Genetic spectrum of cardiomyopathies with neuromuscular phenotype

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1. ABSTRACT

Neuromuscular disorders are known to be associated with cardiac disease but often the cardiovascular symptoms can be difficult to unravel due to low physical activity in this patient group and thereby low strain on the heart. On the other hand, cardiomyopathy or cardiac arrhythmogenic disease may be the first sign of an underlying neuromuscular disorder. Indeed, of the more than 40 genes that have been found to be associated with different types of cardiomyopathies, 25% also cause neuromuscular disorders as allelic forms. In this review we have elucidated the main genetic disorders involving a combination muscular and cardiac symptoms high-lighting the symptoms and signs specific for each disorder, including dystrophinopathies, laminopathies, myotonic dystrophy, desmin-related myopathy, congenital muscular dystrophies, and limb-girdle muscular dystrophies. The importance to investigate for underlying neuromuscular disorder in patients presenting with cardiomyopathy or cardiac arrhythmogenic disease is emphasized.

2. INTRODUCTION

Cardiomyopathies are a heterogeneous group of cardiac disorders with structural or functional abnormalities of cardiac muscle often of genetic origin (1,2). For many years this definition included the phrase "of unknown origin", but since the first evidence of gene mutations causing these type of cardiac disorders the new "genetic era" in studying cardiomyopathies arose. A substantial amount of fundamental data has been accumulated since then leading to a number of important discoveries on cardiomyocyte function and pathology. Pooling these data with clinical information from the large patient registers, prospective and retrospective studies resulted in an updated classification of cardiomyopathies and, importantly, a positional statement on genetic counseling and testing in cardiomyopathies (13) (2). The area of cardiomyopathy genetics grows rapidly and several excellent reviews have been recently published focusing on genetic background of various cardiomyopathies and the consequences of patient genotyping in terms of genetic counseling, prognosis and treatment (4,5).

Going back to the history of the first cardiomyopathy-associated mutation we should remember that this discovery became possible only due to previous research on origins of neuromuscular disorders. The first cardiomyopathy-associated gene was dystrophin, well known to cause Duchenne and Becker muscular dystrophies (6,7). Common involvement of heart muscle in the form of dilated cardiomyopathy in these X-linked muscular dystrophies prompted the search of dystrophin gene mutations in patients with X-linked dilated cardiomyopathy even without muscle phenotype. Since then more than 40 genes have been found to be associated with different types of cardiomyopathies of which 25% also cause neuromuscular disorders as allelic forms (Table 1). The connection between cardiac and neuromuscular symptoms is due to concomitant expression of the gene product both in skeletal and cardiac muscle, and some times even in smooth muscle cells. This especially concerns structural proteins of myocytes, such as dystrophin and sarcoglycans, desmin and titin. Some of these genes code for structural proteins that also have a regulatory function in gene expression and mechano-transduction (*LMNA, LDB3, MYOZ*) (8-11). It is generally accepted that the resulting phenotype from dysfunction of these genes can be predominantly either muscular, cardiac or both. However, the genotype-phenotype correlations are not always clear. In some cases the predicted protein change and alteration of a functional domain promote a particular form of the disease. This is often the case for LMNA/C or desmin gene mutations (12,13). At the same time a certain mutation can lead to the development of all phenotypic forms of the disease, often even in the same family, probably due to gene-gene interactions and the effect of modifying genes, environmental factors or life style. As a result a patient with suspected genetic cardiomyopathy should always be examined for subclinical muscle symptoms and the family investigation should include proper neurological examination and several biochemical and functional muscle tests. The vice versa situation means that cardiovascular examination must be an obligatory part in management of a patient and his relatives with neuromuscular disorder. The latter is usually routine to the neurologists and myologists being aware of cardiovascular complications of neuromuscular disorders since these complications contribute to a substantial number of deaths, and many excellent reviews, original studies and guidelines are available on this subject (14-18). The cardiologists, however, might have some difficulties in establishing the diagnosis in a patient with cardiomyopathy and mild muscle symptoms or isolated CK elevation due to the variety of neuromuscular disorders, complicated classification and rare occurrence of the diseases (19). Many neuromuscular disorders can lead to cardiomyopathies, but only in some of them cardiovascular presentation can clearly precede muscle symptoms and those patients might initially be seen by cardiologists. If heart failure and arrhythmic symptoms are dominating the clinical picture, then the muscle phenotype cannot easily be unraveled and must be specifically searched for. If obtained, the data on skeletal muscle investigation, both histological, biochemical and functional, can considerably facilitate the following genetic diagnosis making the gene

list much shorter. Therefore, this review focuses on cardiomyopathies accompanied by neuromuscular symptoms, their genetic background and clinical picture and propose a first draft to a diagnostic algorithm facilitating the proper diagnosis.

3. CARDIOMYOPATHIES WITH NEUROMUSCULAR SYMPTOMS

3.1. X-linked DCMP and dystrophinopathies

X-linked dilated cardiomyopathy is most commonly caused by mutations in the dystrophin gene. This was this first gene, described in connection with cardiomyopathies in 1993 and the story behind this important discovery originates from well-known neuromuscular diseases – Duchenne and Becker muscular dystrophies (6,7). Thus these three allelic disorders clearly illustrate a common pathogenesis constructing the basis of both cardiomyopathies and neuromuscular disorders.

Dystrophin is the largest known gene in human genome. It spans over 2.5×10^6 base pairs on the X chromosome and corresponds to about 0.1% of the human genome (20,21). The gene has 79 exons, but more than 95% of it consists of introns. Such as huge size together with other non well-established factors make it very prone to mutations, mostly by copy number variation (deletion/duplication) mechanisms (70-75% of cases). Generally, deletions of the N-terminal part of the gene, resulting in loss of the open reading frame, causes Duchenne muscular dystrophy and deletion of the inner part of the gene without frame shift causes the milder form of Becker muscular dystrophy. However, this rule has many exceptions with frame shift mutations in Becker dystrophy and non-frame shift mutations in Duchenne dystrophy. Point mutations and splice site mutations have also been described in both phenotypes and may contribute to up to 25% of DMD. The dystrophin gene has three tissue-specific promoters – B, M, and P - driving its expression predominantly but not exclusively in brain, muscle and cerebellar Purkinje cells respectively. It has been shown that in many tissues the lack of expression of a certain tissue-specific form can be partly compensated by the expression from other promoters (22,23). However, this mechanism may vary in different organs comprising one of the major causes of XL-DCMP development.

Heart involvement is a well-known clinical issue in Duchenne/Becker muscular dystrophy. The patients with Duchenne muscular dystrophy are mostly diagnosed by 5 years of age due to marked proximal muscle weakness and inability to walk properly. These children often have to use a wheelchair before their teens and respiratory insufficiency due to diaphragm involvement is the major cause of death unless nocturnal ventilation is introduced in the treatment. The severity of muscle symptoms often masks cardiovascular complications and reduced physical activity postpones the development of cardiac symptoms. In contrast, the cardiac involvement in Becker muscular dystrophy can determinate the prognosis since respiratory problems and skeletal muscle symptoms manifest later and by late teens the patient can still be physically active and

Cardiomyopathies with neuromuscular phenotype

Table 1. Genes associated with cardiomyopathies and neuromuscular disorders

Gene	Protein	Cardiac Phenotype	NMD	Cases of combined cardiac and NMD phenotype
ACTC	Cardiac actin	HCMP, DCMP, RCMP, LVNC		
DES	Desmin	DCMP, RCMP. HCMP	Desmin myopathy /myofibrillar myopathy	Yes (12)
SGCD	delta-sarcoglycan	DCMP	LGMD2F	Yes (87, 105)
MYH7	Beta-myosin heavy chain	HCMP, DCMP	Distal myopathy (Laing) Hyaline body myopathy (AD) Myosin storage myopathy and cardiomyopathy (AR)	Yes (106)(in case of AR myosin storage myopathy)
MYBPC3	Myosin-binding protein C	HCMP, DCMP		
TNNT2	Cardiac troponin T	HCMP, DCMP, RCMP		
VCL	Metavinculin	HCMP		
CSRP3	Muscle LIM protein	HCMP, DCMP		
TPM1	lpha-tropomyosin	HCMP, DCMP		
TTN	Titin	HCMP, DCMP	Autosomal dominant myopathy with proximal muscle weakness and early respiratory failure (HMERF) LGMD2J Congenital myopathy with fatal cardiomyopathy Tibial muscular dystrophy (Udd myopathy)	Yes (97)
ACTN2	Alpha-Actinin 2	DCMP		
MYOM	Myomesin	HCMP		
OBSCN	Obscurin	HCMP		
TNNI3	Cardiac troponin I	HCMP, DCMP, RCMP		
PLN	Phospholamban	DCMP, HCMP		
CALR3	Calreticulin	HCMP		
JPH2	Junctophillin	HCMP		
LDB3	Cypher/ZASP	DCMP, LVNC	myofibrillar myopathy ZASP-related	?
MYH6	Alpha-myosin heavy chain	DCMP, HCMP		
MYL2	Cardiac myosin light chain (regulatory)	HCMP		
MYL3	Cardiac myosin light chain (essential)	HCMP		
TNNC1	Cardiac troponin C	HCMP, DCMP		
TCAP	Telethonin	HCMP, DCMP	LGMD 2G	?
LMNA	Lamin A/C	DCMP, HCMP, RCMP, AF, CCD	LGMD1B Congenital muscular dystrophy Charcot-Marie-Tooth neuropathy Emery-Dreifuss muscular dystrophy Hutchinson-Gilford progeria syndrome Lipodystrophy, familial partial, type 2; AD FPLD2 Mandibuloacral dysplasia with type A	Yes (36, 40)
ABCC9	SUR2A	DCMP		
EYA4	Eyes-absent 4	DCMP		
SCN5A	Sodium channel	DCMP and CCD		
MYOZ2	Myozenin 2	HCMP		
NEB	Nebulin (Nebulette)	DCMP	Nemaline myopathy 2	?
TMPO	Thymopoetin LAP2	DCMP		
PSEN1	Presenilin 1	DCMP and Alzheimer		
PSEN2	Presenilin 2	DCMP and Alzheimer		
CRYAB	Alpha-B crystallin	DCMP, HCMP	Myofibrillar myopathy (desmin-related myopathy)	Yes (61, 107)
CAV3	Caveolin 3	HCMP, DCMP, Long QT syndrome, SIDS	Distal myopathy with caveolin defect Idiopathic hyperCK-emia LGMD1C Rippling muscle disease	Yes (92)
DYS	Dystrophin	DCMP	Duchenne/Becker muscular dystrophies	Yes (24)
TAZ/G4.5	Tafazzin	DCMP, LVNC, Endocardial fibroelastosis	Barth syndrome	
Fukutin	Fukutin	DCMP	LGMD2M Fukuyama congenital muscular dystrophy Walker-Warburg syndrome	Yes (79, 80)
FKRP	Fukutin-related protein	DCMP	LGMD2 Congenital muscular dystrophy Muscle-eye-brain disease Walker-Warburg syndrome	Yes (108, 109)
EMD	Emerin	DCMP, AF	Emery-Dreifuss muscular dystrophy	Yes (110)
FHL1	Four and a half LIM domain 1	HCMP, CCD, AF	Emery-Dreifuss muscular dystrophy X-linked myopathy with postural muscle	Yes (84, 111)

Cardiomyopathies with neuromuscular phenotype

			atrophy Scapuloperoneal myopathy	
FHL2	Four and a half LIM domain 2	DCMP	?	?
MYLK2	Myosin light chain kinase 2	HCMP		
MYO6	Myosin VI	HCMP and deafness		
PDLIM3	PDZ LIM domain protein 3	DCMP		
MYPN	Myopalladin	DCMP		
LAMA4	Laminin alpha-4	DCMP		
ILK	Integrin-linked kinase	DCMP		
RBM20	RNA-binding protein 20	DCMP		
ANKRD1	Ankyrin repeat domain-containing protein 1	DCMP		
PRKAG2	AMP-activated protein kinase	HCMP, WPW		
GLA	Alpha-galacrosidase	HCMP/Fabry disease		
LAMP2	Lysosome-associated membrane protein 2	HCMP/Danon disease		
HFE	Hemochromatosis gene	HCMP/hereditary hemochromatosis		
LAMA2	Laminin alpha2	CMP	MDC1A (congenital muscular dystrophy)	Yes (112, 113)

Abbreviations: HCMP: hypertrophic cardiomyopathy, DCMP: dilated cardiomyopathy, RCMP: restrictive cardiomyopathy, ARCV: arrhythmogenic right ventricular cardiomyopathy, LVNC: left ventricular non-compaction, AF: atrial fibrillation, AD: autosomal dominant, AR: autosomal recessive

disease progression be milder. Therefore, the cardiomyopathy in Duchenne/Becker muscular dystrophy does not represent a major diagnostic difficulty since the original diagnosis is established long before any cardiac complication. X-linked DCMP represents the third clinical form of dystrophin deficiency (23-25). Typically muscle symptoms are represented only by serum CK elevation or mild muscle weakness. Usually skeletal muscle phenotype is either absent or too mild to cause active patients complains and can be observed during neurological examination or electromyography only. Morphological examination of skeletal muscle often reveals mild dystrophic changes. In some cases the borderline between X-linked DCMP and Becker type of muscular dystrophy is difficult to establish, but it is accepted that patients manifesting with cardiac symptoms and with only CK elevation as a marker of skeletal muscle involvement are diagnosed with DCMP. Such an isolated damage of cardiac tissue has its molecular background. It has been shown that most of dystrophin mutations described by now cluster either in the N-terminal part of the gene or in its midrod domain and these two different localizations govern the variance in the mechanism and clinical picture of the disease (25,26). In the former case the deletions or insertions often involves the muscle promoter of the dystrophin gene, abolishing expression in cardiac and skeletal muscle. However, in skeletal, but not cardiac muscle cells this is partly compensated by the expression from the other promoters – brain or Purkinje fiber (22). Therefore, in this type of mutation the dystrophin expression in heart muscle is almost absent while keeping traces of the protein in skeletal muscles.

Due to X-chromosome localization of dystrophin gene cardiomyopathy patients are exclusively males and females represent the obligatory carriers. Most often dystrophin-associated DCMP manifests at the age of 5-20 with heart failure symptoms and heart dilation, however rare late manifestations may also occur. Cardiac arrhythmias or conduction block is not typical for dystrophin-associated cardiomyopathy in contrast to lamin or desmin associated cases, but can be observed in later stages of heart failure. The disease has a rapid progression to congestive heart failure and patients are often schedules to transplantation list in 2-3 years after disease manifestation. In the majority of cases marked CK elevation is observed, but normal range can also be seen and does not exclude dystrophin as a causing gene. In general, the highest level of CK elevation typically occurs in N-terminal type of mutations and the milder elevation is usually observed in mid-rod domain mutations (22,24). In dystrophin associated cardiomyopathy morphological examination of cardiac tissue can be very informative since it always reveals either absence or severe reduction of dystrophin expression in cardiomyocytes. Again, the former is more typical for the N-terminal type of mutations and the latter for midrod domain mutations. If cardiac biopsy is not performed the examination of skeletal muscle sample for dystrophin expression can also be informative showing dystrophin reduction (but not absence) and myopathic changes.

The frequency of dystrophin associated DCMP is quite low and reported to be in a range between 4-7% of all patients with DCMP (24,27). However, it was shown that among patients with DCMP and CK elevation 71% was constituted by dystrophin-associated DCMP. Importantly, dystrophin mutations are revealed in 22.8% of males with DCMP manifesting before 30 years (24). X-linked inheritance is typical and the majority of males with DCMP manifesting before 30 years and family history typical for X-linked disorders have dystrophin gene mutations. However, due to the possibility of sporadic mutations family history can be absent. Summing up all previous reports it is recommended to search for dystrophin alterations in all DCMP male patients with elevated CK level regardless of family history. Dystrophin gene screening is not routinely performed in all clinical genetic centers and instead immunostaining of cardiac/muscle tissue can be the first diagnostic step. Since most of DCMP-associated mutations localize in N-terminal or central part of the gene, the combination of antibody against various epitopes of the protein must be used. The alteration of normal dystrophin distribution or lack of dystrophin along with a normal -spectrin staining as a control prompts dystrophin gene mutation analysis, first

searching for copy number variation (MPLA or multiplex PCR), and thereafter for point mutations or small size nucleotide changes by sequencing analysis of the entire coding/splice site regions (28).

3.2. Laminopathies

Laminopathies are a group of diseases with the common denominator to be caused by alterations in the genes encoding nuclear lamina and its associated proteins (29,30). The diseases cover a wide spectrum of disorders dominated by muscular dystrophies with or without cardiac involvement, but also isolated cardiomyopathy, different types of lipodystrophies, peripheral neuropathies and progeria syndromes (13,30). In this review we will focus on isolated cardiomyopathies and cardiomyopathies with neuromuscular symptoms.

The nuclear lamina consists of the protein lamin, which is a type V intermediate filament building up the inner nuclear cytoskeleton of all cells in the human body. The function of lamins are not fully known but except for being a structural scaffold for the nuclear cytoskeleton it has been implicated in DNA replication, DNA transcription and chromatin organization (8,31). There are three different lamin genes, *LMNA, LMNB1* and *LMNB2*, but the majority of the above listed diseases are caused by mutations in the *LMNA* gene located on chromosome 1q21.2-q21.3 and coding for the proteins lamin A and the alternatively spliced lamin C.

The muscular dystrophies caused by *LMNA* mutations are autosomal dominant and autosomal recessive Emery-Dreifuss muscular dystrophy (EDMD2 and EDMD3) and limb girdle muscular dystrophy type 1B (LGMD1B) while an X-linked form, EDMD type 1 (EDMD1) is caused by mutations in the gene *EMD* coding for the lamin-associated protein emerin (32). EDMD is characterized clinically by early contractures and slowly progressive dystrophy and atrophy of the skeletal muscles of the proximal limbs. LGMD mainly affect the pelvic and shoulder girdle muscles with slowly progressive dystrophy and no or only mild contractures.

Cardiomyopathy due to *LMNA* mutations usually has a dilated phenotype with rather late manifestation, at around 30-40 years of age. However, several cases with restrictive or hypertrophic phenotype have been reported recently (33,34). The most typical feature of lamin A/C-associated cardiomyopathies are conduction and rhythm disturbances. Thus, in a meta analysis of 299 patients with *LMNA* mutations and either muscular dystrophy or only cardiac disease 18% of patients under the age of 10 had evidence of delayed atrioventricular conduction while over 90% of patients older than 30 had a conduction disorder with 44% requiring pacemaker (35). The conduction disorder usually precedes the ventricular dilatation and the decreased contractility that eventually leads to heart failure. It has been reported that sinus bradycardia and conduction abnormalities can not only precede heart dilation, but also remain the only disease manifestation (36-38). Therefore familial or sporadic cases of progressive conduction disorder or arrhythmia can be one of the manifestations of

LMNA mutations. Importantly not only conduction disorders, but also cardiac arrhythmias, mostly often atrial fibrillation or ventricular tachycardia are typical features of lamina A/C-associated cardiomyopathies. It has been shown that in 30% of cases cardiac rhythm abnormalities are represented by isolated atrial fibrillation or ventricular tachycardia without any signs of conduction disorders (36,39,40). In some cases cardiomyopathy is associated with serum CK elevation, but this is not a constant sign of the disease and, in contrast to X-linked dilated cardiomyopathy this elevation is usually rather mild, typically 2 to 4 times of normal range (40,41). Since clinically overt neuromuscular symptoms are not a part of the specific cardiac phenotype, it cannot be revealed only on the basis of clinical history, physical examination or CK level. However, careful neurological examination, electromyography or muscular biopsy often reveals mild signs of muscle disease.

The frequency of lamin A/C associated dilated cardiomyopathies among all cases of DCMP is reported to be 3.6% and among familial cases around 7.5% (40). However, the frequency of *LMNA* mutations among patients with familial DCMP and conduction abnormalities is quite high and reported to be 30% by several independent studies (41). Notably, no lamin gene mutations have been found among cases with isolated DCMP without rhythm or conduction abnormalities. In clinical practice the search for *LMNA* mutations should not be restricted to only familial cases since rather late manifestation of the heart failure symptoms can mask disease in the relatives, and diagnostic work-up should ideally include thorough examination of the family members. Elevated CK level does not have a predictive value in searching lamin mutations, but in case of a combination of DCMP, conduction abnormalities and elevated CK the possibility to find a *LMNA* mutation is very high (41). Until now there are no exact data on the frequency of *LMNA* mutation in patients with isolated cardiac conduction disease since all reported studies included very few number of patients.

One of the most important and interesting findings of genotype-phenotype correlations is that the cardiomyopathy of patients having laminopathy, either with or without muscular symptoms, is related to a significant risk of sudden death. In the meta-analysis mentioned above van Berlo and co-workers found that 46% of the deaths in the studies were sudden (compared to 18,9% predicted in the age group 25-65 years) and not correlated to having either dilated cardiomyopathy or pacemaker (35). On multivariate analysis only NYHA functional class III and IV and history of competitive sports were independent predictors of sudden death. Importantly the risk of sudden death is still present in patients with implanted pacemakers, which means that an implantation of intracardiac defibrillator (ICD) in patients with laminopathies should be considered more carefully than in dilated cardiomyopathies in general. It was also shown that, in spite of rather late manifestation, DCMP due to lamin gene mutation has a rapid progression with a high rate of heart transplantation. Herchberger and co-authors showed that among DCMP patients having undergone heart transplantation 9% carry

lamin A/C gene mutation underlining the severe prognosis of laminopathies.

In conclusion, lamin gene mutations should be considered among DCMP as well as HCMP or RCMP patients with either conduction defects or tachyarrhythmia and disease manifestation in their third to fourth decade of life. Taking into account the high rate of ventricular tachycardia and SCD in patients with lamin A/C mutations, implantation of intra cardiac defibrillator (ICD) should be considered.

3.3. Desmin-related cardiomyopathy

Desmin-related cardiomyopathy is another primary genetic cardiomyopathy that often coincides with neuromuscular phenotype. Desmin-related myopathies and cardiomyopathies are linked to mutations of desmin or other genes affecting intermediate filament structure or function. Desmin is the main intermediate filament of all types of muscle cells – skeletal, cardiac and smooth muscle in the postnatal period, providing structural/mechanical cytoskeletal functions and serving as an anchor for multiple cellular organelles (42,43). Desmin filaments interconnect myofibrils to nuclear and outer cellular membranes, being part of desmosomal and costamere structures and, thus, providing mechanical integrity and force transmission to muscle cells. Desmin, along with some other Z-disk associated proteins, has also been shown to play an important role in mechanosensing and mechanotransduction (44,45). The fact that desmin was the second gene after dystrophin identified as a cause of DCMP lead to the hypothesis that cytoskeletal abnormalities is a major cause of heart dilatation in cardiomyopathies (46,47). However, with the subsequent identification of many sarcomeric genes also being involved in the development of dilated cardiomyopathies, this lost support. Actually, desmin-related cardiomyopathies/myopathies illustrate both the diversity of underlying genes mutated, as well as the variation of phenotypes resulting from mutation within a disease causing gene.

Due to high expression of desmin in all types of muscle cells most of patients with *DES* gene mutation have concomitant muscle and cardiac phenotype with predominant involvement of either of these systems. Only 22 % of patients have isolated cardiac or skeletal symptoms and in the rest of the cases thorough patient examination lead to recognition of both skeletal and cardiac symptoms (12). In approximately half of all cases cardiomyopathy presents as dilated cardiomypathy. However, desmin-related cardiomyopathy in addition may present as RCMP, HCMP or ARVC . The fact that the age of dilated cardiomyopathies manifestation (mean age 46) is significantly later than that of RCMP (mean age 33) or HCMP (mean age 28) along with our own observations, suggest that heart hypertrophy or restrictive filling pattern can represent an early stage of the disease further transforming to DCMP and severe systolic dysfunction (12). The disease manifestation is usually in the age group 20 to 40 in cases of autosomal-dominant inheritance, but in rare cases of autosomal-recessive inheritance the symptoms

appear in early childhood and the disease progresses more rapidly (12,48,49). Myopathic symptoms include distal and proximal muscle weakness and atrophy (50). Since overt myopathy can develop subsequent to initial symptoms of cardiomyopathy these symptoms should be specifically searched for by thorough neurological examination and electromyography in cases with unknown genetic cause. Mild CPK elevation is typical for desmin-related cardiomyopathy but in most of the cases it does not exceed 2-4 times normal levels. However, even in cases with isolated muscular phenotype the CK elevation can be absent, therefore the absence of biochemical skeletal markers does not exclude myopathy in the patients.

Another typical sign of desmin-related cardiomyopathy is conduction abnormalities and arrhythmias similar to lamin A/C associated cardiomyopathies. As in the case of laminopathies they can markedly precede left ventricular dysfunction, but cases of isolated conduction disorder are not common and eventually myocardial remodeling usually develop. Atrioventricular block is the most typical desmin-related arrhythmic disorder along with right bundle branch block and sinoatrial conduction abnormalities. Atrial and ventricular tachycardia can be observed, but, in contrast to lamin-associated cardiomyopathy, are combined with conduction abnormalities and structural myocardial changes rather than isolated. Desmin-related cardiomyopathy can present with predominantly right chamber dilation and malignant ventricular arrhythmias and therefore, in spite of the low frequency of desmin mutations overall in the disease, cases of arrhythmogenic right ventricular cardiomyopathy (ARVC) should be considered for possible underlying desmin mutations (51-54). In spite of the high rate of pacemaker implantation in patients with desmin-related cardiomyopathy they are not protected from SCD, therefore ICD implantation should be considered in those with malignant ventricular arrhythmias.

Morphological examination of the skeletal or cardiac muscle can be very informative in cases of desmin-related cardiomyopathy. Desmin is a filamentous protein and its proper polymerization is assured by highly ordered hydrophilic and hydrophobic amino acids of the central rod domain (43,55). Most of desmin mutations interfere with polymerization properties leading to formation of desmin aggregates in muscle cell cytoplasm (56,57). This can be observed in biopsy material as positively stained aggregates by anti-desmin immunostaining of skeletal or cardiac muscle or as granulofilamentous material on electron microscopy (50,58,59). On conventional morphological hematoxiin/eosin staining of skeletal muscle these aggregates also can be seen as amorphous protein deposits. In case of such observation in patients with cardiomyopathy with or without skeletal muscle symptoms the screening of desmin gene usually results in identification of desmin mutation. However, some clinically relevant desmin mutations do not interfere with polymerization properties and do not lead to aggregate formation so the absence of such aggregates after immunostaining of heart or muscle tissue with anti-desmin antibody does not rule out desmin mutations (10,57).

In desmin-related myopathy/cardiomyopathy some genotype-phenotype correlation can be traced. For example, most of the isolated neuromuscular phenotypes have been described in patients with rod domain 2B mutations while most of the isolated cardiac phenotypes are due to head or tail domain mutations outside the central rod (12,49). However, since this rule has many exceptions and the gene is relatively small it is necessary to perform full gene screening in every case. Important to note is that smooth muscle involvement can also be present in patients with desmin-related myopathy/cardiomyopathy in form of swallowing difficulties, obstipation or diarrhea symptoms (60). Their identification can also be informative for guiding genetic investigation of the disease.

Alpha-B crystalline is a heat shock chaperon protein involved in many cellular processes. A pathogenic mutation was first described in desmin-related myofibrillar myopathy and since alpha-B crystalline is involved in desmin filament stabilization, the altered protein lead to formation of desmin aggregates and protein depositions. The original family described by Vicart had, apart from muscle phenotype, signs of HCMP and cataract (61). Later, Inagaki described alpha-B crystalline mutation as a cause of isolated familial DCMP (62). However, the frequency of isolated aB-crystallin–associated cardiomyopathies appears to be very low.

In conclusion, desmin-related cardiomyopathies in two thirds of the cases coincide with skeletal muscle involvement in the form of distal or proximal myopathy and/or mild CPK elevation (2-4 times above normal range). In case of a combination of AV block with any type of cardiomyopathy – dilated, hypertrophic or restrictive - a thorough neurological examination including electromyography should be performed and when possible be followed by immunostaining of muscle of heart or muscle biopsy with anti-desmin antibody.

3.4. Cardiomyopathy in myotonic dystrophy

Myotonic dystrophy is a multisystem disorder with autosomal-dominant inheritance and multiple system involvement. It is the most common form of muscular dystrophy with estimated prevalence approximately 1.8:1000. Two genes have been identified to cause the disease, DMPK and ZNF9, leading to DM type 1 and DM type 2, respectively (57,63). It is a classical unstable repeat disorder and both types of the disease develop from the expansion of polynucleotide repeats, $(CTG)\times n$ in the 3' untranslated region of the DMPK gene in case of DM1, and $(CCTG)\times n$ in the first intron of the ZNF9 gene in case of DM2 (64). Even though these genes were mapped in 1992 and 1998, the molecular pathogenesis of the disease still remains elusive. Both genes code for non-structural proteins, dystrophia myotonica proteinkinase gene (DMPK) and zinc finger protein 9 gene (ZNF9) and multisystem presentation of the disease supports the hypothesis of their importance for normal function of not only skeletal muscle. CNS symptoms are frequently the cause for investigations that may subsequently lead to the diagnosis of myotonic dystrophy. This may include intellectual impairment, daytime somnolence, and behavioral problems. Actually, 68% of persons with DM1 have a neuropsychiatric disorder, most commonly autism spectrum aberrations or ADHD (65).

The currently most accepted hypothesis of DM molecular pathogenesis is based on a theory of a dominant negative effect of mRNA and aberrant expression of neighboring genes due to abnormal number of polynucleotide repeats (66,67). It has been shown that CTG expansion in DMPK1 gene can lead to abnormal splicing of several distantly located genes, including chloride channel, cardiac troponin T and insulin receptor genes, giving genetic basis for the variety of clinical symptoms, including myotonia, arrhythmias and insulin resistance (68). At the same time the hypothesis of aberrant expression of neighboring genes is supported by the fact that mice knocked for SIX5 gene, which is located in close proximity to the DMPK gene, present with cataract, which is a common clinical sign in DM. Even more intriguing is the fact that some of the DM1 patients have Brugada-like ECG pattern and ventricular cardiac arrhythmias, and that the SCN5A gene, which is responsible for the majority of genotyped cases of Brugada syndrome, is located in close proximity to DM2 locus, 3q21 (69). However, the detailed effects of CTG/CCTG repeats' effect on transcriptional regulation and expression of neighboring and distant genes are yet to be elucidated.

Currently, muscle biopsy and electromyography do not have a primary role in the diagnostic process and genetic analysis should be performed directly after getting the clinical clues. However, if the latter is not easily available, muscle biopsy demonstration of fiber size variability and centronuclear localization together with myotonic changes on electromyography can be helpful. Genotyping for DM1 and DM2 are available now in many centers and is performed mainly either by real-time PCR or by Southern blot. It helps to confirm the diagnosis as well as to establish the number of pathological repeats.

The classical clinical phenotype of the congenital, more severe, DM1 includes myotonia, cardiac arrhythmias, mental retardation and learning handicap, cataract and endocrine disorders together with typical myopathic face appearance. However, clinical presentation and severity of DM1 depends on the form of the disease, namely congenital, infantile, juvenile or adult onset, and on the genetic type. It has been noted, that the number of CTG repeats correlates with the severity of muscle and neurological symptoms, leading to the most severe congenital form in patients with more than 1000 repeats. Due to genetic instability the number of repeats tend to increase with next generations, leading to the clinical phenomenon of anticipation - lowering the age of manifestation and increasing the severity of the disease in successive generations. This might be important for clinical diagnosis of later onset classical forms where the presence of children with typical facial features and learning disorders may become a clue for the diagnostic work up.

The congenital form of the disease manifests in the pre/postnatal period with reduced fetal movement,

hypotonia and facial weakness, typically with "carp-mouth" appearence, respiratory insufficiency and later development of typical dysmorphic features, delayed speech and motor development and mental handicap. Due to severe and characteristic clinical features the diagnosis is usually established early in childhood. Cardiovascular involvement might appear in the second decade of life. Cardiac complications are not often a major feature of this congenital form of the disease, but cardiomyopathy, LBBB and mitral prolapse have occasionally been reported.

The childhood onset form of DM1 quite differs in phenotype compared to the congenital form. In this form neonatal hypotonia is almost absent and typical dysmorphic features and motor alterations are not typically present. The most typical complaints of this form are learning difficulties, speech disorder and psychosocial problems. Cardiac complications often manifest during the second decade of life and can be noticed far before correct diagnosis is established. There are several case reports published where arrhythmic syndrome was the initial manifestation of the disease and even the only one by the age of 17 with no muscle or psychological symptoms (70). The patient can attract medical attention due to syncope or cardiac arrest. Therefore it is extremely important to consider DM when examining a child with unexplained cardiac arrhythmias.

The adult onset form of DM1 is a classical form of the disorder, often with typical facial muscle weakness and ptosis leading to characteristic facial appearance. Myotonia is usually present early, but the patient may remain undiagnosed until more severe muscle symptoms, such as distal and proximal muscle weakness and respiratory complications appear. Another typical feature is an excessive daytime sleepiness, early boldness in men and insulin resistance. Patients become physically disabled by the age 50-70, but cardiac complications can manifest much earlier. Keeping in mind that sudden cardiac death is not uncommon in these patients it is worthwhile to perform some simple diagnostic examination such as test for ocular or grip myotonia, note typical facial features, actively ask about daytime sleepiness or offspring with learning difficulties in patients with unexplained arrhythmias.

There is no common opinion regarding the severity of cardiac involvement and the number of CTG repeats. There is no clear evidence that the severity of cardiac abnormalities correlate with the number of the repeats and several studies showed conflicting results on this association (70-73). The most common cardiac complications in DM patients are arrhythmic disorders in form of tachyarrhythmias and conduction abnormalities. Clinically they manifest as syncope, palpitations or as cardiac arrest. Supraventricular arrhythmias and atrial fibrillation are more common, but ventricular tachycardia can also be present, retrospectively being traced in 50% of patients with sudden cardiac death (SCD) (64). Conduction abnormalities include SA and AV block of various degree, bundle branch block or alterations of intraventricular conduction leading to left ventricular asynchrony (74). Brugada-like phenomenon has also been described in

patients with DM1 (69). Sudden death occurs in 8% of the patients and originates both from ventricular tachyarrhythmia and conduction defects. It has been shown that the presence of atrial fibrillation and ECG abnormalities are the most predictive factors in terms SCD (72). Structural and functional cardiac abnormalities have also been described in MD patients, mostly in a form of cardiomyopathy: left ventricular non-compaction. In addition to conventional Doppler echocardiography the tissue Doppler is able to reveal early impairment of cardiac function such as diastolic dysfunction and reduction of LV relaxation time as well as RV diastolic dysfunction. The latter was shown to correlate with the occurrence of ventricular arrhythmias, probably, being one of key mechanisms in its pathogenesis (71). Importantly, cardiac arrhythmias can be induced by physical exercise or by electrophysiological provocation, therefore MD must be taken in a consideration in a patient with exercise-induced tachycardia. There is evidence that prophylactic pacemaker or ICD implantation can be beneficial in prevention of SCD in patients, but until now there are no commonly accepted evidence-based guidelines or recommendations on this issue.

In summary, cardiac arrhythmias, conduction defects and even SCD might be the first symptoms of MD in childhood onset and adult onset forms far before onset of clinically evident myopathy and in rare cases can remain the only symptom of the disease for some time. Therefore it is important to consider MD in cases with idiopathic tachyarrhythmia and conduction defects both in children and in adults. Obtaining the accurate history with active questions about infantile period, learning and mental abilities, daytime sleepiness together with typical facial appearance, ocular and grip myotonia, CK elevation and endocrine function, Holter ECG and Tissue Doppler Echo can facilitate the proper diagnosis.

3.5. Cardiomyopathy in congenital muscular dystrophies and limb-girdle muscular dystrophies

There are several rare or newly described genes, which have been shown to cause cardiomyopathies and/or myopathies. For many of these genes the number of existing reports is very few and a frequency of the reported mutations are not clearly established yes. This is limiting the broad genotype-phenotype correlations or recommendations for diagnostic algorithms. However, we consider some of these genes important to mention in diagnostic workup of cardiomyopathies.

3.5.1. FKRP

FKRP (fukutin-related protein) gene is coding a putative glycosyltransferase, important for -dystroglycan glycosylation and providing integrity to dystrophin-associated complex and connection of this complex to extracellular matrix. This gene causes several neuromuscular disorders such as LGMD2I and congenital muscle dystrophy. All reported patients are either homozygous for C826A mutation or compound heterozygous. Since the gene is highly expressed both in skeletal and cardiac muscle, patients with LGMD2I frequently have severe cardiac involvement in form of

dilated cardiomyopathy, often more severe in men and in compound heterozygotes than in C826A homozygotes (75-77). Cardiomyopathy is manifesting early and in heterozygous patients the penetrance is 100% by age 40 (78). Due to severe heart failure it can represent the first manifestation of the disease. Neither rhythm disturbances, nor conduction abnormalities are typical for FKRP-associated dilated cardiomyopathy. Muscle symptoms are overt before age 20, but disease duration is quite long and patient stay ambulant for many years. Heart failure due to dilated cardiomyopathy or respiratory failure represents the major causes of death. CPK elevation is usually marked (×6-20) and muscle symptoms present as proximal weakness, myalgia or exercise-induced muscle cramps. Since all reported patients carry at least one C826A substitution the genetic analysis for this mutation can be the easiest way to identify FKRP-related cardiomyopathy.

3.5.2. Fukutin

The Fukutin gene is also involved in - dystroglycan glycosylation and its homozygose or compound heterozygose mutations are found in Fukuyama type congenital muscular dystrophy, LGMD and several other neuromuscular disorders. These mutation are particular frequent in Japanese population due to the founder effect of a 3-kb insertion in the 3' non-coding region of the protein. Later there were several reports from Japanese authors describing Fukutin mutation as a cause of dilated cardiomyopathy with CK-elevation and a milder limb girdle muscular dystrophy manifesting much later than the cardiomyopathy (79,80). However, the frequency of these mutations seems to be very low (below 1%) and there were no reports until now about Fukutin gene mutations in cardiomyopathy patients from other populations.

3.5.3. FHL1

FHL1 (four and a half limb domain 1) is another X-linked gene recently identified in cardiomyopathies/myopathies. It is coding for the Z-line associated protein FHL1, which has been shown to be important in the process of muscle cell hypertrophy and mechanotransduction (81-83). It has been shown to be a causative gene for several myopathies (X-linked myopathy with postural muscle atrophy and hypertrophy, X-linked scapuloperoneal myopathy, reducing body myopathy) and recently also for a form of Emery-Dreifuss muscular dystrophy negative for emerin and lamin mutations by familial linkage analysis (84,85). All index cases develop cardiac disease in form of supraventricular or ventricular arrhythmias, significant heart hypertrophy and atrial dilation but no conduction abnormalities. SCD was also reported. It has been shown that approximately 25% of male carriers have isolated cardiac manifestation of the disease without overt muscle symptoms (84). CPK elevation is usually very mild in the range of 2-6 times normal. Another typical picture in the described families was dysphonia. Therefore in male patients with HCMP and atrial fibrillation, especially if CPK elevation or dysphonia is noted FHL1 gene can be considered as a causative. It is also important to obtain detailed family history for EDM symptoms (early joint contractures and muscle weakness)

as well as for establishing the type of inheritance (X-linked).

Another protein with four and half limb domain structure - FHL2- has been reported to be altered in a patient with DCMP in a Japanese population (86). Despite the fact that data on muscle phenotype and CPK elevation are not available for the reported case, keeping in mind a close association of cardiomyopathies and myopathies for other four and half limb domain proteins, this gene might also be considered in cardiomyopathy patients with muscle symptoms.

3.5.4. Sarcoglycanopathies

Sarcoglycanopathies are another group of neuromuscular and cardiac disorders, where the recessive mutation lead to the several types of LGMD, namely LGMD2 C,D,E and F. In spite of the fact that dilated cardiomyopathy is a common clinical sign in this disease group, especially in LDMD2F due to sarcoglycan-delta mutations, the case of isolated DCMP without any muscular symptoms due to sarcoglycan-delta mutation was only once described (87). Later it was shown that sarcoglycans at least very rarely cause isolated cardiomyopathy (88). Since almost all sarcoglycanopathies described by now have autosomal-recessive mechanism, the possibility of autosomal-dominant isolated DCMP due to sarcoglycan mutation now is questioned (89).

3.5.5. Caveolin

Caveolin is a major component of the caveoli – plasma membrane rafts highly enriched by cholesterol and sphingo- lipids. There are three caveolin proteins, Cav1, Cav2 and Cav3, which are expressed in a tissue-specific manner and involved in regulation of endocytosis, lipid homeostasis, membrane channel distribution and positioning as signal transduction (90). Caveolin 3 is predominantely expressed in skeletal muscle cells and cardiomyocytes, thus leading to a number of neuromuscular disorders, e.g. LGMD 1C, and cardiac disorders (90). The identification of *CAV3* mutation in solely cardiac disorders was first described for arrhythmic discorders, such as long QT syndrome and sudden infant death syndrome, both without any evident muscular symptoms. On cardiomyocyte membrane caveolin 3 co-localizes with sodium channel subunit, coded by SCN5A gene, providing its proper action during action potential and leading to malignant cardiac arrhythmias when mutated. Later, *CAV3* mutation was described in a patient with isolated HCMP without any neuromuscular phenotype or elevated CK level and in several DCMP patients where cardiomyopathy was combined with myopathy and elevated CK (91-93). Though rare, caveolin 3 mutations can be considered in patients with cardiomyopathies, especially in case of late-onset DCMP, myopathy and elevated CK level.

3.5.6. Emerin

Emerin is another component of nuclear lamina coded by the X-linked *EMD* gene. It is well studied in connection to X-linked Emery-Dreifuss muscular dystrophy where a mutation in this gene contributes to approximately 60% cases (94). Most of Emery-Dreifuss

muscular dystrophy patients have cardiac involvement in the form of conduction disturbances, atrial fibrillation and supraventricular or ventricular arrhythmias. There was one report on a familial case of isolated atrial fibrillation without any signs of contractures, progressive muscle weakness or CK elevation (95). Until now this is the only available report on isolated cardiac phenotype due to an emerin gene mutation.

3.6. Several new and rare cardiomyopathy-associated genes with muscle-specific phenotype

Titin is the largest known protein in the nature so far since its coding sequence spans over 346 exons resulting in a protein of 3000kDa. It is involved in the intrasarcomeric cytoskeleton, providing tension properties to myofilaments and ensuring the diastolic relaxation of the heart. Titin has been implicated to several neuromuscular disorders, such as LGMD2J and congenital myopathies (96,97). Titin gene (*TTN*) mutations have also been described in cases of isolated DCMP without clinically detectable skeletal muscle disease and in one HCMP patient without mentioning the detailed clinical phenotype in reference to muscle symptoms or CK (98-100). Therefore the report on congenital muscular dystrophy with severe dilated cardiomyopathy is the only publication so far describing titin mutation leading to both myopathy and cardiomyopathy (97). Due to enormous length of this gene the epidemiological study on actual occurrence of titin mutations in patients with cardiomyopathies is difficult to perform.

A different disease entity in the disorders involving cardiac and skeletal muscle is the channelopathy called Andersen-Tawil syndrome (101). The clinical picture, with varying penetrance, include muscular weakness, periodic paralysis, dysmorphic features and ventricular arrhythmias. Most of these patients (approximately 60-70%) have a mutation in the potassium ion channel gene (*KCNJ2*), coding for the inward potassium rectifier Kir2.1. In cardiac myocytes this affects cardiac repolarization leading to a prolonged QT duration and this disease is now included in the classification of long QT syndromes (LQT type 7). This syndrome should therefore be considered when ventricular ectopies or runs of ventricular tachycardia are combined with episodes of muscular weakness. ECG may reveal a prolonged QT interval and often a prominent U-wave. Dysmorphic features include craniofacial features, skeletal and dental anomalies, but may be very subtle or lacking.

Recently some new genes involved in the development of neuromuscular disorders have been described as a cause of various cardiomyopathies, such as Cypher/ZASP (*LDB3*) in DCMP and LVNC, nebulette (*NEBL*) in DCMP and telethonin (*TCAP*) in DCMP and HCMP (102104). However, in none of these reports clinical data about neuromuscular function in these patients have been mentioned leaving unclear if cardiomyopathy was the only isolated phenotype. More data are needed to clarify whether these genes can cause cardiomyopathies combined with subclinical muscle symptoms or isolated elevated CK levels.

4. CONCLUSION

Neuromuscular disorders are known to be associated with cardiac disease but often the cardiovascular symptoms can be difficult to unravel due to low physical activity in this patient group and thereby low strain on the heart. On the other hand, cardiomypathy or cardiac arrhythmogenic disease may be the first sign of an underlying neuromuscular disorder. In this review we have elucidated the main genetic disorders involving a combination muscular and cardiac symptoms high-lighting the symptoms and signs specific for each disorder.

As a first outline of an algorithm we can see three patterns guiding us to what genetic analyses to primarily aim for. First, if marked increase in CK-levels are found in a patient with unknown cardiomyopathy one should consider to investigate the genes coding for dystrophin, fukutin-related protein as well as other genes causing muscular dystrophy. Second, if arrhythmias or conduction disorders are part of presenting symptoms combined with neuromuscular symptoms, mutations in the genes coding for lamin A/C, DMPK, desmin or FHL1 should be searched for. Third, when neuropsychatric symptoms prevail concomitantly with arrhythmias (or more rarely cardiomyopathy) myotonic dystrophy should be investigated for, especially if there are also skeletal muscle symptoms.

In general it is very important to look for mild neuromuscular symptoms in patients with idiopathic cardiomyopathies or cardiac arrhythmias and to carefully take a family history inquiring about muscle weakness, early cardiac symptoms or sudden death in family members. The type of inheritance may also be a guide to the putative underlying genetic disorders, e.g. X-linked inheritance as in Duchenne, Becker and Emery-Dreifuss muscular dystrophies, but also other characteristics of inheritance, e.g. anticipation as in myotonic dystrophy.

We are still in the early phase of making genotype-phenotype correlations and over the coming years we will hopefully be able to make even more useful algorithms to guide diagnostic work-up and treatment in the group of patients with combined cardiac and muscular disorders.

5. ACKNOWLEDGEMENT

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Abbreviations: SCD: sudden cardiac death, HCMP: hypertrophic cardiomyopathy, DCMP: dilated cardiomyopathy, RCMP: restrictive cardiomyopathy, ARCV: arrhythmogenic right ventricular cardiomyopathy, LVNC: left ventricular non-compaction, AF: atrial fibrillation

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