



CASE REPORT

Complex phenotype linked to a mutation in exon 11 of the lamin A/C gene: Hypertrophic cardiomyopathy, atrioventricular block, severe dyslipidemia and diabetes



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Received 15 April 2016; accepted 13 July 2016
Available online 3 September 2017

KEYWORDS

Hypertrophic cardiomyopathy;
Lamin A/C;
LMNA gene;
Dyslipidemia;
Diabetes;
Atrioventricular block

Abstract The lamin A/C (*LMNA*) gene encodes lamins A and C, which have an important role in nuclear cohesion and chromatin organization. Mutations in this gene usually lead to the so-called laminopathies, the primary cardiac manifestations of which are dilated cardiomyopathy and intracardiac conduction defects. Some mutations, associated with lipodystrophy but not cardiomyopathy, have been linked to metabolic abnormalities such as diabetes and severe dyslipidemia. Herein we describe a new phenotype associated with a mutation in exon 11 of the *LMNA* gene: hypertrophic cardiomyopathy, atrioventricular block, severe dyslipidemia and diabetes.

A 64-year-old woman with hypertrophic cardiomyopathy and a point mutation in exon 11 of the *LMNA* gene (c.1718C>T, Ser573Leu) presented with severe symptomatic ventricular hypertrophy and left ventricular outflow tract obstruction. She underwent septal alcohol ablation, followed by Morrow myectomy. The patient was also diagnosed with severe dyslipidemia, diabetes and obesity, and fulfilled diagnostic criteria for metabolic syndrome. No other characteristics of *LMNA* mutation-related phenotypes were identified. The development of type III atrioventricular block with no apparent cause, and mildly depressed systolic function, prompted referral for cardiac resynchronization therapy.

In conclusion, the association between *LMNA* mutations and different phenotypes is complex and not fully understood, and can present with a broad spectrum of severity.

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PALAVRAS-CHAVE

Miocardíopatia hipertrófica;
Lâmina A/C;
Gene LMNA;
Dislipidemia;
Diabetes;
Bloqueio auriculoventricular

Fenótipo complexo associado a uma mutação no exão 11 do gene da lâmina A/C: miocardíopatia hipertrófica, bloqueio auriculoventricular, dislipidemia grave e diabetes *mellitus*

Resumo O gene LMNA codifica a lâmina A/C, com importante papel na manutenção da coesão nuclear e organização da cromatina. Mutações neste gene estão geralmente associadas a doenças denominadas laminopatias. As manifestações cardíacas primárias destas mutações são miocardíopatia dilatada e defeitos da condução intracardiaca. Algumas mutações, associadas a lipodistrofia, mas não cardiomiopatia, estão também associadas a alterações metabólicas, como diabetes ou dislipidemia grave. Assim, descrevemos um novo fenótipo associado a uma mutação no exão 11 do gene LMNA: miocardíopatia hipertrófica, bloqueio auriculoventricular, dislipidemia grave e diabetes.

Apresentamos a situação clínica de uma doente de 64 anos de idade, com miocardíopatia hipertrófica e mutação patogénica identificada no exão 11 do gene LMNA (c.1718C>T, Ser573Leu). A doente apresentou-se com hipertrofia ventricular grave sintomática, obstrutiva, refratária à terapêutica médica. Foi submetida a ablação septal por álcool e, posteriormente, a miectomia cirúrgica. Foi também diagnosticada dislipidemia grave, diabetes e obesidade, cumprindo os critérios para síndrome metabólica. Não foi identificada nenhuma outra característica fenotípica associada a mutações no gene LMNA. A doente foi ainda submetida a terapêutica de ressincronização cardíaca após o desenvolvimento de bloqueio auriculoventricular completo, sem causa aparente, na presença de ligeiro compromisso da função sistólica ventricular.

A correlação de mutações no gene LMNA com diferentes fenótipos é complexa e ainda não completamente compreendida, englobando um largo espectro de gravidade clínica.

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Introduction

The lamin A/C (*LMNA*) gene is mapped to the long arm of chromosome 1 (1q21-23) and contains 12 exons.¹ This gene encodes lamins A and C, nuclear envelope proteins with an important role in nuclear cohesion and chromatin organization. They are critical to the performance of the peripheral nervous system, skeletal muscle, osteoblastogenesis and bone formation, and are also involved in the prevention of muscle fat infiltration.²

Mutations in the *LMNA* gene are linked to several diseases, called laminopathies, which display heterogeneous phenotypes, including Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, Dunnigan-type familial partial lipodystrophy (FPLD type 2), Charcot-Marie-Tooth disease, mandibuloacral dysplasia, Hutchinson-Gilford progeria syndrome, atypical forms of Werner syndrome and restrictive dermopathy.²⁻⁵ Regarding cardiovascular disease, the phenotype is typically dilated cardiomyopathy with conduction defects (atrial arrhythmia or atrioventricular [AV] block), progression to heart failure and a high incidence of sudden cardiac death.^{3,6-8} There is only one case report of hypertrophic cardiomyopathy associated with mutations in this gene,³ and other rare associations with ventricular hypertrophy,^{3,4,9} left ventricular noncompaction and arrhythmogenic right ventricular dysplasia have been described.¹⁰

Disorders caused by *LMNA* mutations, like FPLD type 2, are also linked to metabolic abnormalities characterized

by abnormal fat distribution, insulin resistance, diabetes, dyslipidemia, high blood pressure, hepatic steatosis and increased risk for coronary heart disease.^{4,5,9,11}

The lipodystrophic and myopathic phenotypes are thought to be mutually exclusive, but in rare cases heterozygous *LMNA* mutations are associated with cardiac and skeletal muscular involvement.^{9,12-14}

In this report we describe a new phenotype linked to a mutation in exon 11 of the *LMNA* gene: hypertrophic cardiomyopathy, AV block, severe dyslipidemia and diabetes.

Case report

The authors present the case of a 64-year-old woman with metabolic syndrome – obesity (body mass index 30 kg/m²), severe dyslipidemia (fasting serum triglycerides [TG] 960 mg/dl, total cholesterol [TC] 273 mg/dl, high-density lipoprotein cholesterol 40 mg/dl) and diabetes (HbA1c 6.8%) – who presented in January 2013 with fatigue on minimal exertion in NYHA functional class II. On cardiac auscultation, a systolic murmur was audible along the upper left sternal border, increasing with the Valsalva maneuver. The electrocardiogram (ECG) revealed sinus rhythm with normal interventricular conduction. Transthoracic echocardiography (echo) identified severe left ventricular hypertrophy (LVH), with basal septal wall 21.7 mm and posterior wall 11.8 mm, systolic anterior motion of the mitral valve and a dynamic left ventricular outflow gradient of 111 mmHg

at rest. There was no family history of cardiac disease. Genetic screening, testing a panel of 51 genes associated with cardiomyopathies by oligonucleotide-based target capture followed by next-generation sequencing, identified a point mutation in exon 11 of the *LMNA* gene (c.1718C>T, p.Ser573Leu). Besides obesity, diabetes and severe dyslipidemia, no other phenotypic characteristics related to the *LMNA* mutation were identified.

Despite medical treatment with bisoprolol and amlodipine, the patient's heart failure symptoms worsened and septal alcohol ablation was performed. A satisfactory final result was achieved with symptomatic improvement and gradient reduction (maximum subaortic gradient of 25 mmHg at rest and 37 mmHg after the Valsalva maneuver, with septal basal wall of 14.2 mm, measured six days after the procedure).

Several months later, despite optimized medication, heart failure symptoms worsened, with progression of LVH (basal septal wall 18.3 mm) and recurrence of outflow obstruction (124 mmHg at rest). Morrow myectomy was performed with a good final result (maximum subaortic gradient of 10 mmHg after Valsalva maneuver). After surgery the ECG revealed sinus rhythm and a left bundle branch block pattern, with QRS duration of 160 ms. The patient remained clinically stable under treatment with bisoprolol, amlodipine, spironolactone, furosemide, rosuvastatin and metformin. Three months later she presented at the emergency department with seizure and worsening fatigue. A pattern of complete AV block at 30 bpm was detected and a temporary transvenous cardiac pacemaker was implanted. After 48 hours of bisoprolol washout, the AV block pattern persisted and the patient remained pacemaker-dependent. Echo evaluation showed mild LVH (septal wall 12.1 mm and posterior wall 12.8 mm), no left ventricular outflow tract obstruction, paradoxical septal motion and left ventricular ejection fraction of 45%. Considering her history of heart failure, the reduction in ejection fraction and the broad QRS complex, a cardiac resynchronization device was implanted.

Regarding the metabolic disorder, laboratory tests on admission revealed a fasting serum TG level of 3260 mg/dl and TC of 640 mg/dl. Although there were no acute complications related to severe dyslipidemia, in order to achieve rapid and effective lowering of TG values and to prevent complications due to hypertriglyceridemia, particularly acute pancreatitis, therapeutic plasma exchange was performed. Treatment with lipid-lowering agents was also intensified, with up-titration of rosuvastatin and addition of bezafibrate and ezetimibe, and beta-blocker therapy was reintroduced. The patient was discharged, and at the first reassessment one month later she was asymptomatic, with 100% pacing capture and a significantly improved lipid profile. At six-month follow-up she remained in NYHA functional class I.

Discussion

Mutations in the *LMNA* gene are associated with a highly heterogeneous group of phenotypes. The molecular mechanisms through which lamin A/C mutations lead to such phenotypic variability are poorly understood. Several hypotheses have been advocated, including mechanical

shearing, differential gene regulation by interaction with nuclear chromatin, and interaction between mutant lamins and other nuclear proteins.¹⁵

Of the 12 exons composing the human *LMNA* gene, exons 11 and 12 are specific for lamin A, while mutations in the other exons (1-10) affect both variants (lamin A and C).³ Usually, mutations affecting both splice forms result in more severe phenotypes, and, mutations in exon 11 – affecting only the globular domain specific to the lamin A isoform – are associated with milder phenotypes regarding lipodystrophy and myopathy, as was the case with this patient.^{3,13}

Cardiac involvement with lipodystrophy has been previously associated with *LMNA* mutations, but the cardiac phenotype is usually dilated cardiomyopathy associated with conduction defects. In contrast, our patient had a pattern of hypertrophic cardiomyopathy, and conduction disturbances requiring pacemaker implantation. Her systolic dysfunction (as demonstrated by left ventricular ejection fraction of 45%), broad QRS, and history of heart failure prompted the implantation of a cardiac resynchronization device.¹⁵ For patients with AV block and systolic dysfunction, biventricular pacing not only reduces the risk of mortality and morbidity, but also leads to better clinical outcomes, compared with right ventricular pacing.¹⁶

The *LMNA* mutation identified in our patient (c.1718C>T, Ser573Leu) was first documented in 2003 by Taylor et al.¹⁷ This mutation had been identified in heterozygosity in a patient with dilated cardiomyopathy and conduction defects¹⁷ and in homozygosity in a patient with arthropathy, tendinous calcinosis, and progeroid features without any type of cardiomyopathy.¹⁸ Because heterozygosity for this mutation can cause cardiomyopathy without lipodystrophy or lipodystrophy without cardiomyopathy, Lanktree et al. suggested that additional factors, genetic or environmental, may contribute to the precise tissue involvement.¹⁹ This specific mutation has not previously been associated with hypertrophic cardiomyopathy. However, the significant LVH (septal thickness 21 mm) in the absence of other identifiable cause, and the identification of a single pathogenic mutation in a sarcomere-related gene (point mutation in exon 11 in the *LMNA* gene, in a panel of 51 genes associated with cardiomyopathies), suggested a causal association between the molecular genetic findings and the cardiac phenotype in this patient.

In conclusion, the association between *LMNA* gene mutations and different phenotypes is complex and not fully understood, and can present with a broad spectrum of severity. Of note, the occurrence and severity of myopathic and lipotrophic phenotypes are not related and the correlation of newly identified mutations and individual clinical phenotypes is mandatory. We report a new and complex phenotype linked to a mutation in exon 11 in the *LMNA* gene (c.1718C>T, p.Ser573Leu) associated with hypertrophic cardiomyopathy, atrioventricular block, severe dyslipidemia and diabetes.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Author contributions

ARF and DB were responsible for the conception, design and drafting of the article. All the authors made substantial contributions to the article, through data acquisition, data interpretation and revision. All authors gave their final approval of the version to be submitted.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

The authors thank Dr. Gabriel Miltenberger Miltényi (MD, PhD, molecular geneticist), for his contribution to the literature review of the mutation reported in this case.

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