated cardiomyopathy.
Conclusions: Cardiac involvement as a consequence of *LMNA* mutations generally has a more aggressive natural history than other forms of non-ischemic dilated cardiomyopathy. A high index of suspicion and prompt referral for genetic testing are essential for appropriate therapeutic management.

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PALAVRAS-CHAVE
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Laminopatias: uma caixa de Pandora com insuficiência cardíaca, bradiarritmias e morte súbita

Resumo
Introdução: O gene LMNA codifica proteínas que têm um papel estrutural e funcional importante a nível do núcleo celular. As suas mutações foram encontradas em 6% de todas as formas de miocardiopatia dilatada (MCD) e em 33% das formas que cursam com perturbações no sistema de condução.
Objetivos e métodos: Partindo da descrição de um caso clínico, é feita uma revisão da evidência existente acerca dos mecanismos fisiopatológicos, manifestações, estratificação de risco e tratamento das laminopatias com atingimento cardíaco.
Caso clínico: É apresentado o caso clínico de um homem de 46 anos com critérios de voltagem bizarros para hipertrofia ventricular esquerda no ECG, dilatação e ligeira depressão da função sistólica ventricular esquerda e bloqueio auriculoventricular de 1.° grau, arritmias ventriculares não mantidas polimórficas em Holter e história de morte súbita familiar. O teste genético foi positivo para mutação no gene LMNA. Foi submetido a estudo eletrofisiológico no qual não se induziram arritmias ventriculares. O doente foi mantido sob vigilância clínica e ecocardiográfica e implantado detetor de eventos.
Discussão: Fenotipicamente, o atingimento miocárdico é indistinguível do das outras formas de MCD idiopática. As arritmias ventriculares são frequentes e a forma de melhor estratificar o risco de morte súbita está ainda por definir. Estão disponíveis resultados de poucos estudos e com um número muito limitado de doentes, sendo que os fatores de mau prognóstico identificados por estes foram: fração de ejeção < 45%, TV não mantidas, sexo masculino e presença de qualquer forma de bloqueio auriculoventricular. Dada a fraca evidência disponível, as indicações formais para implantação de CDI em prevenção primária neste contexto não são ainda diferentes das indicações convencionais noutras formas de MCD idiopática.
Conclusão: O atingimento cardíaco como consequência da mutação no gene LMNA apresenta uma história natural geralmente mais agressiva do que a maior parte das demais formas de MCD não isquémica. Um índice de suspeição elevado e o pedido atempado do teste genético são essenciais para a estratégia terapêutica.

Introduction

The proteins lamin A and C polymerize to form the nuclear lamina, a meshwork of filaments on the nucleoplasmic side of the nuclear envelope, which separates the internal nuclear membrane from chromatin[1] and is found in all differentiated cells of the organism. This mesh has a structural function, maintaining the shape and size of the nucleus. Nuclear lamins also play a role in gene regulation, DNA replication, RNA splicing, anchoring of other nucleoplasmic proteins, function and position of nuclear pores and heterochromatin organization.[2,3]

LMNA, the gene encoding lamin A/C, is located on chromosome 1 (locus 1q21.2-21.3).[4] In 1999, an *LMNA* mutation was shown to cause autosomal dominant Emery-Dreifuss muscular dystrophy.[5]

Since then, over 450 mutations in this gene have been described and are implicated in a range of other diseases, which differ in their phenotypic expression and affect various organ systems including muscles, fatty tissue and peripheral nerves, as well as systemic involvement in the case of progerias. These entities are termed laminopathies, as shown in Table 1.

Many mutations linked to laminopathies also affect the heart, in the form of dilated cardiomyopathy (DCM), with or without involvement of other striated muscle, conduction disturbances and propensity for sudden death.

The mechanism through which lamin A/C deficiency causes these phenotypes is not fully understood. Two hypotheses have been proposed: one in which cell death is caused by loss of structural integrity at the nuclear level; and the other in which gene expression explains the phenotypic alterations through abnormal interaction with transcription factors in protein synthesis.[2,6] The disease is expressed histologically by fibro-adipose degeneration and atrophy of the affected tissues. At the level of cell ultrastructure, there may be partial membrane rupture, disorganization of the nuclear membrane pores and vacuolization.[7,8]

From the standpoint of practical cardiological management, these diseases can be considered as a single entity – cardiomyopathy associated with *LMNA* mutations, with or without different types of muscle involvement.

The development and accessibility of genetic study has led to more frequent identification of *LMNA* mutations in patients who would previously have been diagnosed as