DILATED CARDIOMYOPATHY PRODUCED BY LAMIN A/C GENE MUTATIONS

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Abstract

Lamin A/C gene (LMNA) associated cardiomyopathy is a form of dilated cardiomyopathy with poor prognosis and high mortality, and a rapid evolution toward end-stage heart failure and malignant ventricular arrhythmias associated with increased risk of sudden cardiac death. It is transmitted in an autosomal dominant manner and is characterized by age-dependent high penetrance and variable expression. Screening of first degree relatives of proband patients by means of clinical evaluation, electrocardiogram, echocardiography and genetic analysis is useful for the early diagnosis of the disease. Drug therapy and non-pharmacological measures in the early stages of the disease seem to improve the prognosis of these patients.

Keywords: dilated cardiomyopathy, LMNA gene, ventricular arrhythmias, sudden death

Introduction

Cardiomyopathies are heterogeneous diseases in which alterations of heart muscle structure and function are the main characteristics. Dilated cardiomyopathy (DCM) is characterized by cardiac chamber dilation and systolic dysfunction in the absence of coronary artery disease or other conditions associated with pressure or volume overload. Right ventricular dilation and insufficiency may be present, but it is not necessary for the diagnosis.

Beyond extrinsic factors that cause myocardial injury with evolution towards cardiac dilation (ischemia, infections, medications, hormonal disorders, nutritional deficiencies), the genetic mutations are an important etiologic factor for dilated cardiomyopathy. They produce the so-called idiopathic dilated cardiomyopathy which is consistent with the familial form of DCM from the European Society of Cardiology classification of cardiomyopathies[1]. There are approximately 30 genes related to the pathogenesis of DCM, encoding proteins with very different functions in myocardial cell physiology, involved in contraction and relaxation, calcium homeostasis, cytoskeleton proteins, proteins involved in transmitting mechanical forces, and nuclear membrane proteins with a role in nuclear stability and regulation of gene expression, RNA splicing, transcription and energetic metabolism[2]. However, only 20-30% of the patients with primary dilated cardiomyopathy have a known genetic defect [3]. This area is still open to research, with enormous progress in identifying new genes or new mutations in the known genes involved in the pathogenesis of this disease.

The prevalence of dilated cardiomyopathy in the general population is unknown, but in adult population it is estimated to approximately 1/2500 individuals, representing 50% of all patients with the diagnosis of DCM. It occurs at any age, regardless of gender and ethnicity [4]. The inheritance of the mutation responsible for the disease is estimated to approximately 90%, influenced by incomplete, age-dependent penetrance (meaning that not all carriers of the genetic defect will develop the disease and that the phenotype becomes manifest usually after the fourth decade of life) and variable expression (only certain features of the disease may be present in some individuals) [5]. The disease transmission within the family is probably underestimated and sometimes favors erroneous classification as a de novo mutation. Genetic defects involved in the pathogenesis of DCM can be transmitted in a autosomal dominant, autosomal recessive, X-linked or mitochondrial manner. The diagnosis of familial dilated cardiomyopathy is established if the condition (primary dilated cardiomyopathy) is affecting at least two first degree relatives. The presence of positive family history is a less sensitive criterion for the diagnosis of familial disease, a family member may be completely asymptomatic and without ECG changes but with left ventricular dysfunction and dilatation identifiable with imaging investigations, hence the importance of screening...
family members [6,7]. When the full definition of the disease was used in the cardiovascular screening the familial form was found in 20-35% of cases, but when the left ventricular dilatation was used as the sole criterion for diagnosis the prevalence was 48% [2].

**Purpose**

The present review article intends to summarise the latest information on dilated cardiomyopathy associated with LMNA gene mutations. The research on genetic causes and their clinical and therapeutic impact are continuously developing generating results with great influence on diagnostic and therapeutical conduct.

**LMNA gene: pathophysiology, epidemiology, genetic testing**

Until recently the genes reported as most frequently involved in the development of DCM have been TNNT2 (cardiac troponin T), LMNA (A/C nuclear lamins) and MYH7 (myosin heavy chain) [2]. A recent study sequenced the entire TTN gene which encodes titin, the largest human protein; their study has showed that TTN truncating mutations are the most common known genetic cause of dilated cardiomyopathy [8].

No clear relationship is established between the genotype (gene, mutation) and the clinical phenotype, except LMNA gene, which proved to be associated with conduction defects, malignant ventricular arrhythmias and supraventricular arrhythmias preceding the development of left ventricular dilatation and heart failure [2]. Lamins A and C are intermediate filaments located between the nuclear membrane and the chromatin, having an important role in maintaining the shape and nuclear structure, translation and transcription regulation, position and function of nuclear pores, and chromatin organization. LMNA gene encodes two isoforms, lamin A and lamin C, resulting from alternative splicing. Laminin A has 98 aminoacids in addition to laminin C. They are expressed in many types of differentiated tissues, forming nuclear lamina by polymerization of laminin molecules in the nucleus, resulting a network of intermediate filaments attached to the internal nuclear membrane which has a supporting role for chromatin organization, gene regulation, DNA replication and RNA splicing. Mutations of this gene can cause several clinical entities, including dilated cardiomyopathy with minimal or no skeletal myopathy, Emery-Dreifuss muscular dystrophy, Charcot-Marie-Tooth neuropathy, Dunningan partial familial lipodystrophy, progeria and other overlapping syndromes, all known as laminopathies [9]. They all have in common a certain degree of nuclear fragility, altered nuclear architecture, impaired nuclear signaling and transcriptional activation by altering abnormal adaptive and protective mechanisms. In vitro studies on fibroblasts have shown that the result of these changes is a nuclear susceptibility to mechanical stress rupture subsequently leading to cell death [10]. In humans LMNA mutations are heterozygous with minimal or no reduction of lamins A and C levels, but with various degrees of structure and function imparement, thus explaining the multitude of variations in the phenotype of the disease. Multiple mutations in the same gene, known as allelic heterogeneity, may cause identical or completely different phenotypes. The most common clinical entities caused by LMNA mutations are cardiolaminopathies, characterized by cardiac dilation with progressive heart failure, conduction abnormalities and arrhythmias; skeletal myopathy may be present in varying degrees or absent. The disease has a poor prognosis with increased mortality, especially from sudden death and progressive heart failure [2,5,11,12].

In familial LMNA-DCM mutations are found with a frequency of 6-8%, but among patients with associated conduction defects their frequency rises to 30% [13]. Although there are no clearly established clinical criteria to differentiate the LMNA-DCM from other dilated cardiomyopathies, the presence of conduction abnormalities or arrhythmias associated with ventricular dysfunction is suggestive of LMNA-associated dilated cardiomyopathy (LMNA-DCM), especially if skeletal muscle involvement is present, regardless of degree [14]. The LMNA mutations responsible for dilated cardiomyopathy are transmitted in a autosomal dominant manner meaning that the offsprings of a patient have 50% chances to inherit the genetic defect.

Genetic testing for DCM patients is now possible in many genetic laboratories by protocols for the most frequently involved genes in the ethiopathogenesis of the disease, but with high costs and with minimal influence on therapy, so it is not done routinely. But, for LMNA mutations, the things are changing due to the high risk of sudden death of the mutation carriers, making the genetic analysis necessary. There are attempts in discovering a non-genetic, lower-cost, diagnostic test for LMNA-DCM; Narula et al. used the quantitative expression of the mutated LMNA (using the mRNA levels in blood and the lamin A/C immunostain in endomyocardial biopsy) with a 100% sensitivity and a 87% specificity in predicting the LMNA mutation. The expression of mRAN in blood was lower in LMNA carriers comparing with wild-type LMNA mutation. The genetic, lower-cost, diagnostic test for LMNA-DCM; Narula et al. used the quantitative expression of the mutated LMNA (using the mRNA levels in blood and the lamin A/C immunostain in endomyocardial biopsy) with a 100% sensitivity and a 87% specificity in predicting the LMNA mutation. The expression of mRAN in blood was lower in LMNA carriers comparing with wild-type LMNA individuals or with DCM patients of another genetic cause, so it is a potential biomarker for the monitoring of the quantitative expression of LMNA mutated gene [15].

**LMNA cardiomyopathy: clinical characteristics, prognostic and therapeutic features**

The onset of LMNA-DCM is usually in adulthood, with a penetrance directly related to the age of mutation carriers, as Pasotti et al. observed in their study. They estimated a penetrance of 100% after age of 60 years [16]. Just like all types of dilated cardiomyopathy, the main characteristics are left ventricular dysfunction and dilation, associated in the majority of cases with arrhythmias and ECG abnormalities preceding the onset of ventricular dysfunction. The initial symptoms of the disease can be
represented by conduction disorders, with or without symptoms of arrhythmia or heart failure, including thromboembolic events from ventricular mural thrombi. LMNA-DCM has a worse prognosis compared to other forms of DCM with a higher mortality and faster progression towards end-stage heart failure. Most patients suffer an adverse event by the fifth decade of life; the most common events leading to death are malignant ventricular arrhythmias followed by end-stage heart failure [17]. Pasotti et al. showed in their retrospective analysis that about 70% of patients with LMNA-DCM develop a cardiac adverse event within 5 years from diagnosis due to malignant arrhythmias (66%) or terminal heart failure requiring heart transplant [16].

Conduction defects and rhythm disturbances that may occur in the natural course of the disease include atrioventricular block of any degree, bundle branch or fascicular blocks, minor intraventricular conduction delay, supraventricular arrhythmias, atrial fibrillation, atrial flutter, paroxysmal supraventricular tachycardias, supraventricular premature beats) and ventricular arrhythmias (ventricular premature beats, sustained or unsustained ventricular tachycardias, ventricular fibrillation). Brodt et al. analyzed the temporal relationship between the onset of ECG changes and the onset of ventricular dysfunction in carriers of LMNA mutations and calculated that the ECG changes precede the ventricular dysfunction with approximately 7 years. All the patients included in the study, except one, had ECG changes at the time of diagnosis of left ventricular structural or functional abnormalities. They considered that even the minor ECG abnormalities represent an early sign of the disease and a longstanding, severe dilated cardiomyopathy with no ECG abnormalities is unlikely to be produced by a LMNA mutation [18].

It is proven that the carriers of a LMNA mutation are at increased risk for malignant ventricular arrhythmias and sudden cardiac death before the onset of heart failure [19] and the risk rises afterwards [16]. Van Rijsingen et al. analyzed in a retrospective study, the risk for malignant ventricular arrhythmias of LMNA mutation carriers, disregarding their clinical state, and the eventual predicting factors of this risk. Their study confirmed the increased risk of sudden cardiac death, ventricular arrhythmias and end-stage heart failure of these individuals and identified four independent risk factors of ventricular arrhythmias: unsustained ventricular tachycardia, ejection fraction below 45% at diagnosis, male sex and non-missense mutations (insertions-deletions, truncating or mutations affecting splicing). Their multivariate analysis showed that the risk rises and the age of onset lowers with the number of these risk factors [20], hence the importance of periodic clinical evaluation. Up to date, although the importance of cardiodefibrillator was unanimously accepted as life saving, the optimal moment of implantation was not established. Van Rijsingen et al. consider the ICD as being appropriate for the high risk patients with 2 or more risk factors, earlier than the guidelines recommend.

The high penetrance and the aggressiveness of the disease together with the theory of the favorable effect of early pharmacologic treatment (beta-blockers, ACE inhibitors) and non-pharmacologic (cardiodefibrillator, cardiac resynchronization) on prognosis added weight to the importance of familial screening. Moretti et al. compared the clinical features of patients with DCM diagnosed through familial screening (non-proband patients) to those with sporadic forms of DCM (proband). Their results showed that patients diagnosed through familial screening were younger, with less severe symptoms at diagnosis (NYHA I and II classes) and with later need for cardiac transplantation. There was no significant differences in clinical state, all caused mortality (including the moment of sudden cardiac death or malignant ventricular arrhythmias) and there was no difference in the rate of ventricular dysfunction progression, although through the entire study period the non-proband patients maintained a higher ejection fraction than those with sporadic form of disease. They have concluded that the familial screening helps in early diagnosis and treatment of DCM, improving the outcome but with no significant influence on the long-term natural history. The authors observed that in the non-proband group the pharmacologic treatment for heart failure was less intense comparing with the proband group, possibly with a negative effect on the outcome. The theoretical beneficial effect of the early treatment, before the onset of symptoms, on the long-term outcome is yet to be proven by future studies [21].

Conclusions:

1. LMNA-DCM is a genetic, autosomal dominant disease with high, age dependent penetrance and variable expression.
2. It is characterized by arrhythmias and conduction defects preceding the onset of heart failure.
3. It has a severe prognosis, with a high risk of malignant ventricular arrhythmias and evolution towards end-stage heart failure and need for heart transplantation.
4. Mutation carriers have a high arrhythmic risk before the onset of heart failure.
5. Early pharmacologic treatment and defibrillator implantation could favorably influence the long-term outcome of the mutation carriers.
6. Familial screening through clinical examination, ECG and echocardiography has a significant importance in early DCM diagnosis.

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