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Low-symptomatic skeletal muscle disease in patients with a cardiac disease – Diagnostic approach in skeletal muscle laminopathies

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ABSTRACT

Mild skeletal muscle symptoms might be accompanied with severe cardiac disease, sometimes indicating a serious inherited disorder. Very often it is a cardiologist who refers a patient with cardiomyopathy and/or cardiac arrhythmia and discrete muscle disease for neurological consultation, which helps to establish a proper diagnosis. Here we present three families in which a diagnosis of skeletal muscle laminopathy was made after careful examination of the members, who presented with cardiac arrhythmia and/or heart failure and a mild skeletal muscle disease, which together with positive family history allowed to direct the molecular diagnostics and then provide appropriate treatment and counseling.

1. Introduction

Discrete skeletal muscle symptoms, which are associated with cardiac disease and which are present especially in younger patients sometimes could indicate a serious systemic inherited disorder. The term ''discrete symptom'' usually describes a mild symptom, which could bother patients, but it is not disabling or it does not exclude them from everyday life. Discrete symptoms are often neglected both by patient and by his/her physician. Patients easily adapt to the restrictions, associated with subclinical disease of skeletal muscles. This is also related to a doctor who observes the symptoms, like abnormal gait pattern, local muscle atrophy, mild muscle weakness causing problems when climbing stairs or getting up from the squatting position. Some skeletal muscle symptoms or abnormal results of diagnostic test almost always lead to diagnostic steps, e.g. joint contractures or elevated creatinine kinase, while others need longer observation before any diagnostic action, e.g. slight muscle weakness or pain, which

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might be explained by excessive physical effort, radiculopathy or psychosomatic disease. When similar muscle symptoms are also found in patient's relatives, it could further support the hypothesis of inherited disease: it helps to establish a diagnosis, to calculate a risk of recurrence of a disease in patient's progeny and to choose adequate therapeutic approach.

Since the majority of genetic skeletal muscle diseases might be associated with defect of cardiomyocytes and subsequent cardiomyopathy with heart failure and/or arrhythmia, they are increasingly perceived as systemic disorders and they are treated by both neurologists and by cardiologists/internists [1]. Inherited skeletal muscle diseases with proved cardiological component include but are not limited to dystrophinopathies [4,5], Emery-Dreifuss muscular dystrophy (EDMD1) [2,3], in limb-girdle muscular dystrophies (LGMD): sarcoglycanopathies associated with defect in α- β- γ- or δ-subunits of the dystrophin-associated sarcoglycan complex (LGMD2D, E, C, F, respectively) [6,7], titinopathies (LGMD2J) and LGMD2I associated with mutations in fukutin-related protein (FKRP), both types of myotonic dystrophy (DM1, DM2) [8], nemalinopathies [9], desminopathies [10] and Danon disease [11].

Patients with diagnosed heart disease presenting symptoms which are suggestive for skeletal muscle disease should be asked about similar symptoms in their family members, and their relatives should also consulted. It is important to establish possible familial nature of a disease and trait of inheritance (dominant, recessive) and to select genes for molecular testing. Isolate discrete muscle symptoms, which are to be looked for in family members, include e.g. slight elbow and ankle contractures, muscle atrophy in hands, shoulder instability, muscle pain, lack of reflexes, elevated creatinine kinase (CK).

We present below a diagnostic approach which resulted in diagnosis of skeletal muscle laminopathy in members of 3 different families. Initially they presented with cardiac failure and/or arrhythmia what prompted them to search for medical attention. Further detailed examination revealed then a mild skeletal muscle disease, which together with positive family history allowed to initiate molecular diagnostics and to provide appropriate treatment and counseling.

2. Family reports

2.1. *Family 1*

31-years old male (II:2) was referred to a neuromuscular consultation because of slowly progressing weakness of the lower limbs, hindering from climbing stairs and getting up from a squatting and sitting position. Since the school years he was perceived as less agile than peers and he had worse results in running. At the age of 31 he was implanted pacemaker DDD type because of atrioventricular block (AVB) II grade (2:1) with episodes of bradycardia of 21/min. Conduction disorders were seen on ECG done routinely during obligatory periodic testing at work. The patient did not report syncope; however he noticed decreased tolerance of physical effort and periodic edemas of the legs. On echocardiography borderline enlargement of the left atrium was found (4.2 cm) with general

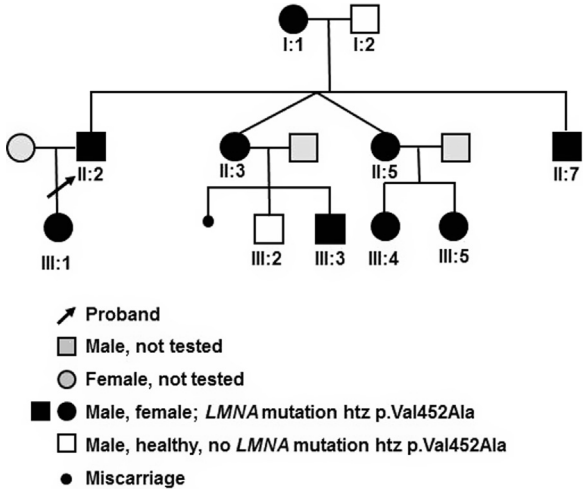

Fig. 1 – Pedigree of the Family 1. Note autosomal dominant trait of inheritance.

hypokinesia of the left ventricle, while ejection fraction (EF) was within the normal range (60%). NTproBNP was at the level of 66.9 pg/mL (N < 400 pg/ml). On neurological examination there were observed waddling gait, lumbar hyperlordosis, slight elbow and ankle contractures, cervical spine rigidity, slim shoulder girdle with preserved strength of arms and lack of tendon reflexes in mm. biceps and mm. triceps. Diagnostic tests showed moderately increased level of creatine kinase (CK) – 404 U/l, then 310 U/l (N < 170 U/l). Electromyography (EMG) revealed myopatic pattern in the m. biceps brachii. The family history (Fig. 1) revealed that slight elbow contractures and cervical spine rigidity were observed in 29-years old twin sisters of the proband (II:3, II:5), and waddling gait in 52-years old mother (I:1). Neurological examination was done in the proband's mother (I:1), father (I:2), sister (II:3) and 18-years old brother (II:7). The proband's mother (I:1) has been less agile than peers since childhood. At the age of 35 there were noticed problems with climbing stairs and standing from squatting position. She did not seek medical attention. On neurological examination waddling gait, lumbar hyperlordosis, slight cervical spine rigidity and lack of Achilles tendon reflexes were observed. No skeletal muscle wasting or contractures were seen. Periodically she has palpitations. In previous ECG atrioventricular block II Wenckebach type was found, but no diagnostics was initiated then. At the age of 52 the patient was qualified to a gynecological procedure. During routine evaluation before surgery a conduction defect was found. On 24-hours Holter monitoring AVB II Wenckebach type was confirmed again; it was leading to night bradycardia (HR 35/min). In addition 3 pauses (the longest of 2.5 s) was seen. No complex ventricular arrhythmia was observed. On echocardiography borderline enlargement of the left atrium was found (4.3 cm), slightly impaired diastolic function and decreased EF (45%). NTproBNP was 40.3 pg/mL. At that time the patient I:1 had been implanted with a pacemaker DDD type. The proband's father (I:2) was healthy. The proband's sister (II:3) was weaker and less clever than peers. She had scoliosis. She was not able to walk on heels. Since childhood cervical spine rigidity and trace elbow contractures were noted. No muscle

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