Rev Port Cardiol. 2017;36(9):669.e1–669.e4

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

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

Ana Rita G. Francisco*, Inês Santos Gonçalves, Fátima Veiga, Mónica Mendes Pedro, Fausto J. Pinto, Dulce Brito

Cardiology Department, Santa Maria University Hospital, CHLN, CAML, CCUL, Faculty of Medicine, University of Lisbon, Lisbon, Portugal

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.

* Corresponding author.
E-mail address: ana.r.francisco@gmail.com (A.R.G. Francisco).

http://dx.doi.org/10.1016/j.repc.2016.07.018

PALAVRAS-CHAVE
Miocardiopatia 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: miocardiopatia 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 miocardiopatia dilatada e defeitos da condução intracardíaca. 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: miocardiopatia hipertrófica, bloqueio auriculoventricular, dislipidemia grave e diabetes.

Apresentamos a situação clínica de uma doente de 64 anos de idade, com miocardiopatia 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.

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/m^2), 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