A novel mutation in limb girdle muscular dystrophy

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We describe a patient with limb girdle muscular dystrophy with evidence of a D596N novel mutation of the *LMNA* gene. He presented with a dilated cardiomyopathy and heart failure. He successfully underwent a cardiac rehabilitation program without cardiovascular complications. Clinicians should suspect a variety of a wide array of diseases including laminopathy, dystrophinopathy, sarcoglynopathy and LGMD 2I. Further studies should focus on determining the specific mode of inheritance and genetic testing should be considered in these patients.

Key words: Limb girdle muscular dystrophy, dilated cardiomyopathy, LMNA gene, mutation, cardiac rehabilitation, atrioventricular block.

Limb girdle muscular dystrophy (LGMD) is a genetically heterogeneous disease that may be autosomal recessive (2A-J) or autosomal dominant (1A-1F) (1-2). The distribution of muscle weakness is similar between the dominant and recessive forms; however while the adult-onset form is slowly progressive, the recessive form ranges from asymptomatic carriers to individuals with severe weakness even in patients carrying the same mutation within the same family (1-2).

LGMD 1B is an autosomal dominantly-inherited, slowly progressive pelvic girdle weakness with late involvement of humeral muscles and sparing of the peroneal and tibial muscles. Affected individuals present with age-related atrioventricular cardiac conduction disturbances, dilated cardiomyopathy and the absence of early contractures. This disease has been linked to chromosome 1q11-q21 (3-4). The onset is usually before 20 years of age and serum CK activity can be mildly to moderately elevated (1).

Mutations in the *LMNA* gene encoding the nuclear membrane protein lamin A/C have been associated with several distinct diseases (5-16) (Table 1). The nuclear lamina is a proteinaceous layer apposed to the inner nuclear membrane. It is composed of a family of polypeptides, the lamins, highly conserved in evolution. In humans, there are two major types of lamins: A-type lamins (consisting of lamins A and C) found primarily in differentiated cells, and B-type lamins (lamins B1 and B2) that are found in all nucleated cells (4).

Lamins A and C, the products of the *LMNA* gene, are nuclear intermediate filament proteins and are the major

Table 1. Disorders associated to mutations in the LMNA gene encoding the nuclear membrane protein lamin A/C (3, 6-9, 19, 10-12, 23, 13, 3, 14-15).

- Autosomal dominant dilated cardiomyopathy with conduction system disease
- Autosomal dominant and recessive Emery Dreifuss Muscular Dystrophy
- Limb girdle muscular dystrophy type 1B with atrioventricular conduction disturbances
- Autosomal recessive type 2 Charcot Marie Tooth
- Mandibuloacral dysplasia
- Dunnigan-type familial partial lypodystrophy
- Generalized lipoatrophy, insulin-resistant diabetes, leukomelanodermic papules, liver steatosis and cardiomyopathy
- Hutchinson-Gilford progeria syndrome
- Atypical Werner syndrome
- Restrictive Dermopathy

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structural components of the lamina network that underlies and supports the nuclear envelope. Nuclear fragility and mislocalization of the nuclear envelope protein emerin are two defects induced by a lack of the A-type lamins. These observations reveal that organization and structural integrity of the nucleus are critical factors in the origins of certain dystrophic and cardiovascular diseases (11, 13).

Mechanisms by which mutations in *LMNA* cause tissue specific disorders are poorly understood. Two models have been proposed. The "mechanical stress hypothesis" model suggests that the lamins and their associated proteins form a filamentous nucleoskeleton that supports the nuclear envelope (NE). It has been suggested that the mutations in lamin A/C cause structural abnormalities within the lamina causing fragility in the NE, particularly in contractile tissues such as skeletal and cardiac muscle. The second model proposes that mutations in lamin A/C cause change in gene expression, which promote the pathophysiology of the various diseases (14).

Naturally occurring mutations in *LMNA* have been shown to be responsible for distinct diseases called laminopathies, including dilated cardiomyopathy with or without conduction defect and with and without variable skeletal muscle involvement (17-19, 4, 20). Thus lamin A/C is the first known nucleophillic protein which plays a role in human disease (8).

Case Report

A 37 year-old Latin American man with suspected LGMD and dilated cardiomyopathy was referred to our outpatient Phase II Cardiac Rehabilitation Program. The patient claims that 5 years prior to the evaluation he had an episode of mononucleosis and at that time a blood chemistry analysis revealed a very high creatinine kinase (CK) level. He noticed progressive muscle weakness and respiratory difficulty at night. Two years later he developed a viral gastroenteritis and a routine chest radiograph revealed cardiomegaly, later developing a decompensated congestive heart failure.

The patient referred his mother had normal CK value and his father died at 70 years of age due to a myocardial infarction. Parents are 2nd degree cousins. His mother had one spontaneous abortion, one female stillbirth, one son that died at the age of 14 months of unknown cause and one daughter that died at the age of 13 after a tonsillectomy. He has two living sisters with normal CK.

On initial examination, he was a thin young man that presented proximal muscle weakness and atrophy at shoulder and hip girdle more prominent on the right side. There was no muscle hypertrophy. He presented with significant lumbar lordosis, a waddling gait without need of assistive devices and the Gower maneuver was positive. The deep tendon reflexes were diminished. The rest of the physical exam was normal. He presented a slightly high serum aldolase and CK MB (cardiac muscle) with a total CK of 1,161 U/L.

A 24-hour ECG monitoring revealed a sinus rhythm with frequent premature ventricular contractions (PVC's). A bi-dimensional echocardiogram (2D-ECHO) demonstrated a left ventricular ejection fraction (LVEF) of 35%. A Radionuclide Ventriculogram, multigated acquisition (MUGA) scan and cardiac catheterization also revealed a LVEF of 34-35%, global hypokinesis and mild to moderate pulmonary hypertension with normal coronary arteries.

A needle electromyogram (EMG) performed on upper and lower extremities revealed increased polyphasic potentials and increased motor unit recruitment on proximal muscles. The nerve conduction studies were normal.

A muscle biopsy showed a mild myopathy/dystrophy, no overt necrosis or degeneration/regeneration, however there were many centrally located nuclei.

Basic metabolic panel, thyroid function test, carnitine profile, ANA test, C- reactive protein and sedimentation rate were normal. Epstein Barr Virus, Cytomegalovirus and Chagas disease antibody titers were normal.

He completed the Phase II Cardiac Rehabilitation Program without any complications achieving the capacity to tolerate aerobic activity for a total of 45 minutes at an intensity of 5.0 metabolic equivalents (METs). His body fat decreased 5.7% and the total body weight increased 5.5 Kg. A 1786G→A (D596N) mutation was detected in exon 11 of the *LMNA* gene. Mutation analysis of the *LMNA* gene in this patient demonstrated a base pair change that results in an aspartic acid to asparagine amino acid change at residue 596. D596N is a non-conservative amino acid change. Relatives were not available for cardiac studies or further genetic testing.

In comparison to the initial examination performed 2 years earlier, the proximal muscle weakness had slowly progressed with loss of 1 grade in the [Medical Research Council (MRC) scale]. He was unable to walk on heels and climb stairs. He had no other congestive heart failure episode.

The most recent studies demonstrated an ECG with low voltage in the frontal plane, anterolateral and high lateral; ST-T changes consistent with myocardial disease, sinus bradycardia and PVC's. The echocardiogram revealed no change in the LVEF.

Discussion

In a meta-analysis of clinical characteristics of 299 carriers of *LMNA* gene mutations, the ECG findings

revealed cardiac dysrhythmias in 92% of the patients after the age of 30 years and heart failure was reported in 64% after the age 50 (18). Sudden death was the most frequently reported mode of death (46%) in both the cardiac and the neuromuscular phenotype. ECG findings typically showed a low amplitude P wave and prolongation of the PR interval with narrow QRS complex (21). In the case we have presented the patient developed heart failure at the age of 33 and skeletal muscle weakness was already present. He demonstrated no significant cardiac conduction abnormalities and the PVC's were less frequent at the final stage of the cardiac rehabilitation program.

The genetic tests revealed a new mutation of the *LMNA* gene demonstrating a base pair change that results in an aspartic acid to asparagine amino acid change at residue 596. To our knowledge, this mutation has not been reported previously in the literature in other patients with *LMNA*-associated syndromes.

His parents are second degree relatives without documented skeletal muscle weakness. Since relatives were not available for cardiac studies or further genetic testing the mode of inheritance could not be determined. The variable premature deaths of siblings suggest that they might have presented with some degree of manifestation of this disease. Clinicians should suspect other diseases including laminopathy, dystrophinopathy, sarcoglynopathy and LGMD 2I. Further studies should focus on determining the specific mode of inheritance and genetic testing should be considered.

Patients with adult-onset cardiac disorders or myopathy with limb girdle distribution are often associated with frameshift mutations presumably leading to a truncated protein(22). Mutations in the same codon of *LMNA* exon 11 are characterized by remarkable variability of clinical findings(23).

Our patient presented LGMD with dilated cardiomyopathy and a novel mutation of the *LMNA* gene. Proper diagnosis could aid in early discovery, family genetic counseling and management of possible fatal complications.

Resumen

Se describe un paciente con distrofia muscular de la faja pélvica tipo 1B con evidencia de una nueva mutación D596N del gen *LMNA*. El paciente presenta una cardiomiopatía dilatada y fallo cardiaco. El pudo completar un programa de rehabilitación cardiaca de forma satisfactoria sin complicaciones cardiovasculares. En pacientes con debilidad muscular asociada a cardiomiopatía o aquellos con cardiomiopatía de origen desconocido se debe sospechar una gran variedad de enfermedades tales como laminopatía, distrofinopatía, sarcoglinopatía y distrofia muscular de faja pélvica 2I. Estudios más extensos se deben enfocar en determinar la manera específica de herencia de esta enfermedad.

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Abbreviations:

2D-ECHO, Bi-dimensional echocardiogram; BMI, body mass index; CK, creatinine kinase; CRP, c-reactive protein; CV, conduction velocity; DCM-CD, dilated cardiomyopathy with conduction defect disease; EDMD, Emery Dreifuss Muscular Dystrophy; ECG, electrocardiogram; EMG, needle electromyogram; *LMNA*, lamin A/C; LGMD, limb girdle muscular dystrophy; LVEF, left ventricular ejection fraction; METs, metabolic equivalents; MU, motor unit; MUGA, multigated acquisition; NE, nuclear envelope; PVC's, premature ventricular contractions

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