Review

Cardiomyopathy in neuromuscular disorders

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Abstract

Many neuromuscular disorders affect more than skeletal muscle. Because of the common structural and now more apparent molecular features between skeletal and cardiac muscles, many of the neuromuscular disorders also result in cardiovascular complications. Cardiomyopathy and conduction system diseases are the most frequent extramuscular features seen with many muscular dystrophies. The most common pediatric neuromuscular diseases with cardiac involvement will be discussed, including Duchenne muscular dystrophy, the sarcoglycanopathies, the laminopathies, Friedreich ataxia and Myotonic dystrophy. Although different molecular mechanisms lead to cardiac and skeletal muscle dysfunction in each of these disorders, the primary cardiac consequences include arrhythmias and cardiomyopathy that may or may not lead to congestive heart failure. As different experimental therapies are moving into clinical trials, the effect on the cardiac aspects of disease must be considered. Similarly, as treatments for cardiomyopathy are being tested, the effects on skeletal muscle must be determined.

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Keywords: Muscular dystrophy; Myotonic dystrophy; Cardiomyopathy; Arrhythmia

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Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMD, Becker Muscular Dystrophy; DMD, Duchenne Muscular Dystrophy; EDMD, Emery Dreifuss Muscular Dystrophy; FKRP, fukutin related protein; LGMD, limb girdle muscular dystrophy; XLDCM, X-linked dilated cardiomyopathy.

Grant support: Muscular Dystrophy Association, Doris Duke Charitable Foundation, NIH.

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doi:10.1016/j.ppedcard.2007.08.005
1. Introduction

Neuromuscular disorders are a diverse group of neurological conditions. They range from childhood onset to adult onset, with specific diseases having the ability to present in either childhood or adulthood. Often, the underlying etiology can be molecularly determined through genetic testing. Elucidating the detailed genetic etiology is informative not only for diagnosis and for genetic counseling, but, increasingly, this information is being used to guide therapy. Neuromuscular disease, including the muscular dystrophies and myopathies, is most commonly diagnosed by examining a muscle biopsy, although with some forms of muscular dystrophy, genetic testing has become standard as a result of increased accuracy coupled with its less invasive nature. Dystrophic muscle biopsy samples show an abnormally large distribution of myofiber size, indicative of concomitant degeneration and regeneration; an increased number of myofibers with centrally placed nuclei, thought to represent regeneration; and replacement of myofibers by adipose and connective tissue. The replacement of myofibers by fibrofatty infiltration reduces the myofiber mass and causes muscle weakness.

2. Structural differences between cardiomyocytes and skeletal myofibers

Skeletal muscle is composed of elongated multinucleate cells, or myofibers, that are organized together into fascicles. Within each myofiber are contractile elements, the sarcomeres, which are arranged end to end into myofibrils. Sarcomeres are composed of actin-containing thin filaments, myosin-containing thick filaments, and a series of additional proteins that regulate the interaction between actin and myosin. In contrast, cardiac myocytes are singly nucleated or binucleate cells with a rectangular shape. At the ultrastructural level, cardiomyocytes and skeletal myofibers share the sarcomeric structure. However, the overall organization of the cells within the muscle or the heart differs considerably as an adaptation for the distinct functions of cardiac and skeletal muscle. In addition to the differences in overall cellular architecture within the tissue or organ, cardiomyocytes and skeletal myofibers differ in calcium handling and importantly, their regenerative capacity. When injured, skeletal muscle regenerates readily from the additional fusion of mononucleated myoblasts to the syncytium of the skeletal myofiber. In contrast, cardiac muscle has, at best, a limited regenerative capacity where injury most commonly results in increased connective tissue or scar. Therefore, gene mutations producing degeneration of skeletal muscle can similarly produce degeneration of cardiac muscle. Many of these gene mutations cause cardiomyopathy in these neuromuscular diseases, specifically dilated or hypertrophic cardiomyopathy (DCM or HCM), as well as cardiac rhythm disturbances. Heart failure has significant morbidity in neuromuscular disease, in part because symptomatic heart failure may go undetected due to compromise of the skeletal muscle function and reduced physical activity. In one study where the etiology of DCM was determined in 34% of pediatric cardiomyopathy patients, 26% of these cases were associated with neuromuscular disease [1]. Therefore, the contribution of neuromuscular disease to pediatric cardiomyopathy is significant.

3. Duchenne muscular dystrophy and the dystrophin glycoprotein complex

In common to both skeletal myofibers and cardiomyocytes is the capacity of the cells to undergo deformation with contraction and to withstand force associated with contraction. Because of the need to withstand contractile forces, both cardiomyocytes and skeletal myofibers require special adaptations. Often, it has been these special adaptations that are the targets of inherited neuromuscular disease. The dystrophin protein complex was first identified for its role in maintaining muscle membrane stability because many of the genes encoding this complex lead to muscular dystrophy and cardiomyopathy, indicating that both skeletal myofibers and cardiomyocytes require this complex to link the cytoskeleton to the plasma membrane, or sarcolemma, and to the extracellular matrix [2]. Proteins within the dystrophin-associated protein complex include dystrophin, the sarcoglycans, dystroglycan, dystrobrevins, syntrophins, sarcospan, caveolin-3 and nitric oxide synthase.

3.1. Genetics of DMD/BMD

The most common form of muscular dystrophy is Duchenne and Becker muscular dystrophy (DMD and BMD, respectively). DMD and BMD are caused by mutations within the dystrophin gene, located on the X chromosome and are inherited as an X-linked recessive conditions. The dystrophin gene has 79 exons that encode 14 KB of cDNA spanning over 2.4 MB of chromosome Xp21. The dystrophin gene is currently the largest gene in the human genome. There are three active promoters at the 5' end of the gene and additional internal promoters that drive expression of smaller amino-terminally truncated gene products. The promoters within the gene confer tissue-specific expression, accounting for aspects of the extramuscular disease. DMD is caused by mutations that change the reading frame of the dystrophin transcript, resulting in a premature stop codon and
instability of the transcript, whereas BMD-associated mutations tend to maintain a reading frame or reduce levels of the transcript [3].

Approximately 30–40% of DMD cases are associated with new spontaneous mutations due to the gene’s large size, and, therefore, there is no family history of muscular dystrophy. Approximately 65% of the mutations causing DMD and BMD are large deletions in the gene, 5% are duplications and 35% are point mutations or small insertions or deletions [4–6]. Immunohistochemistry using anti-dystrophin antibodies on muscle biopsy sections shows a near complete absence of dystrophin at the muscle fiber sarcolemma in DMD muscle and often a decreased amount of dystrophin in BMD muscle. On immunoblot of muscle proteins, DMD muscle has little or no dystrophin protein (<3%) [7]. BMD muscle shows decreased dystrophin size and/or abundance [7]. For many males with symptoms consistent with DMD, 60% can achieve a confirmed diagnosis by gene deletion testing and, if negative, DNA sequencing can identify a majority of the remaining cases. Gene testing can often eliminate the need for a muscle biopsy for diagnosis.

The loss of dystrophin produces instability of the dystrophin-associated proteins, and immunoreactivity for these proteins is reduced at the sarcolemma. The destabilization of the dystrophin and its associated proteins renders cardiomyocytes and myofibers susceptible to contraction-induced damage in the form of plasma membrane leakiness. This membrane instability gives rise to leakage of cardiac and skeletal muscle proteins into the serum. Commonly, there is a persistent elevation of creatine kinase that declines only with declining muscle mass. Creatine kinase release from cardiac muscle mass can also occur, but the presence of “cardiac-specific” proteins such as CK-MB fraction or even cardiac troponins may actually reflect skeletal muscle disease in muscular dystrophies, since regenerating skeletal muscle also expresses these proteins. Therefore, in the setting of ongoing muscle regeneration, as seen in muscular dystrophies, the presence of “cardiac specific proteins” is not cardiac-specific and must be interpreted with caution [8]. In addition, episodes of increased cellular breakdown can occur, and these can affect the heart. A mechanism of acute episodes of myocardial cell damage prior to cardiomyopathy has been proposed based on identification of an acute elevation in cardiac specific proteins, specifically troponins, in DMD patients with chest pain and/or ECG changes and could be indicative of acute transient myocardial cell damage [9].

3.2. Neuromuscular disease in DMD/BMD

In DMD, symptomatic muscle disease onset occurs between the ages of one and five, typically manifesting with motor delays, gait abnormalities, frequent tripping or falling and/or difficulty climbing stairs. Boys have a characteristic waddling gait and toe walking due to bilateral weakness in the proximal muscles of the hip girdle and legs. Due to these weaknesses, boys with DMD experience difficulty rising from the floor and need to use their hands to push off the floor and walk up the thighs into a standing position, called a Gower’s sign. The weakness is accompanied by muscle pseudohypertrophy, which is an apparent enlargement of the muscles, typically calf, caused by infiltration of adipose and connective tissue into the degenerating muscle. The disease progresses to a widespread weakening of the musculature and loss of ambulation between 9 and 12 years on average. The average life expectancy is 20–30 years, with the cause of death most frequently from respiratory failure or cardiac complications, and survival being determined by the degree of support the patient chooses including ventilatory support. With BMD, the symptoms are the same as DMD, however the age of onset is later and disease progression is slower. Males with BMD typically lose ambulation after the age of 16.

3.3. Cardiomyopathy in DMD/BMD

Cardiac involvement in DMD and BMD includes cardiomyopathy and arrhythmias. The incidence of cardiomyopathy increases with age in DMD patients, and the prevalence varies with the methods used for detection. Pre-clinical cardiac involvement can be detected in as high as 26% of boys under the age of six and rises to 62% between the ages of 6 and 10 years. Specifically, ECG changes can be seen at these early ages as a shortened PQ segment, prolonged QT interval and increased QT:PT ratio [10]. In addition, pre-clinical cardiomyopathy is evident on echocardiogram with reduced ejection fraction or an alteration in the ratio of the pre-ejection period to the left ventricular ejection time [10]. With increasing sensitivity in cardiac screening, additional studies are necessary to update the statistics on pre-clinical cardiac involvement. Clinically significant cardiomyopathy usually develops in the second decade. Cardiomyopathy can be evident at 10 years of age and is nearly universal in DMD patients over the age of 20. Approximately 70% of boys with BMD have cardiac involvement by age 20 [11]. The average age for having fractional shortening <25% in DMD is 16.8±1.0 years and 30.4±3.4 years in BMD [12]. Cardiologists should be proactive in screening DMD and BMD patients for cardiomyopathy to increase early detection. The typical symptoms of cardiomyopathy, as would show in an active person, may not be present in DMD patients and therefore anyone with symptoms secondary to cardiac dysfunction such as weight loss or gain, cough, increased fatigue, or orthopnea with decreasing ability to tolerate daily activities, should be evaluated. Early screening by echocardiogram can identify early cardiac involvement.

3.4. Heart failure in DMD

Monitoring heart failure in DMD is difficult because the typical symptoms of reduced exercise tolerance are difficult to discern in the nonambulatory patient. In wheelchair bound DMD patients, symptoms referable to heart failure may include increased fatigue, difficulty sleeping, difficulty with concentration and more subtle variants of poor performance. Noninvasive measures of heart failure have not been shown to be reliable indicators of heart failure. Plasma ANP and BNP levels are not sensitive markers for the early detection of cardiac systolic dysfunction in DMD patients. Although, an increase in ANP
and BNP along with a decrease in deceleration time of early diastolic filling and systolic dysfunction are associated with poor prognosis [13]. It is important to monitor DMD and BMD patients for cardiomyopathy because early diagnosis and treatment of DCM has been demonstrated to lead to left ventricular remodeling in DMD and BMD patients when drug therapy was administered after the first abnormal echocardiogram [14]. In order to achieve early diagnosis and treatment, recommendations are for DMD patients to undergo echocardiography every 2 years up to the age of 10 and annually thereafter [12,15]. Recommendations for BMD patients vary widely from annual echocardiograms starting in the second decade of life and routinely every 2 years thereafter in the absence of echocardiographic findings [12] to every five years [15]. In addition, 24-hour Holter monitor should be considered annually in DMD patients over the age of 8 and especially if left ventricular dysfunction is present [12] (Table 1).

Therapies for dilated cardiomyopathy can be applied to individuals with dystrophin mutations including angiotensin converting enzyme (ACE) inhibitors and β-adrenergic blockade. Both of these agents have been associated with improved outcome in both ischemic and nonischemic forms of dilated cardiomyopathy. In a recent study, 69 patients with DMD or BMD were studied for the presence of cardiomyopathy [14]. Of these, approximately half had abnormal left ventricular function and size at the time of entry into the study. Those with evidence of cardiomyopathy were initiated on ACE inhibitors and/or β-adrenergic blockade. The majority of these patients showed improvement or normalization of left ventricular function and size consistent with cardiac remodeling that has been reported after myocardial infarction [14].

ACE inhibitors can also be used for prevention of left ventricular dysfunction. Through cardiac remodeling, these agents may actually prevent left ventricular dysfunction and halt or limit cardiomyopathy progression. One study of 80 DMD patients from 10 centers examined whether cardiomyopathy could be inhibited [16]. Twenty patients were excluded from the study because of reduced left ventricular function at baseline; the average age of recruitment was 9.7 years, suggesting that a subset of patients already have cardiac involvement at this young age. Fifty-seven patients participated in the study. Half received perindopril and half received placebo. After three years, all patients were placed on perindopril for two additional years. No patients were receiving corticosteroids or β-adrenergic blockade. After five years, one patient in the long term perindopril treatment group showed a decline in left ventricular function to <45% whereas eight patients in the placebo then two years of perindopril showed a decline in left ventricular function <45%. It is likely that this approach is not limited to perindopril and instead is a class effect of ACE inhibitors. Angiotensin receptor blockers (ARBs) have been shown to be effective in isolated cardiomyopathy. Thus, it is likely that cardiomyopathy prevention can be achieved with ARBs. Interestingly, ARB treatment with losartan was recently tested in the animal model of dystrophin mutations showing benefit for skeletal muscle function [17]. Therefore, it is possible that this strategy translated to human patients may offer some improvement for skeletal muscle function as well, although this has not been formally tested.

Advances in cardiac imaging will facilitate early detection of cardiomyopathy in asymptomatic patients such as in DMD boys. Myocardial strain changes, calculated by tissue Doppler, provides a quantitative assessment of regional wall motion of the left ventricle [18,19]. Presymptomatic DMD patients with normal left ventricular function by conventional 2-dimensional echocardiography have been identified as having negative strain profiles (indicating shortening or compression) in the posterolateral wall of the left ventricle and some only in the outer layer of the posterolateral segment as compared to controls [20]. Based on these studies, we would advocate that surveillance for left ventricular function and treatment should begin before the age of 10 in DMD patients. Ideally, treatment should begin prior to the onset of overt cardiomyopathy. This strategy is not routinely adopted because of the argument that perhaps there is no benefit to preventing cardiomyopathy [21]. This rationale for delaying treatment is not well founded, since it has been shown...

Table 1
Cardiomyopathy/arrhythmia screening, medication and device recommendations in pediatric neuromuscular disease

<table>
<thead>
<tr>
<th>Cardiomyopathy/arrhythmia screening</th>
<th>Medication/device</th>
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<tbody>
<tr>
<td>Echocardiogram</td>
<td>Holter monitor</td>
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<tr>
<td>Initial screen and frequency with negative findings</td>
<td>Initial screen and frequency with negative findings</td>
</tr>
<tr>
<td>DMD</td>
<td></td>
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<tr>
<td>Initial: age 6 yr</td>
<td>Initial: age 6 yr</td>
</tr>
<tr>
<td>Frequency: 1–2 yrs</td>
<td>Frequency: 1–2 yrs</td>
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<tr>
<td>Initial: age 10 yr</td>
<td>Initial: age 10 yr</td>
</tr>
<tr>
<td>Frequency: 1–2 yrs</td>
<td>Frequency: 1–2 yrs</td>
</tr>
<tr>
<td>DMD — carrier female</td>
<td></td>
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<tr>
<td>Initial: age 20–30 yr</td>
<td>Initial: age 20–30 yr</td>
</tr>
<tr>
<td>Frequency: 5 yrs</td>
<td>Frequency: 5 yrs</td>
</tr>
<tr>
<td>Lamin A/C</td>
<td></td>
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<tr>
<td>Initial: age 10 yr</td>
<td>Initial: age 10 yr</td>
</tr>
<tr>
<td>Frequency: 2–3 yrs</td>
<td>Frequency: 2–3 yrs</td>
</tr>
<tr>
<td>Myotonic dystrophy (classical form)</td>
<td></td>
</tr>
<tr>
<td>Initial: age 10–20 yr</td>
<td>Initial: age 10–20 yr</td>
</tr>
<tr>
<td>Frequency: 2–3 yrs</td>
<td>Frequency: 2–3 yrs</td>
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</tbody>
</table>

ACE: angiotensin converting enzyme; BMD: Becker muscular dystrophy; DMD: Duchenne muscular dystrophy; ICD: implantable cardiac defibrillator.

* Medication recommendations are based on experience; studies have not been performed to support this recommendation.
that reduced left ventricular function is a good predictor of cardiovascular events. The prudent course of action, consistent with routine management of isolated cardiomyopathy, is to offer treatment. Given the relative rarity of DMD, it is not clear that large enough clinical trials can be carried out to provide definite evidence dictating management strategy [22]. This uncertainty has led to considerable debate regarding the appropriate management of these patients [23,24].

### 3.5. Arrhythmia management in DMD/BMD

Cardiac arrhythmias are highly prevalent in DMD and BMD. The earliest changes that are seen frequently involve sinus tachycardia and premature ventricular beats. As high as 33% of DMD patients age 12 to 24 years had at least two asymptomatic premature ventricular beats with 58% having had at least one premature ventricular beat [25] and 17% experienced sinus tachycardia (age range of 5 to 22.5 years) [12,25]. Arrhythmias, once identified, can be treated with medical therapy or device implantation. Because the frequency with which arrhythmias occur in DMD and BMD patients is unknown, preventative defibrillator placement is a difficult decision. In patients with more advanced stages of disease, this can be complicated by kyphoscoliosis and muscle wasting. If surgery is not an option, external portable home defibrillators are an alternative to be discussed with patients and caregivers.

### 3.6. Ventilatory support in DMD

In DMD, the respiratory muscles weaken during the second decade leading to hypoventilation. Reduced pulmonary function from neuromuscular disease leads to increased pulmonary arterial pressure and can affect right ventricular, and ultimately, left ventricular function. Guidelines for pulmonary care have been developed and are increasingly being adopted [26]. Most commonly, DMD patients elect nocturnal ventilatory support, and nocturnal support has improved survival [27]. During the third decade, nocturnal support may be insufficient and DMD patients may elect full time supported ventilation. With increased pulmonary ventilatory support, improved supportive care, particularly to correct scoliosis that can also lead to impaired cardiopulmonary function, and a general social acceptance of disabled individuals, many DMD patients are surviving longer and beyond 25 years. Accompanying the increased survival is an increase in cardiac complications because cardiomyopathy and arrhythmias generally appear in the middle second decade in DMD. As discussed above, left ventricular dysfunction can be treated with ACE inhibition and β-adrenergic blockade. However, guidelines for the arrhythmia management in these patients have not been developed (Table 1).

### 3.7. Female carriers of dystrophin mutations

Female carriers of dystrophin mutations are heterozygous for dystrophin gene expression. As such, these individuals are at increased risk for developing skeletal muscle disease and cardiomyopathy. Skeletal muscle involvement has been reported in up to 24% of DMD and 20% of BMD carriers [28]. Even in the absence of skeletal muscle involvement, the risk of cardiomyopathy is at least 10%. As high as 41% of DMD and 27% of BMD female carriers have been seen as having an abnormality on either echocardiogram or ECG [29–32]. Dilated cardiomyopathy has been identified in approximately 7–8% of DMD carriers (age range 18 to 69 years) [28,31,32]. ECG abnormalities similar to those identified in DMD boys, have been identified in dystrophin mutation carriers, in up to 50% of DMD and 40% of BMD carriers [31]. Heart failure in DMD and BMD carriers is rare [31]. Female carriers of DMD and BMD are recommended to have an echocardiogram and ECG at diagnosis or after the age of 16 years and at least every five years thereafter, or more frequently if abnormalities are identified. Carriers with skeletal muscle or cardiac symptoms should be evaluated more frequently [15]. Genetic diagnosis of the DMD patients is very helpful and should be determined as to help identify carriers among female relatives.

### 3.8. X-linked dilated cardiomyopathy

X-linked dilated cardiomyopathy (XLDCM) is allelic to DMD and BMD and caused by mutations in the dystrophin gene. It was first described in one family with affected males and manifesting carrier women [33] and was then found to be associated with the dystrophin gene [34, 35]. XLDCM is different from DMD and BMD in that subjects affected with XLDCM have little to no skeletal muscle disease [35]. The severity of the dilated cardiomyopathy is variable, ranging from males with severe cardiomyopathy and congestive heart failure occurring in late teens or early 20’s with rapid progression of ventricular failure, to female carriers developing mild cardiomyopathy later in life [33,34,36].

Several amino-terminally truncated forms of dystrophin are generated through tissue-specific promoters that encode smaller dystrophin products. For example, there are three active promoters in cardiac muscle, and mutations that target cardiac-specific expression regions offer one explanation for XLDCM. Dystrophin mutations specific to XLDCM have clustered towards the 5′ end of the dystrophin gene [37], although other mutations have been identified [36,38–40]. Interestingly, the mutations in the 5′ end of the gene may not obey the frame shift hypothesis that has been used to explain skeletal muscle pathology. Mutations have been identified in the 5′ muscle [34,41–43], brain, and heart promoters, causing cardiac disease. In addition, transcription studies in XLDCM patients with mutations at the 5′ end of the dystrophin gene have detected upregulation of the brain and Purkinje isoforms of dystrophin in skeletal muscle but not in cardiac muscle [42,44–46]. Such upregulation may compensate for the lack of muscle isoform, and the absence of this upregulation in cardiac muscle could account for cardiomyopathy.

### 3.9. Genetic testing and gene specific therapy in DMD

DMD is estimated to occur in 1:3500 live male births, although this number may no longer be accurate given the availability of genetic testing and its impact on reproduction. The MD STARnet
is an ongoing project to reassess this number [47]. Genetic testing should be performed for all DMD and BMD patients to provide not only valuable information for prognosis, but also because there are emerging therapies that may be mutation specific. Gene correction strategies are currently in testing in large animal models where the goal is to restore dystrophin expression in DMD. Oligonucleotide-induced exon skipping is the process by which modified nucleotides interact with the transcribed RNA to induce bypass of the mutated exon. This induced exon skipping is designed to create internally truncated proteins that remain in frame and therefore functional [48]. At present, this methodology appears not to target the heart very effectively. A distinct approach to mutation specific therapy promotes protein translational read-through of premature stop codons, or “stop-codon therapy”. Approximately 15–20% of DMD patients develop disease based on having a small mutation that creates a premature stop codon. The aminoglycoside antibiotic gentamicin can induce read-through of the stop codon by means of its interactions with the large subunit of the ribosome. In the mdx mouse, which lacks dystrophin due to a stop codon in exon 23, treatment with gentamicin produced significant levels of dystrophin protein expression [49]. A novel agent, PTC124, was developed to also promote read-through of stop codons without the similar negative side effect profile of gentamicin [50]. Functional studies on mice administered PTC124 have identified full length dystrophin in the Duchenne mouse model and increased levels of γ-sarcoglycan, consistent with the production of dystrophin and stabilization of the dystrophin membrane complex [50]. PTC124 seems to be specific for promoting read-through of premature stop codons however has not been shown to affect normal termination. PTC124 is currently in clinical trials for boys with DMD with identified mutations causing a premature stop codon.

4. Limb girdle muscular dystrophy

The sarcoglycan components are important for function of the dystrophin protein complex and its role in maintaining muscle membrane stability. Autosomal recessive mutations in the genes encoding α-sarcoglycan, β-sarcoglycan, γ-sarcoglycan and δ-sarcoglycan lead to limb girdle muscular dystrophy (LGMD) that phenocopies what is seen in DMD and BMD, yet follows different genetic inheritance because these genes are encoded on autosomes. These diseases are referred to as “sarcoglycanopathies”. The phenotype of LGMDs involve skeletal muscle and in some of the types, also cardiac muscle. Onset, progression and distribution of weakness vary considerably among patients and genetic subtypes [51]. The diseases caused by sarcoglycan mutations tend to be early onset with a mean age of skeletal muscle onset around six to eight years with a more severe presentation, resembling that of DMD in many aspects. The course of sarcoglycan disease is progressive with loss of ambulation occurring during the second decade of life. Overall, these LGMDs are much less frequent than DMD, and their frequency is increased in parts of the world where consanguinity occurs. A diversity of α-sarcoglycan gene mutations has been described in patients throughout the world, and because of this range of mutations, there is a range of phenotypic severity. The specific types of LGMD associated with cardiac involvement are LGMD2C (γ-sarcoglycan), LGMD 2D (α-sarcoglycan), LGMD2E (β-sarcoglycan), and LGMD2F (δ-sarcoglycan).

Cardiac involvement is related to the type of LGMD. Overall, the cardiomyopathy associated with α-sarcoglycan gene mutations is less common than what has been described for LGMD patients with β-, γ- or δ-sarcoglycan gene mutations. There is a single common mutation associated with the gene encoding γ-sarcoglycan in LGMD 2C, and this mutation has been described in LGMD 2C patients from around the world. Because of this single mutation, this has allowed characterization of the cardiomyopathy associated with this mutation [52]. In this study, ten patients were examined with six showing tall R waves in right precordial leads with an abnormal R/S ratio. Echocardiography identified right ventricular dilatation and/or free wall hypertrophy in four patients. β-sarcoglycan (LGMD2E) disease has been associated with dilated cardiomyopathy; these cases include lethal cardiac failure at ages 14 to 30, one patient with dilated cardiomyopathy (age of 24) and two patients with arrhythmias (2nd and 3rd decade) [53,54]. The severity of cardiac involvement in LGMD 2E may be correlated to the degree of skeletal muscle functional impairment [53]. δ-sarcoglycan (LGMD2F) [55] has been associated with dilated cardiomyopathy.

Screening recommendations for dilated cardiomyopathy in patients with sarcoglycanopathies parallel those for DMD and BMD patients based on the similar phenotypic presentation of skeletal disease. Therapy recommendations are also similar to DMD and BMD with ACE inhibitors and β-adrenergic blockade once cardiac involvement is identified. A case can also be made for preventative therapy to slow progression of cardiomyopathy, however has not been demonstrated in clinical trials.

Fukutin-related protein (FKRP) gene mutations have been identified as causing LGMD2I [56,57]. FKRP is localized at the skeletal muscle sarcolemma and localization at the membrane is required for the dystrophin glycoprotein complex to be intact [58]. In addition, it has been suggested that FKRP specifically associates closely with the dystrophin protein complex as mutations in FKRP can cause a variable loss of β-dystroglycan and a reduction in α-, β-, and γ-sarcoglycan [59]. LGMD2I disease begins within the first to third decade of life with moderate and progressive shoulder and pelvic girdle muscle weakness and dilated cardiomyopathy [60,61]. There is a more severe congenital form, congenital muscular dystrophy or MDC1C, also resulting from FKRP mutations. The majority of Europeans with LGMD2I have a common FKRP founder mutation, C826A (L276I) [62,63]. Along the phenotypic spectrum of this gene, subjects have been described as having dilated cardiomyopathy with minimal skeletal muscle weakness or wasting [63]. Symptomatic dilated cardiomyopathy presented in these patients in their second and third decades without muscle involvement. This characteristic could be indicative of other DCM only patients who may be carrying FKRP mutations and, therefore, an argument could be made for more frequent testing of the FKRP gene in DCM only patients.

Fukutin gene mutations are most prevalent in the Japanese population. Two forms of skeletal muscle disease can occur. The
severe form is a congenital muscular dystrophy (Fukuyama-type congenital muscular dystrophy, FCMD) with severe muscle wasting and peak motor function from two to eight years of age and a maximal motor ability of unassisted sitting. Mental retardation also occurs in this severe form due to brain malformation [64–67]. The congenital form in Japan is caused by a founder mutation of 3 kb retrotransposon insertion in the FKTN1 gene, homozygously or heterozygously. In the less severe form, patients presented with dilated cardiomyopathy and had adult-onset muscle weakness [68]. These patients were also of Japanese descent. The age of onset of dilated cardiomyopathy was from age 11 up to age 46, with variable onset and severity of skeletal muscle involvement [68].

5. Lamin A/C cardiomyopathy

Mutations in the gene encoding the nuclear membrane protein lamin A/C have been associated with multiple distinct diseases including autosomal dominant dilated cardiomyopathy with conduction system disease, autosomal dominant Emery–Dreifuss muscular dystrophy (EDMD) [69], autosomal recessive EDMD [70], LGMD1B [71], autosomal recessive Charcot–Marie–Tooth Type 2 [72], mandibuloacral dysplasia [73], familial partial lipodystrophy [74–76] and Hutchinson–Gilford progeria [77].

The lamin A/C gene (LMNA) is composed of 12 exons consisting of a 24 KB coding region of the gene. Laminas A and C are two different proteins produced by alternative splicing from the same gene. Identical along their first 566 amino acids, lamin A and C differ only in the carboxyl terminus. As specialized proteins of the intermediate filament protein family, lamin A/C is found at the inner nuclear membrane where it forms a scaffold that interacts with a network of membrane bound and nucleoplasmic proteins in addition to chromatin. The intranuclear lamins are believed to play an important role in chromosome organization and function, protein and RNA trafficking and gene regulation in addition to forming a support structure for the inner nuclear membrane. The lamin A and C proteins interact via their conserved central rod domain to form a coiled-coil dimer. Laminas A and C are broadly expressed in many different cell types and are primarily expressed in terminally differentiated cells; however it is unknown how LMNA mutations led to tissue-specific phenotypes. In general, mutations within the α-helical rod domain tend to cause isolated dilated cardiomyopathy and are highly penetrant [78].

5.1. Pure dilated cardiomyopathy with conduction disease

Autosomal dominant DCM with conduction system disease from LMNA mutations is characterized by early onset DCM. Typically, conduction system disease occurs prior to apparent DCM on echocardiogram, although DCM can occur in the absence of conduction disease. DCM due to LMNA mutations carries a high risk for sudden death. A review of compiled data from 299 LMNA mutation carriers, of which 109 did not have any skeletal disease, showed significant cardiac involvement [79]. Of those without skeletal disease, 54 had left ventricular dilation and 73 were identified with dysrhythmias. Dysrhythmias were reported with increasing age and were equally distributed between carriers who presented with either a neuro muscular phenotype or cardiac-restricted phenotype. Other studies report similar findings of left ventricular dilation and a high penetrance of conduction disease [80]. The conduction disease has been in the form of AV nodal and bundle branch block, atrial fibrillation, and/or ventricular arrhythmias including both ventricular tachycardia and fibrillation [80–82]. The average ages of onset of conduction disease is typically early and has been seen in the late teens and early 20’s whereas the dilated cardiomyopathy has a later onset, in the 30 to 40’s [80–83].

5.2. Dilated cardiomyopathy with skeletal disease

The diseases due to LMNA mutations associated with skeletal muscle disease include: EDMD, LGMD1B and CMT2B1. EDMD, both autosomal dominant and autosomal recessive, are characterized by early contractures of the elbow flexors, Achilles tendons and neck extensors and slowly progressive weakness of scapulocepheral muscles [84,85]. Although skeletal muscle involvement is the presenting feature of these diseases, EDMD patients have cardiomyopathy with atrioventricular conduction defects [70]. LGMD1B has the characteristic distribution of muscle weakness similar to other LGMDs and lacking contractures. Skeletal muscle involvement is the presenting feature of this disease. LGMD1B has been associated with dilated cardiomyopathy and atrioventricular cardiac conduction disturbances in addition to skeletal involvement [71]. The phenotype described for CMT2B1 is one of an axonal neuropathy, which includes diminished deep-tendon reflexes, distal amyotrophy of lower limbs, distal motor deficits in upper and lower limbs, and decreased sensory potentials [72]. Cardiac involvement was not assessed in this study. CMT2B1 is inherited as autosomal recessive.

5.3. Other LMNA disease

The other forms of disease caused by mutations in LMNA are not typically associated with skeletal muscle disease. Partial lipodystrophy is a disorder in which an absence of subcutaneous adipose tissue in the trunk and limbs occurs while retaining intra-cavitary fat deposits [86]. Mandibuloacral dysplasia is characterized by mandibular and clavicular hypoplasia, acros teolysis, delayed closure of the cranial suture, joint contractures and types of A and B patterns of lipodystrophy. Patients with LMNA mutations with mandibuloacral dysplasia did not report cardiovascular or skeletal muscle involvement [73]. Hutchinson–Gilford progeria is characterized by post-natal growth retardation, midface hypoplasia, premature atherosclerosis, micrognathia, absence of subcutaneous fat, alopecia and osteodysplasia with osteolysis and fractures with a median age at death of 13.4 years due to coronary artery disease. These individuals are not affected with cardiomyopathy. These forms of disease caused by mutations in LMNA demonstrate the underlying importance that the LMNA A and C proteins have as nuclear
membrane components in every cell type. Although these seven diseases are all caused by mutations within the LMNA gene, there is little genotype/phenotype correlation.

5.4. Management of cardiomyopathy and conduction disease

Screening recommendations for LMNA mutation carriers are baseline echocardiogram at first recognition of carrying the mutation. Following that, assessment is recommended every two to three years for dilated cardiomyopathy. The question arises on when to initiate medical therapy in these patients, and the answer is similar to that given in those with DMD, although this has not been shown in a clinical trial. The benefit of afterload reduction achieved by treatment with ACE inhibitors/ARBs and/or β-adrenergic blockade is clear for cardiomyopathy patients without muscular dystrophy, and there is no need to avoid this regimen in muscular dystrophy patients. Although the underlying gene defect of the lamin A/C gene is different from the dystrophin gene, prevention or slowing of DCM progression may be equally effective in these patients.

Arrhythmia management is essential in those with LMNA mutations. Annual ECG and Holter monitor for signs of arrhythmias are recommended. Both bradyarrhythmic and tachyarrhythmic rhythm disturbances occur and include sinus and atrioventricular node dysfunction, atrial fibrillation and ventricular arrhythmias. Specific to LMNA mutation carriers, pacemakers do not usually node dysfunction, atrial fibrillation and ventricular arrhythmias occur and include sinus and atrioventricular node dysfunction, atrial fibrillation and ventricular arrhythmias. Specific to LMNA mutation carriers, pacemakers do not seem to prevent against sudden death [79]. One study found that of those without skeletal involvement, sixteen died suddenly were compared to nineteen in the neuromuscular group, and of those sixteen without skeletal muscle involvement, ten had a pacemaker compared to six in the neuromuscular group who did have a pacemaker [79]. These findings have been substantiated in a study of LMNA mutation carriers who had defibrillators with eight out of nineteen having DCM plus conduction system disease and no skeletal involvement [87]. The mean left ventricular ejection fraction was 58% in this population. Forty-two percent of LMNA mutation carriers without left ventricular dysfunction showed appropriate use of their defibrillators over three years [87]. Therefore, prophylactic, primary prevention of sudden cardiac death with an implantable cardioverter defibrillator should be considered for those with LMNA mutations.

6. Friedreich ataxia

Friedreich ataxia is the most common inherited ataxia. Carrier frequency for Caucasian population is 1:60 to 1:90 [88,89]. The disease onset is between ten and fifteen years of age with nearly 100% penetrance by the age of 25 [90]. The presenting symptom is ataxia in the majority of cases [91,92], resulting from a combination of spino-cerebellar dysfunction and impaired proprioception. Disease progression entails other neurological features of extensor plantar reflexes, dysarthria, weakness, absent ankle and knee jerks, hearing loss, loss of position sense and/or vibration sense in lower limbs, and eye involvement such as optic atrophy and saccades [90]. Diabetes mellitus and impaired glucose intolerance occur [93]. Scoliosis and pes cavus are features in approximately two thirds of patients [90]. Cardiomyopathy has been described in two-thirds of Friedreich ataxia patients [90,94,95]. Echocardiography may reveal left ventricular hypertrophy that is more commonly concentric ventricular hypertrophy [96–99]. ECG abnormalities have shown T wave inversion, left axis deviation and repolarization abnormalities [96,100,101]. Dilated cardiomyopathy has been seen later in the course of the disease [99]. Hypertrophic cardiomyopathy may become more symptomatic later in the course of the disease with exertional dyspnea, palpitations and anginal pain. Congestive heart failure and arrhythmias are the most common cause of death.

Friedreich ataxia is an autosomal recessive disease caused by homozygous mutations in the FXN gene on chromosome 9q13 encoding the frataxin protein. In these patients, 96% have as their disease causing mutation a GAA triplet-repeat expansion in intron 1 of the gene; the remaining 4% are compound heterozygotes with one allele bearing the GAA expansion and an inactivation mutation on the second allele. The full mutation ranges from 66 to 1700 GAA repeats. There is a genotype/phenotype correlation between the size of the GAA expansion with the size of the shorter of the two expanded GAA repeats showing better correlation to severity of disease [102], specifically with age of onset and duration of disease [90]. Some debate exists whether repeat expansion size correlates with the degree of left ventricular hypertrophy; some have observed that a larger expansion on smaller sized allele may be associated with more ventricular hypertrophy [98,103,104], whereas other studies have not found a correlation [95].

The pathogenesis of Friedreich ataxia arises from a deficiency of the frataxin protein. Frataxin is localized to the mitochondria and is required for biogenesis of iron–sulfur cluster and therefore for the synthesis of enzymes in the respiratory chain complexes I to III. Frataxin is thought to play a role in regulation of mitochondrial iron content; affected individuals show evidence of abnormal mitochondrial iron accumulation however this is likely a secondary disease manifestation. Frataxin deficiency leads to reduced antioxidant defense, deficient mitochondrial function and increased oxidative damage. Friedreich ataxia patients show deficient ATP production and cellular oxygenation in post-exercise skeletal muscle [105,106] and defective myocardial energy production [107,108]. Therefore deficient energy metabolism is likely the cause of cardiac hypertrophy in Friedreich ataxia [108].

Management of cardiomyopathy in Friedreich ataxia patients should be focused on screening by ECG and echocardiogram starting at an early age. Arrhythmias should be managed with antiarrhythmia therapy or medical device implantation. Idebenone has been shown to reduce cardiomyopathy in an animal model and in roughly half the patients with Friedreich ataxia [109,110]. This agent is thought to work downstream from the iron–sulfur defects in the mitochondria of Friedreich ataxia patients.

7. Myotonic dystrophy

Two types of Myotonic dystrophy have been identified with the overall incidence of myotonic dystrophy being 1 in 8000. Type 1 (DM1) is associated with a dominantly inherited
trinucleotide repeat expansion on chromosome 19q13. Myotonic dystrophy type 2 (DM2) is associated with a dominantly inherited tetranucleotide repeat expansion on chromosome 3q13–q24. DM1 and DM2 are characterized by skeletal muscle disease, the most common of which is myotonia, seen as impaired relaxation after muscle contraction. Electromyography reveals repetitive muscle fiber discharges of varying frequency and amplitude. Myotonic dystrophy is a multisystemic disease and causes endocrine dysfunction that includes diabetes mellitus and testicular atrophy, frontal balding, cataracts, cardiovascular disease and mental retardation in the most severe form. The congenital form of DM1, a result of a very large CTG repeat expansion, has generalized hypotonia, weakness, and respiratory compromise. Cardiac complications are prevalent in myotonic dystrophy, although they are believed to exist at a reduced frequency in DM2; however additional studies are needed to confirm this observation. Cardiac involvement is most prominent in the form of atrial fibrillation and ventricular arrhythmias due to diffuse myocardial fibrosis preferentially degenerating the conduction system tissue, however cardiomyopathy and atrioventricular heart disease have also been seen [111–116]. Cardiac complications in the form of ventricular dilation can be present in congenital myotonic dystrophy at birth. Individuals with myotonic dystrophy are at risk for cardiac and respiratory complications with anesthesia, sedation and neuromuscular blocking agents [117–119].

The molecular etiology of DM has been complex. It is now known that the transcribed DM1-associated CTG repeat is itself toxic [120]. The CTG expansion is in the 3’ end of the DMPK gene and the 5’ end of the adjacent Six5 gene. Mice with either gene deleted display features of DM, including cardiac conduction abnormalities with DMPK and cataracts with Six5 deletion, but neither model displays myotonia [121]. Transcribed CUG expansions bind RNA processing proteins, and internuclear aggregates of these seen in skeletal and cardiac muscle dictate a role in pathology [122,123]. The muscleblind (MBNL) class of proteins is found in these aggregates and is thought to lead to abnormal muscleblind function including aberrant RNA splicing. Similarly, the CUG binding protein is also significantly elevated [124]. Gene deletion of muscleblind 1 is associated with myotonia in muscle [125]. Abnormal RNA splicing is now understood to play an essential role in the pathogenesis of myotonic dystrophy with several genes being implicated in defective splicing [126]. The mRNAs encoding the insulin receptor, chloride channel, and cardiac troponin T have been identified as having abnormal splice forms in DM patients [114,125,127]. The chloride channel is implicated in aspects of myotonia, and defects of troponin splicing are thought to contribute to cardiomyopathy [114].

The increased arrhythmia and sudden cardiac death risk should be managed with annual ECG and Holter or event monitor and careful history for pre-syncope or syncopal episodes since conduction system defects are more common than cardiomyopathy and heart failure [128,129] (Table 1). It has recently been suggested that left ventricular noncompaction can occur in myotonic dystrophy [130,131]. The decision when to implant pacemakers in myotonic dystrophy patients remains a class 2 indication according to American Heart Association and American College of Cardiology guidelines. A recent study has supported that a prolonged His-ventricular (HV) interval can be used to determine the timing of pacemaker implantation [132].

8. Conclusions

There is an emerging view that screening and prevention for cardiac disease associated with neuromuscular disorders should replace treating these complications as they arise. Given the high prevalence of cardiovascular disease associated with neuromuscular disorders, preventive approaches are increasingly being adopted, particularly with regard to prevention of sudden death. For a preventive approach to be effective requires knowledge of the genetic mutation since not all neuromuscular disorders, especially the muscular dystrophies, have accompanying cardiac disease. In addition, knowledgeable cardiologists should be routinely evaluating these patients. Given the early age of onset in these disorders, this likely includes the pediatric as well as the adult cardiologist. Finally, since these are rare disorders, the utility of appropriate animal models is critical. It may be that the animal model is a sufficient venue to determine which therapies should be adopted in human patients, particularly when these therapies are well tolerated and have a reasonable side effect profile.

Acknowledgements

This work was supported by the Doris Duke Charitable Foundation, the NIH and the Muscular Dystrophy Association.

References


