



## ORIGINAL ARTICLE

# Cardiac diseases as a predictor warning of hereditary muscle diseases. The case of laminopathies

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Mutations in the *LMNA* gene are associated with a wide spectrum of disease phenotypes, ranging from neuromuscular, cardiac and metabolic disorders to premature aging syndromes. Skeletal muscle involvement may present with different phenotypes: limb-girdle muscular dystrophy type 1B or *LMNA*-related dystrophy; autosomal dominant Emery-Dreifuss muscular dystrophy; and a congenital form of muscular dystrophy, frequently associated with early onset of arrhythmias. Heart involvement may occur as part of the muscle involvement or independently, regardless of the presence of the myopathy. Notably conduction defects and dilated cardiomyopathy may exist without a muscle disease.

This paper will focus on cardiac diseases presenting as the first manifestation of skeletal muscle hereditary disorders such as laminopathies, inspired by two large families with cardiovascular problems long followed by conventional cardiologists who did not suspect a genetic muscle disorder underlying these events. Furthermore it underlines the need for a multidisciplinary approach in these disorders and how the figure of the *cardio-myo-geneticist* may play a key role in facilitating the diagnostic process, and addressing the adoption of appropriate prevention measures.

**Key words:** laminopathies, risk stratification, genetic counselling

## Introduction

Muscular dystrophies (MD) are a heterogeneous group of inherited disorders that share similar clinical features and dystrophic changes on muscle biopsy, associated with progressive weakness (1-4). Weakness may be noted at birth or develop in late adult life. Some patients manifest with myalgias, rhabdomyolysis, or only raised serum creatine kinase

(CK) levels without any symptoms or signs of weakness.

Early- or childhood-onset muscular dystrophies may be associated with profound loss of muscle function affecting ambulation, posture, and cardiac and respiratory function. Late-onset muscular dystrophies may be mild and associated with slight weakness and inability to increase muscle mass (3, 4). A better understanding of the molecular bases of MD has led to more accurate definitions of the clinical features and a new classification.

Knowledge of disease-specific complications, implementation of anticipatory care, and medical advances have changed the standard of care, with an overall improvement in the clinical course, survival, and quality of life of affected people (5-9).

Muscular dystrophies can present an autosomal dominant, autosomal recessive, or a X-linked pattern of inheritance and can result from mutations affecting structural proteins localizable to the sarcolemma, nuclear or basement membrane, sarcomere, or non-structural enzymatic proteins (1, 2).

In recent years, cardiac involvement has been observed in a growing number of genetic muscle diseases, and considerable progress has been made in understanding the relationships between disease skeletal muscle and cardiac muscle disease (5-9). Significant advances in respiratory care have only recently unmasked cardiomyopathy as a significant cause of death in MD (10-15).

In several forms of MD, cardiac disease may even be the predominant manifestation of the underlying genetic myopathy and precede of many years the onset of skeletal

muscle involvement. Unfortunately “conventional” cardiologists may be unfamiliar with these diseases due to their low incidence, while an early detection of MD-associated cardiomyopathy is of considerable importance, as a prompt institution of cardio-protective medical or supportive therapies may slow adverse cardiac remodeling and attenuate heart failure symptoms or avoid the occurrence of sudden cardiac death in these patients (16-18).

Standard and dynamic electrocardiography (ECG and ECG Holter) and echocardiography are typically advocated for screening, although very recently, cardiovascular magnetic resonance (CMR) has shown promise in revealing early cardiac involvement when standard cardiac evaluation is still unremarkable (15-17).

This paper will focus on cardiac diseases presenting as the first manifestation of skeletal muscle hereditary disorders such as laminopathies, inspired by two large families with cardiovascular problems long followed by conventional cardiologists who did not suspect a genetic muscle disorder underlying these events.

## Patients

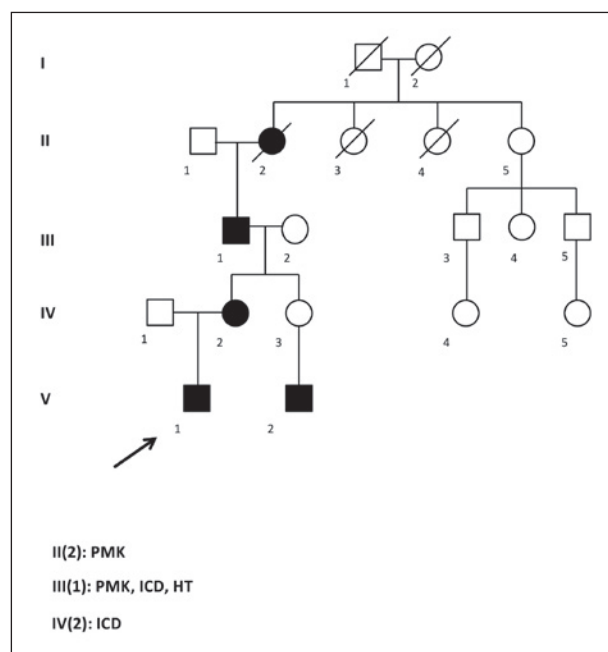
### Family 1

In the first family, the proband was a 15 years old young boy who underwent heart surgery for aortic coarctation. He had a bicuspid aortic valve, present in his cousin too. Family history revealed that the maternal grandfather had been implanted with a pacemaker (PMK) at the age of 50 years upgraded to an implantable cardioverter-defibrillator ICD for severe systolic dysfunction 5 years later, and received heart transplantation (HT) for severe dilated cardiomyopathy, at 60 years. Unfortunately he did not survive post-transplant complications. The great grandmother underwent PMK implantation too (Fig. 1).

During a genetic counselling, requested to investigate a possible genetic background explaining the familial occurrence of aortic valve defects, a cardiomyopathy associated genes NGS panel was performed, that unexpectedly revealed the *c.673C > T* (p.Arg225Ter) mutation in *LMNA* gene, maternally inherited. The mother, asymptomatic carrier of the mutation, underwent cardiological checks which showed a dilated cardiomyopathy and the presence of a first degree atrio-ventricular block, requiring ICD implantation.

### Family 2

In the second family, the index case – a female aged 58y – was referred to our service in May 2016 for an apparently asymptomatic hyperCKemia (2x). An accurate reconstruction of the family history revealed a high frequency of pacemaker (4 sibling) and sudden cardiac death associated to presence of conduction anomalies in her father

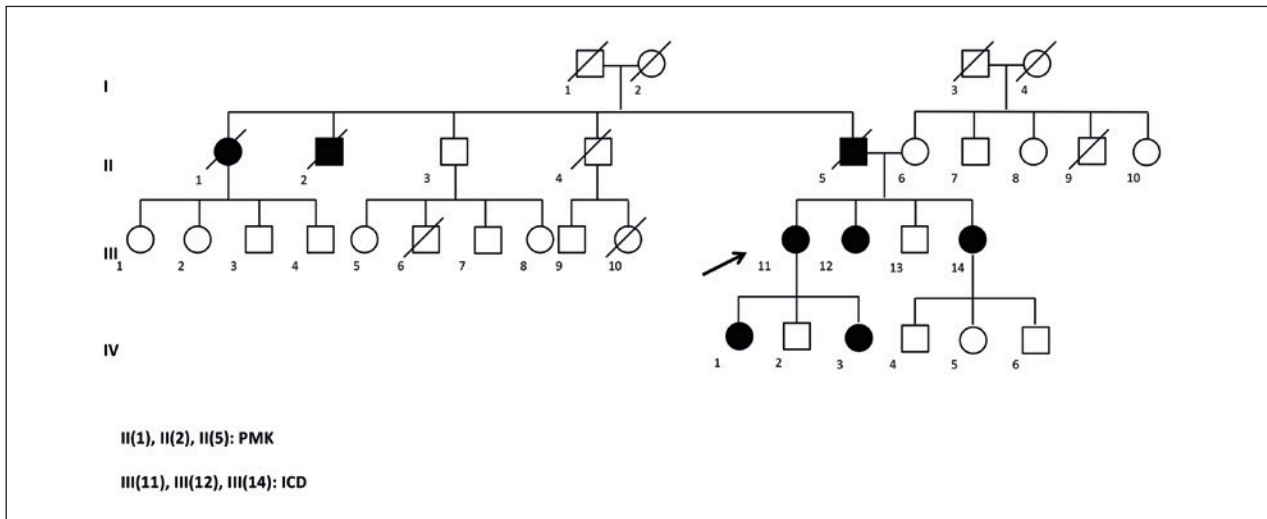


**Figure 1.** Genealogical tree of the 1<sup>st</sup> family.

(Fig. 2). A diagnosis of dilated cardiomyopathy following an acute myocarditis had been previously made because an episode of pneumonia. As during the hospitalization a new cardiological assessment revealed a second degree atrio-ventricular block, the patient was promptly referred to our arrhythmologic Unit to be implanted with an ICD. Based on family history of multiple cardiac devices implantation, a diagnosis of laminopathy was first suspected and subsequently confirmed by *LMNA* gene analysis that showed the mutation *c.207delG* (p.Val70Ser fs X26) in both the proband and her two sisters. In one of them, previously implanted with a PMK for conduction anomalies, an upgrading to an ICD-R was necessary due to the presence of a dilated cardiomyopathy with progressive reduction of the ejection fraction (< 35%). The cardiological assessment of the third sister showed a first degree atrio-ventricular block and a not sustained ventricular tachycardia on the ECG Holter, requiring an ICD implantation.

## Discussion

Laminopathies or *LMNA*-related disorders are rare genetic diseases caused by mutations in *LMNA* gene, which encodes, via alternative splicing, for lamins A and C, structural proteins of the nuclear envelope. These proteins play a role in several cellular processes, and mutations in the *LMNA* gene are associated with a wide range of disease phenotypes, ranging from neuromuscular, cardiac and metabolic disorders to premature aging syn-



**Figure 2.** Genealogical tree of the 2<sup>nd</sup> family.

dromes (19-27). Skeletal muscle involvement may present as autosomal dominant/recessive Emery-Dreifuss muscular dystrophy, LGMD type 1B or *LMNA*-related congenital muscular dystrophy (*LMNA*-CMD).

Lamin A/C gene mutations can be associated with cardiac diseases, usually referred to as ‘cardio-laminopathies’ mainly characterized by arrhythmic disorders and less frequently by left ventricular or biventricular dysfunction up to an overt heart failure (28-32). Heart involvement shows a high penetrance, and almost all patients after the seventh decade of life show cardiac disease, regardless of the presence of the myopathy. On the contrary, conduction tissue defects and dilated cardiomyopathy may exist without muscle disease, although subtle muscle involvement may be present and underestimated (29, 31).

Phenotypic penetrance is age-related but the expression of the disease is extremely heterogeneous, so that muscular and arrhythmic disease can be present in combination in the same patient, or in an independent way or remain hidden for a long time. Moreover, both the severity of the disease and its progression may have a marked inter- and intra-familial variability. Sudden cardiac death may be the only manifestation of the disease (31).

## Conclusions

From a cardiological point of view, characterization of patients affected by “cardio-laminopathy” is of crucial importance, since clinical and prognostic implications, as well as specific management strategies, can be different, particularly with regard to prevention of sudden cardiac death (33-39).

A specific diagnosis – based on an accurate familial/personal anamnesis and/or family pedigree and genetic test-

ing – is currently needed in patients affected by the various manifestations of these diseases. Furthermore, an appropriate risk stratification with referral to expert centres involving a multidisciplinary team for a proper decision-making is recommended.

In this context the medical geneticist can play a key role in reconstructing the family history and addressing the access to NGS sequencing or the appropriate single-gene analysis, ultimately facilitating the diagnostic process.

In addition we hope for a closer cooperation among cardiologists, experts in cardio-myopathies and geneticists to create a new professional figure, the cardio-myogeneticist, with specific expertise and knowledge in all the diagnostic aspects of heart muscle disorders, to improve the management of patients.

## Conflict of interest

The Authors declare to have no conflict of interest.

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