Dilated cardiomyopathy caused by \textit{LMNA} mutations. Clinical and morphological studies

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Abstract

\textbf{Background:} Dilated cardiomyopathy (DCM) is familial in about 20–35\% of patients. The most frequently encountered mutations associated with DCM are found in \textit{LMNA}.

\textbf{Aim:} To define the frequency of \textit{LMNA} mutations in a series of consecutive DCM patients and to evaluate the phenotype of mutation carriers.

\textbf{Methods:} We screened the 12 exons of \textit{LMNA} in a series of 61 Polish patients with DCM diagnosed angiographically, as well as in two DCM families.

\textbf{Results:} Two mutations were detected in 5 mutation carriers (D192G in one proband and Y481Stop in one proband and 3 of his offspring), which represents 3.3\% (2/61) of the DCM patients. These mutations were absent from 100 controls. The D192G mutation was found in a 26-year-old patient with mild DCM and heart failure leading to death within two years after onset of symptoms. Mild conduction disease was also present. Ultrastructural analysis of the endomyocardial biopsy showed a striking alteration of nuclear morphology. This finding can explain nuclear fragility and is in agreement with the pathophysiological mechanical hypothesis of \textit{LMNA} mutations. All four Y481Stop mutation-carriers were affected. Three phenotypes were found: in the proband, cardiac dysrhythmia and pacemaker requirement preceded DCM leading to heart transplantation; the proband's 13-year old daughter had conduction disease (2\textsuperscript{nd} degree A-V block) with subtle skeletal muscle involvement documented by immunofluorescence study; ventricular arrhythmia was detected in the proband's son at the age of 11 and in the proband's daughter at the age of 18. Serum creatine kinase was normal in all mutation carriers.

\textbf{Key words:} dilated cardiomyopathy, lamins, \textit{LMNA}, genetics

Introduction

Familial DCM is generally inherited following an autosomal dominant pattern (70\%), but autosomal recessive and X-linked transmissions also exist [1, 2]. To date, 20 genes have been implicated in autosomal dominant DCM [MIM#115200, 3-7]. The most frequently encountered mutations associated with DCM are found in \textit{LMNA}, coding for lamins A and C, type V intermediate filament proteins. Lamins A and C are located in the lamina which underlies the inner...
nuclear membrane [8]. They contribute to the structural integrity of the nuclear envelope. Furthermore, lamins A and C are considered to have multiple functional domains that participate in chromatin organisation and anchorage of nuclear envelope proteins; they are also known to take part in the process of DNA replication, RNA transcription, cell cycle regulation and in apoptosis [9]. Lamins A and C are encoded by a single gene (LMNA), located on chromosome 1q21 and containing 12 exons, and arise from alternative splicing. LMNA mutations have been causally linked to different clinical phenotypes, including muscular dystrophies, neuropathies and lipodystrophies [10-15]. Cardiac involvement is common, with DCM associated with atrioventricular block found in the vast majority of reported patients [14, 15]. The major cardiac problem in laminopathies is heart failure, conduction disturbances and a variety of dysrhythmias [16]. Of note, sudden death is common (46% of mutations carriers), and heart failure often progresses to end-stage disease requiring heart transplantation [16].

The aim of the study was to define the frequency of LMNA mutations in a series of consecutive Polish DCM patients and to determine the clinical and morphological characteristics associated with DCM due to LMNA mutations.

Methods

Clinical and control series

Sixty-one consecutive patients with DCM, two families and 100 healthy blood donors were screened for mutations in LMNA. Dilated cardiomyopathy was diagnosed on the basis of WHO criteria [17]. Relatives of the index DCM patients were included in the family screening programme; after obtaining written informed consent they underwent a clinical examination, 12-lead electrocardiography, echocardiography and serum creatine kinase (CK) examination [18-20].

Mutation screening

Genomic DNA was prepared from white blood cells. The LMNA coding sequence was amplified by polymerase chain reaction (PCR) using intronic oligonucleotide primers flanking each of the twelve LMNA exons and designed according to published sequences (Genbank accession number: L123399, L12400, and L12401). Each amplified DNA fragment was submitted to both SSCP [21] and denaturing high-performance liquid chromatography (DHPLC) (Helix, Varian) analysis. All PCR samples displaying aberrant SSCP and/or DHPLC profiles compared to wild-type controls were double-stranded sequenced (ABI Prism Big Dye, AppliedBiosystems automatic sequencer). If the DNA alteration caused a non-silent polymorphism, then 200 chromosomes from control individuals were tested.

Endomyocardial biopsy

Right ventricular endomyocardial biopsy was performed using Cordis biopтомe from a femoral transvenous approach. Biopsy material was examined by light microscopy and routine immunostaining. One endomyocardial biopsy sample was processed for ultrastructural study and analysed using a JEM 1200EX electron microscope, as described previously [22].

Skeletal muscle biopsy

The skeletal muscle tissue was analysed by light microscopy, immunostaining and electron microscopy. Immunostaining procedure was performed using four antibodies directed against distinct lamin A/C epitopes (AC2 and AC3 reacting with epitopes lying between amino acids 464 and 572; A4 detecting only lamin A as its recognition site lies after amino acid 572; and AC5, reacting with epitopes lying between amino acids 1 and 171), kindly provided by Prof. Hutchison (Department of Biological Sciences, University of Dundee, Glasgow).

Results

Identification of mutations in LMNA

Sixty-one consecutive patients with DCM were recruited from the Caucasian Polish population and examined for the presence of mutations in the coding sequence and intron/exon boundaries of LMNA. Two distinct mutations were found: a missense D192G mutation and a nonsense Y481Stop mutation. The prevalence of LMNA mutations in the DCM Caucasian population studied was 3.3% (2/61). These two mutations are localised in highly conservative regions, common to both lamin A and C isoforms. The D192G mutation is located in exon 3 of the central alpha-helical domain and was found in one proband. The second mutation, Y481Stop, was located in exon 8 and predicted to lead to a truncated protein, missing respectively 183 and 91 amino acids of the distal part of lamins A and C. We found it in 4 subjects (the proband and in three of his offspring).

Clinical characteristics of mutation carriers

Of the 5 mutation carriers (1-D192G and 4Y481Stop), all were phenotypically affected. The presence of heart failure indicated poor prognosis. In both families there was evidence of heart failure in the family history.

Family A (D192G) consisted of 2 living generations. Of the 5 mutation carriers (1-D192G and 4Y481Stop), all were phenotypically affected. The presence of heart failure indicated poor prognosis. In both families there was evidence of heart failure in the family history.

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cardiac disease, and subsequently through his father, who died at the age of 37 after experiencing symptoms of heart failure for two years; this suggests autosomal dominant transmission of the disease. The proband had first heart failure symptoms at the age of 25, and was diagnosed at the age of 26 while being in NYHA IV class heart failure with mild dilation of the left ventricle (LVEDD=3.4cm/m²) and severe diffuse hypokinesis of the left ventricle (LVEF=20%) (mildly DCM phenotype). Mild conduction system disease (PR=220 ms, intraventricular conduction delay with QRS of 124 ms) was also present (Table I). The proband died of heart failure while waiting for heart transplantation at the age of 27. Ultrastructural analysis of endomyocardial biopsy revealed great nuclear abnormality. Approximately 30% of cardiomyocyte nuclei showed changes in nuclear shape and nuclear matrix organisation. Numerous nuclei were partially or totally devoid of nuclear membrane. The most surprising finding was the accumulation of sarcoplasmic organelles (mitochondria, channels of SR, glycogen granules) within the nucleoplasm (Figure 2). The CK serum level was normal (Table I).

Family B (Y481Stop) consisted of 3 living generations and 14 subjects were screened. (Figure 1B). A nonsense mutation Y481Stop in exon 8 carried by the proband and his three children were identified. The disease may have been transmitted from the proband’s father, who died at the age of 47 of unknown cardiac disease, suggesting autosomal dominant transmission of the disease. In the proband diagnosed at the age of 36 because of

**Legend:** The arrow shows the proband. Filled symbols indicate DCM patients; square, male; circle, female. A half-blackened symbol indicates cardiac abnormalities in unaffected individuals. Open symbols indicate subjects not examined. N – normal subjects. Crossed symbol indicates hypertension. Shaded symbols indicate obligate carriers. Diagonal lines indicate death. Roman numerals indicate generations. Numbers below symbols indicate age at screening, or, in the case of deceased subjects, at death. Numbers above symbols indicate consecutive examined subjects.

**Figure 1.** Family A and family B pedigrees
<table>
<thead>
<tr>
<th>Patient</th>
<th>Mutation</th>
<th>Onset, evolution, follow-up (age)</th>
<th>sCK (U/l)</th>
<th>ECG</th>
<th>PR (ms)</th>
<th>LVEDD/LVESD [mm]</th>
<th>LVFS (%)</th>
<th>LVEF (%)</th>
<th>%LVE</th>
<th>Additional abnormality</th>
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<tbody>
<tr>
<td>A III-1</td>
<td>Asp 192Gly</td>
<td>Onset: 26 y – heart failure symptoms</td>
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<td>A II-1</td>
<td>Deceased at age 37 y, after symptoms of heart failure for 2 years</td>
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<td>A II-1</td>
<td>Baseline: 52 y</td>
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<td>A I-1</td>
<td>Deceased at age 64 y</td>
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<td>A III-2</td>
<td>Baseline: 25 y</td>
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<td>B III-2</td>
<td>Ty481Stop</td>
<td>Onset: 36 y</td>
<td>68</td>
<td>SVT, II degree AVB → PM</td>
<td>62/47</td>
<td>24.1</td>
<td>40</td>
<td>125.8</td>
<td>bicuspid aortic valve</td>
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<td>B III-2</td>
<td>Baseline: 39 y</td>
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<td>B III-2</td>
<td>Transplantation: 40 y</td>
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<td>B I-10</td>
<td>Baseline: 74 y</td>
<td>AF</td>
<td>–</td>
<td>54/33</td>
<td>38.9</td>
<td>213.1</td>
<td>bicuspid aortic valve</td>
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<td>B II-1</td>
<td>Deceased at age 52 y</td>
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<td>B II-2</td>
<td>Baseline: 47 y</td>
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<td>B II-3</td>
<td>Baseline: 49 y</td>
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<td>Baseline: 45 y</td>
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<td>B II-5</td>
<td>Baseline: 35 y</td>
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<td>B II-6</td>
<td>Baseline: 35 y</td>
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<td>B II-7</td>
<td>Baseline: 35 y</td>
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<td>B II-8</td>
<td>Deceased at age 54 y</td>
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<td>B III-1</td>
<td>Baseline: 13 y</td>
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<tr>
<td>B III-2</td>
<td>Ty481Stop</td>
<td>Baseline: 10 y</td>
<td>32</td>
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<tr>
<td>B II-2</td>
<td>Baseline: 44 y</td>
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<td>B II-9</td>
<td>Baseline: 44 y</td>
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<td>B III-2</td>
<td>Baseline: 11 y</td>
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<td>B II-3</td>
<td>Baseline: 6 y</td>
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recurrent syncope, a variety of arrhythmias (supraventricular tachycardia, atrial fibrillation, ventricular arrhythmias) and 2nd degree atrioventricular block treated with pacemaker implantation were found (Table I). At that time, left ventricular function was mildly depressed. During the subsequent 4 years, the patient progressed to terminal heart failure requiring heart transplantation at the age of 40 (Table I). Serum CK level was normal (Table I). The other affected family member was diagnosed with advanced conduction disease (2nd degree atrioventricular block) at the age of 13 and was treated with pacemaker implantation. Ultrastructural study of the skeletal muscle biopsy taken during pacemaker implantation revealed no abnormality. Indirect immunofluorescence analysis of the skeletal muscle biopsy showed that the nuclear envelope staining was similar to the control biopsy when using AC2 and AC5 antibodies (Figures 3A, 3B and not shown). In contrast, the nuclear envelope staining was reduced in the patient’s biopsy compared to the control’s when using AC3 and A4 antibodies (Figures 3A, 3B and not shown) suggesting that both the wild-type and the truncated protein may be translated and stable as well as correctly localised in the nuclear lamina. The remaining two Y481Stop mutations carriers (age 11 and 18) were found to have ventricular arrhythmia (nonsustained ventricular tachycardia, Table I).

Discussion

In this study we found two LMNA mutations in a group of consecutive patients with DCM (prevalence: 3.3%). Arbustini et al. found mutations in LMNA in 5 of 73 consecutive patients with DCM (6.8%) [15]. Taylor et al. found mutations in LMNA in 4 of the 49 studied DCM families (8.2%) [23]. In a combined Canadian-Irish-Polish study, the frequency of LMNA mutations was found to be 4% [24]. Perrot et al. found 3 LMNA mutations in a series of 31 unrelated patients with DCM and

Figure 2. Cytoplasmic organelles (mitochondria) within the nucleus in the cardiomyocyte of the patient with D192G LMNA mutation. Magnification x 25 000.

Figure 3. Comparison of the distribution of anti-lamin antibodies in pectoralis muscle biopsy from control and Y481Stop family B patient by immunofluorescence A. Intensive staining of the nuclei from both control and patient using lamin AC2 antibody. Magnification x 1050. B. Decrease of nucleus staining in patient versus control using lamin AC3 antibody. Magnification x 1050.
conduction disease; hence in the selected population the frequency of LMNA mutations was higher (10%) [25].

The most common clinical manifestation, typical of laminopathy (DCM with atrioventricular block), was presented by the proband of family B. Implantation of a DDD pacemaker was necessary in the 13-year old daughter of the proband because of advanced conduction disease. A meta-analysis of 299 LMNA mutation carriers with cardiac and/or skeletal muscle disorders revealed that cardiac dysrhythmias are present in 92% of patients after the age of 30 and heart failure in 64% of patients after age of 50 [16]. Twenty-eight percent of LMNA mutation carriers received a pacemaker [16]. It has been suggested that electrophysiological study should be considered in all LMNA mutation carriers either after the age of 35 or before pacemaker implantation/re-implantation [16]. Indeed, pacemaker implantation does not prevent sudden death in LMNA mutation carriers [16]. Of the 35 patients who died suddenly, 23 (66%) were documented to have died suddenly before the age of 60 years [16]. Meune et al. indicated that internal cardiac defibrillators (ICD) were better to prevent sudden death [26]. Identification of ventricular arrhythmia in Y481Stop mutation carriers suggests the need for ICD implantation. However, this is a very difficult decision to make in young asymptomatic subjects and a great psychological burden upon the family. Indications for ICD implantation in LMNA mutations carriers, especially in teenagers, need to be better defined.

A less frequently encountered phenotype associated with laminopathy is the presence of DCM without conduction disease, first reported by Genschel et al. [27]. The proband of family A had mildly DCM, no significant arrhythmias, mild conduction disease, and the course of the disease was rapidly progressive heart failure leading to death (the time lapse from the onset of symptoms until death was 2 years). LMNA mutation carriers were found to have a lesser degree of dilation of the left ventricle than expected in comparison to other patients with DCM, who were non-carriers [23]. The presence of mild dilation of the left ventricle with progressive decrease of left ventricular systolic function (mildly DCM) suggests that mechanisms responsible for hypertrophy are failing.

In the present study, all mutation carriers had normal serum CK level. However, immunofluorescence study of the pectoralis muscle biopsy performed in the 13 year-old Y481Stop mutation carrier showed reduced staining of the nucleus when the antibodies used were directed against epitopes lying after the site of the mutation in the tail domain. This suggests that the truncated protein may be translated and stable as well as correctly localized in the nuclear lamina, which is consistent with a dominant negative mechanism. The putative truncated lamin A and C, being unable to interact with their binding partners (http://www.ncbi.nlm.nih.gov), might display altered functions.

Brodsky et al. [11] first reported a family that had a single deletion in exon 6 of LMNA (960delT), in which three different clinical phenotypes were identified. The phenotypes included: pure DCM, DCM with Emery-Dreifuss muscular dystrophy (EDMD)-like symptoms, and DCM with limb girdle muscular dystrophy (LGMD)-like symptoms, thus proving intra-familial variability in the phenotype. In family B, three phenotypes co-existed: DCM with conduction defects, conduction disease with subclinical skeletal muscle abnormality and ventricular arrhythmia. It has been documented that the presence of dysrhythmia and pacemaker requirement precedes the onset of heart failure in LMNA mutation carriers, and age-related penetrance of both dysrhythmia and heart failure takes place [16].

The presence of skeletal muscle involvement, supraventricular arrhythmia, conduction defects and mildly DCM have been found to be predictors of LMNA mutations [23].

Of interest, ultrastructural study of the endomyocardial biopsy of the patient with D192G mutation showed disruption of the nuclear membrane and translocaion of cytoplasmic organelles to the nucleoplasma. These observed changes in the nuclear membrane were also identified in the skeletal muscle of patients with X-linked Emery-Dreifuss dystrophy [22]. This finding can explain nuclear fragility and decreased physical interaction between the nucleus and the cytoskeleton, and is in agreement with the pathophysiological mechanical hypothesis of LMNA mutations [28, 29].

Conclusions

1. Mutations in LMNA were found in 3.3% of a consecutive series of patients with DCM.

2. We found three phenotypes associated with the Y481Stop mutation:
   a. cardiac dysrhythmia, conduction defects with pacemaker requirement preceded the occurrence of DCM with rapidly progressive heart failure;
   b. conduction disease (2nd degree atrioventricular block) associated with subclinical skeletal muscle involvement;
   c. ventricular arrhythmia.

3. D192G mutation is associated with a phenotype of mildly DCM characterised by rapidly progressive heart failure. Mildly conduction disease was also present.

4. Endomyocardial and skeletal muscle biopsies can be helpful in the diagnosis of laminopathies.
5. The presence of heart failure in LMNA mutation carriers indicates poor prognosis.

References
Kardiomiopatia rozstrzeniowa spowodowana mutacjami LMNA. Badania kliniczne i morphologiczne

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Streszczenie


Cel: Określenie częstości występowania mutacji w LMNA i ocena fenotypu nosicieli mutacji.

Metodyka: Zbadano 12 eksonów LMNA u 61 chorych z KMR, jak również w dwóch rodzinach z KMR.

 Wyniki: Zidentyfikowano dwie mutacje u 5 nosicieli mutacji (D192G u jednego probanda i Y481Stop u probanda i trójki jego dzieci), co stanowi 3,3% (2/61) wszystkich chorych z KMR. Nie stwierdziliśmy tych mutacji u 100 osób z grupy kontrolnej.


Wnioski: Obecność niewydolności serca u nosicieli mutacji LMNA oznacza złe rokowanie. Biopsja endomiokardialna i biopsja mięśnia szkieletowym mogą być pomocne w diagnostyce laminopatii.

Słowa kluczowe: kardiomiopatia rozstrzeniowa, laminy, LMNA, genetyka

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