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Contemporary Review

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Electrophysiologic and cardiovascular manifestations of Duchenne and Becker muscular dystrophies

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ABSTRACT

There have been significant advances in the diagnosis and management of the hereditary muscular disorders Duchenne and Becker muscular dystrophy (DMD and BMD). Cardiac electrophysiologic and cardiovascular involvement has long been important in the surveillance, care, and prognosis of patients with both BMD and DMD and is the leading cause of mortality in patients with DMD. With improved long-term prognosis, rhythm disorders and progressive cardiomyopathy with resultant heart failure are increasingly common. This review aimed to provide an overview to electrophysiologists and cardiologists of the cardiac electrophysiologic phenotypes and genetics of BMD and DMD and to highlight the recent discoveries that have advanced clinical course and management. A systematic review was performed of the diagnosis and management of DMD and BMD. The Cochrane Library, PubMed, MEDLINE, Europe PubMed Central, AMED, and Embase databases were accessed for available evidence. The research reported in this paper adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Evidence from randomized controlled trials and studies cited in expert consensus and practice guidelines are examined. Advanced imaging techniques and a spectrum of rhythm disorders associated with the progressive cardiomyopathy are presented. Early initiation of heart failure therapies, the role of cardiac implantable devices, and novel gene therapies approved for use with the potential to alter the disease course are discussed. When profound cardiac and cardiac electrophysiologic involvement is diagnosed and treated earlier, outcomes for DMD and BMD patients may be improved.

KEYWORDS Muscular dystrophy; Duchenne; Becker; Cardiomyopathy; Advanced imaging; Arrhythmia

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Introduction

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are X-linked muscle-wasting diseases cumulatively affecting 1 in 5000 males, with DMD being 3-fold more common than BMD.[1] The cardiac and cardiac electrophysiologic manifestations of both conditions play a significant role in prognosis, disease progression, and mortality. The existing literature on cardiovascular disease in DMD and BMD is reviewed in this paper.

Background

Dystrophin was discovered as the disease-causing gene for DMD and BMD in 1986. It is located on chromosome Xp21.1 and encodes a protein that connects the cytoplasmic actin to the dystrophin-glycoprotein complex at the cell membrane, the sarcolemma.[2] Dystrophin serves as a scaffold in the structural link between the myocyte cytoskeleton and the extracellular matrix. In the disease state, loss of dystrophin disrupts the multimolecular complex of transmembrane and cytosolic proteins. The release of intracellular enzymes, such as creatine kinase, and the uptake of large proteins, such as albumin and vital dyes like Procion orange and Evans blue, into nonnecrotic muscle fibers in DMD indicate that the underlying pathophysiologic mechanism involves the creation of large holes within the sarcolemma itself.[3] These holes allow the destabilization of the sarcolemma and of the transmembrane ion homeostasis, leading to sodium accumulation inside the skeletal muscle cell, followed by calcium ion influx

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and subsequent cellular fibrosis, edema, and apoptosis, as seen in Figure 1.[3] Clinically, the absence or lack of functional dystrophin results in muscle degeneration leading to progressive skeletal weakness, peripheral muscle wasting, cardiomyopathy, arrhythmias, and conduction abnormalities. The variability in clinical presentation of these disorders is related to both the magnitude of dystrophin loss and the specific mutation. Mutations resulting in complete absence of dystrophin cause DMD, whereas mutations resulting in low-level expression or a truncated dystrophin cause the milder phenotype of BMD.[4] BMD has variable pathologic phenotypic expression with milder symptoms and corresponding prognosis.

DMD is a progressive, crippling disease of childhood that is typically considered when toddler boys are noticed to have gait disturbance and fail to meet their physical milestones. It is a hereditary, X-linked recessive disorder that historically was diagnosed by muscle biopsy with accompanying histopathology, immunochemistry, and immunoblotting demonstrating absent or partially reduced dystrophin proteins on the surface membranes of muscle fibers. However, advances in genetic diagnostic modalities have led to most cases being diagnosed by genetic testing.[5–7] By young adolescence, patients often lose the ability to walk. Historically, boys with DMD lose the ability to ambulate between the ages of 7 and 13 years.[8] Despite corticosteroid treatments, 30% of patients lose ambulation by the age of 10 years and 90% by the age of 15 years.[9] Males with DMD also have premature death. A retrospective analysis of DMD patients born between 1961 and 1990 demonstrated that a mean age for cardiac death is 19.6 years.[8] A more recent meta-analysis published in the *European Journal of Epidemiology* demonstrated a pooled median life expectancy of 19.0 years for patients without ventilatory support and 29.9 years with ventilatory support.[10] With increased glucocorticoid therapy, ambulation and survival beyond this age are becoming more common with earlier initiation of noninvasive ventilation and pharmacotherapy as well as other device-based therapies. These changes have improved the life expectancy of DMD considerably in the past several decades. With these current standards of care, many patients with DMD can reasonably expect to live into their fourth decade of life.[10]

Roughly 5%–10% of female carriers show some degree of muscle weakness with variable clinical progression.[11] Carriers are at increased risk of dilated cardiomyopathy; the incidence varies from 10% to 37% across studies, with disease progression occurring at a slower rate.[12] Whereas males are prone to skeletal myopathy and progressive cardiomyopathy, female muscular dystrophy carriers predominantly remain free of skeletal muscle symptoms while still having a predisposition to cardiomyopathy. A 10-year-long cohort study conducted between 1985 and 1995 found preclinical or clinically evident myocardial involvement in 84.3% of women and girls who were carriers of DMD or BMD genes.[13] A 2016 study in Europe reported that 47% of female muscular dystrophy carriers had at least 1 pathologic cardiac magnetic resonance imaging (MRI) finding, either reduced left ventricular ejection fraction (LVEF) or late gadolinium enhancement (LGE). Those who carried genes for DMD had pathologic cardiac magnetic resonance (CMR) imaging findings more frequently and at younger ages.[14] It has been shown that cardiac screening, primarily with transthoracic echocardiography, in known DMD and BMD carriers can reveal occult cardiomyopathy. However, no optimal screening schedule has been established.[15] Novel biomarkers, such as circulating microRNA, have been proposed as additional screening tests that could be used for assessment of occult cardiomyopathy in female muscular dystrophy carriers.[16] The prevailing opinion is that cardiomyopathy is likely to develop in female carriers of genetic mutations known to cause muscular dystrophy even in the absence of skeletal muscle disease. Ultimately, additional research is

Abbreviations

ACE: angiotensin-converting enzyme

BMD: Becker muscular dystrophy

CMR: cardiac magnetic resonance

DMD: Duchenne muscular dystrophy

EDMD: Emery-Dreifuss muscular dystrophy

ICD: implantable cardioverter-defibrillator

LGE: late gadolinium enhancement

LVEF: left ventricular ejection fraction

MRA: mineralocorticoid receptor antagonist

MRI: magnetic resonance imaging

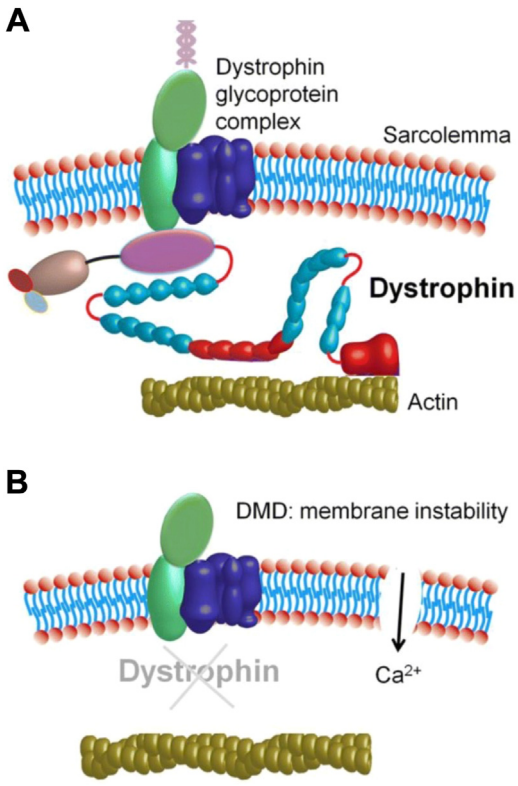

Figure 1
The sarcolemma-dystrophin complex and the evolution of apoptosis in muscular dystrophies. **A:** The wild-state, normal sarcolemma-dystrophin complex. **B:** Disruption of the sarcolemma-dystrophin complex in muscular dystrophies leading to calcium influx–induced apoptosis. DMD = Duchenne muscular dystrophy. From[3] with permission of Dr Joseph Metzger.

required to identify the ideal screening modality and frequency for cardiomyopathy in this population.

BMD is a milder and more clinically heterogeneous phenotype.[17–20] Muscle weakness often starts in adolescence or young adulthood, and the disease progresses more slowly than DMD. Life expectancy is shortened in BMD; death typically occurs before the age of 60 years.[21,22]

Cardiac involvement

Cardiac dystrophin deficiencies are primarily manifested as cardiomyopathy. The mechanism of cardiac muscle involvement is similar to that of skeletal muscle: abnormalities in dystrophin affect the integrity of the sarcolemma and lead to fiber necrosis and replacement of atrial and ventricular myocardium with connective or adipose tissue.[23] Interestingly, there appears to be no direct correlation of the degree of skeletal and cardiac involvement.[17] The dystrophic process also differs between heart and skeletal muscle; whereas skeletal muscle is uniformly affected by degeneration, the heart is predominantly affected initially in the posterior basal region of the left ventricle. Subsequent remodeling leads to ventricular dilation and reduction of the ejection fraction. Compared with other nonneuromuscular dilated cardiomyopathies, the myocardium of DMD patients contains alternating areas of myocyte hypertrophy, atrophy/necrosis, and fibrosis with replacement of myocardium by connective and adipose tissue.[24] With the spreading of fibrosis, ventricular dysfunction, atrial arrhythmias, and ventricular arrhythmias begin to occur.[23] Mutation-dependent differences in the severity and onset of cardiomyopathy in children with muscular dystrophy have been reported.[25]

Historically, the most common cause of death in muscular dystrophies has been respiratory failure.[26] However, with improved respiratory support and extended lifespan, an increasingly important source of morbidity and mortality is cardiomyopathy leading to heart failure and arrhythmias. Cardiomyopathy tends to develop in DMD patients, in many beginning after the age of 10 years, but clinical recognition may be hindered by severe muscle weakness and thoracic deformities.[27] The signs and symptoms of heart failure may be masked in the nonambulatory individual. As a result, cardiac involvement usually remains subclinical in the disease's early stages. With increased survival in patients with muscular dystrophy, diagnostic and therapeutic approaches of multidisciplinary care teams must shift to more anticipatory and proactive care. A series of 3 articles published in *Lancet* in 2018 recommended a multidisciplinary treatment team as shown in Figure 2.[28–30] Hence, a proactive strategy of early diagnosis and treatment with early involvement of a cardiologist is essential to maximize the duration and quality of life.[31] The cardiac manifestations of various muscular dystrophies and the recommended screening protocols are summarized in Table 1.

Diagnosis

Cardiovascular physical examination

A reduction in the anterior-posterior chest dimension typically leads to a systolic impulse displaced to the left sternal border.

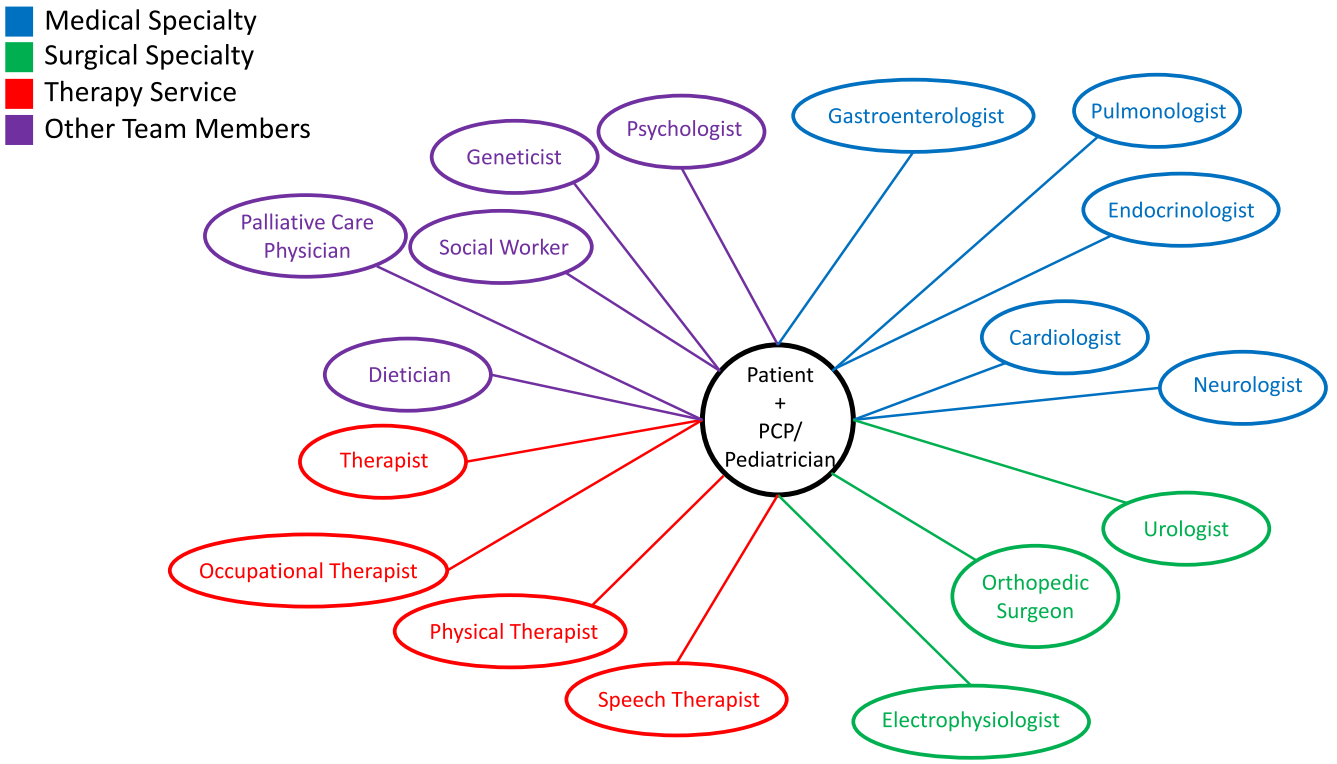

Figure 2
Multidisciplinary teams in muscular dystrophy. A visual representation of the proposed multidisciplinary team[21,29,30] involved in patient care for muscular dystrophy patients. PCP = primary care physician.

Table 1 Cardiac complications and recommended screenings in muscular dystrophies

Dystrophy	Cardiac complications	Recommended cardiac screening
Duchenne muscular dystrophy (DMD)	DCM; symptoms often masked by severity of skeletal myopathy Ventricular arrhythmias	Boys: ECG + TTE every 2 years until age 10; then once a year Girls: when asymptomatic: ECG + TTE every 5 years after age 16
Becker muscular dystrophy (BMD)	50%–70% eventually developing DCM Ventricular arrhythmias	Boys: ECG + TTE every 5 years Girls: when asymptomatic: ECG + TTE after age 16
Emery-Dreifuss muscular dystrophy (EDMD)	DCM Atrioventricular conduction abnormalities Atrial standstill, atrial flutter, atrial fibrillation Sudden death, occasionally in patients with minimal skeletal myopathy	ECG + Holter + TTE annually in affected patients Screening of family members indicated after age 10 (irrespective of symptoms) Consider need for pacemaker and/or defibrillator (particularly for EDMD2 patients with DCM) Consider need for anticoagulation in case of atrial dysfunction
Limb girdle muscular dystrophy (LGMD)	Cardiac involvement most common in LGMD1B (laminopathy) and LGMD 2E and 2I DCM; right and left ventricular fatty infiltration, conduction disorders In heterozygotes, cardiac dysfunction may be the only sign of disease	No formal guidelines; ECG + Holter + TTE probably indicated every 2–5 years
Myotonic dystrophy (DM)	DCM Left ventricular hypertrophy Conduction disturbances (atrioventricular and intraventricular) Atrial fibrillation and flutter Sudden cardiac death (most commonly DM1)	Asymptomatic patients: annual ECG, TTE + Holter every 2 years Electrophysiologic testing in case of syncope, dizziness, palpitations, documented arrhythmias, or family history of sudden death or ventricular arrhythmias Consider need for pacemaker or defibrillator, depending on ECG, Holter, and EP findings

DCM = dilated cardiomyopathy; ECG = electrocardiogram; EP = electrophysiology study; TTE = transthoracic echocardiography.
Modified from[108] with permission of Dr Subha Raman.

Mitral regurgitation may be present because of mitral annulus dilation or posterior papillary muscle dysfunction. This may be manifested as a short midsystolic murmur in the second left interspace and a loud pulmonary component of the second heart sound if pulmonary hypertension is present.[32] In patients with signs of acute exacerbation of chronic systolic or diastolic heart failure, findings on examination can include weight gain with associated findings like jugular vein distention, hepatojugular reflux, rales, new or worsening S3, ascites, and leg edema.

Electrocardiography

The National Heart, Lung, and Blood Institute expert working group on DMD[29] recommends annual cardiac assessment including an electrocardiogram and noninvasive imaging to establish baseline cardiac function and to screen for underlying anatomic abnormalities that could affect long-term cardiovascular health. After the age of 10 years, as the risk of left ventricular dysfunction increases, so should the frequency of assessment, including in asymptomatic individuals. The electrocardiogram shows an abnormality in most (77%–95%) DMD cases in similar rates for age groups between dilated and nondilated cardiomyopathy. The typical initial manifestations include sinus tachycardia, short PR interval, and dominant R waves with an abnormal R/S ratio in lead V_1 due to right ventricular hypertrophy. Ventricular repolarization and conduction disturbances in the right bundle branch are commonly seen. Other characteristic findings include a prolonged QTc interval and a pattern of narrow, deep Q waves in leads I, aVL, V_5, and V_6 or in II, III, aVF, V_5, and V_6.[33,34]

Arrhythmias and conduction disease

The most common arrhythmia is sinus tachycardia, probably because of autonomic dysfunction due to decreased parasympathetic tone and increased sympathetic tone.[35–37] The development of dilated cardiomyopathy typically precedes conduction disease and clinically significant arrhythmias.[38]

Significant arrhythmias, including atrial fibrillation, atrial flutter, and nonsustained and sustained ventricular tachycardia, will develop in ~3% of patients with DMD, with the prevalence increasing to 40% in those with ejection fraction <35%.[39] An insertable loop recorder or smartphone-based applications may be particularly useful in determining the arrhythmia burden.[40]

Atrial fibrillation and atrial flutter are uncommon in patients with DMD or BMD. The 2022 expert consensus from the Heart Rhythm Society recommended the same CHA_2DS_2-VASc paradigm for anticoagulation and pacemakers in DMD and BMD patients as in those without DMD or BMD.[38,39]

Additional studies are needed to better understand the benefit and risks of anticoagulation in these patients, given their increased risk of fall related to skeletal muscle myopathies. Clinically insignificant atrial arrhythmias, such as premature atrial contractions and atrial couplets/triplets, occur with a prevalence of 80% and 11%, respectively.

With the decline in left ventricular function, the incidence of ventricular arrhythmias and the risk of sudden cardiac death increase. The prevalence of frequent premature ventricular contractions is 2%, 13%, and 60% with ejection fractions of >55%, 35%–55%, and <35%, respectively. Likewise, the prevalence of nonsustained ventricular tachycardia is 0%, 7%, and 40% with ejection fractions of >55%, 35%–55%, and <35%, respectively.[39] Interestingly, data from the Pediatric Cardiomyopathy Registry and other similar series demonstrate a low rate of sudden arrhythmic death in the pediatric population in contrast to their adult counterparts.[39,41] Implantable cardioverter-defibrillator (ICD) implementation is discussed later in the Advanced Therapies section.

Echocardiography

The prevalence of myocardial dysfunction is estimated to be 5% in patients aged 0–5 years and 61% by the age of 18 years.[42] Imaging recommendations include an echocardiogram beginning at 6 years of age and then subsequent studies every 1–2 years; after the age of 10 years, asymptomatic individuals are screened at least annually.[30] Echocardiography can show reduced global longitudinal strain in the apical segments and posterolateral wall, often preceding any reduction in LVEF with subsequent reduced global circumferential strain in the septal wall.[43] Few boys will show evidence of hypertrophic cardiomyopathy.

Transthoracic echocardiography imaging may be limited with DMD because of echocardiographic windows that may be mitigated with contrast-enhanced echocardiography. Novel echocardiographic parameters including myocardial strain analysis, serial epsilon measurements, and left ventricular shortening may be predictors of long-term survival.[44]

CMR

In vivo human studies, autopsy data, and preclinical mouse models of DMD have demonstrated that progressive myocardial damage is well underway before LVEF becomes abnormal. Myocardial fibrosis is a marker of myocardial damage—and precursor to progressive cardiac dysfunction—that is detected as LGE on CMR. CMR may have the added ability to identify myocardial damage before a decline in ejection fraction or clinical manifestations.[45] Treatment initiation based on fibrosis seen on MRI is becoming more common, although it has not been specifically studied for clinical outcomes of functional status, heart failure, or significant arrhythmias.

Conventional MRI allows the measurement of global cardiac function and detection of fibrosis, a late manifestation of myopathy. Emerging MRI indicators of myocardial function and structure include the estimation of rotational mechanics and regional strain with MRI tagging; T1 mapping; and T2 mapping, a marker of inflammation, edema, and adiposity that holds the potential for earlier diagnosis and tailored therapy for DMD and BMD.

Perhaps the greatest challenge of CMR for therapeutic treatment is the lack of established parameters and clinical targeted end points. Despite this, CMR has been shown to be superior to echocardiography in assessment of cardiac dysfunction early in the disease course of muscular dystrophies.[46] A recent paper demonstrated LVEF, indexed left ventricular volumes, circumferential strain, and LGE full width half maximum as specific parameters associated with all-cause mortality in DMD and potential clinical markers on CMR studies.[47] A novel 4-dimensional kinematic analysis of CMR focusing on localized strain found that almost 35% of DMD patients demonstrate LGE before any reduced LVEF, suggesting LGE as a good early prognostic predicter of pending cardiomyopathy.[48] In fact, a retrospective analysis of routine CMR in 33 patients with BMD supports early CMR surveillance with LGE assessment to identify occult cardiomyopathies.[49] LGE has also been shown to be associated with increased cardiac adiposity related to muscle breakdown seen frequently in muscular dystrophies.[50] These novel studies emphasize the need for further use of CMR in research, clinical, and diagnostic settings for patients with DMD and BMD.

Medical therapies

Early use of noninvasive ventilation has improved DMD patients' 25-year survival from 0% to 53%.[25] This prolonged survival has led to an increased prevalence of cardiomyopathy, which is now a leading cause of death. Despite such progress, the mean age of survival in the presence of cardiomyopathy is only 16.9 years. To improve survival in the absence of a curative treatment, emphasis has been on treatments that delay the development and progression of cardiomyopathy. Owing to curtailed energy expenditure and oxygen consumption from weakened muscle, most patients with DMD remain asymptomatic for many years in spite of progression of cardiac dysfunction.[26,51] As a result, the proper initiation time of these treatments is not known, and longer duration often leads to adverse effects. Studies are needed to determine the appropriate timing of early treatment and the effect of combination cardioprotective guideline-directed medical therapy on event-free survival.[52]

Corticosteroids and deflazacort

Corticosteroids have been the mainstay for treatment of muscular dystrophies since the 1980s after a randomized, double-blind, 6-month trial found that prednisone improved the strength and function of patients with DMD.[53] A 2021 review paper published in the *Journal of Neuromuscular Diseases* summarized multiple mechanisms of glucocorticoid action in treating dystrophic muscles. First, glucocorticoids are known to modulate gene expression by activating or suppressing transcription. Second, glucocorticoids act as anti-inflammatory agents. Third, glucocorticoids modulate metabolic states by inducing the "fight or flight" stress response. In specific studies

of dystrophic muscle, glucocorticoids are reported to increase features of muscle regeneration, to drive functional improvement through activation of transcription factors like KLF15 (a glucocorticoid receptor–activated factor shown to mediate nutrient use), to accelerate sarcolemma resealing after injury, and to stabilize the sarcolemma before injury.[54] The effects of glucocorticoids on dystrophic cardiac muscle have not been completely assessed and require further study. However, initial retrospective studies of corticosteroids in DMD have found delayed onset of cardiomyopathy and systolic function decline in patients treated with glucocorticoids.[55,56]

Corticosteroids (prednisone, prednisolone) are commonly used therapy for DMD and are usually initiated early in the course of the disease, before substantial physical decline. The 2016 update of the American Academy of Neurology guidelines on corticosteroid treatment in DMD supported the use to improve strength, motor skills, pulmonary function, cardiovascular manifestations, orthopedic complications, and even survival.[57] Randomized clinical trials have demonstrated improvement in muscle strength and function as well as delayed loss of ambulation with corticosteroid use. Treatment with prednisone or deflazacort has also been reported to improve pulmonary function and to reduce mortality and is associated with a smaller increase in the burden of myocardial fibrosis as measured by LGE on CMR.[48,58] The optimal duration of treatment with corticosteroids is not known; longer use is associated with growth delay, osteoporosis, fractures, weight gain, hirsutism, and cataracts. The long-term efficacy of these drugs is uncertain and may be largely outweighed by their adverse effects in nonambulatory patients.[59,60] Intermittent dosing of prednisone as opposed to daily administration has been associated with less muscle adipogenesis and atrophic remodeling in preclinical studies. A randomized, crossover, controlled trial of intermittent prednisone (0.75 mg/kg per day) therapy during the first 10 days of each month for 6 months found that prednisone slowed the deterioration of skeletal muscle function in individuals with DMD, and adverse effects did not negatively affect quality of life.[61]

Deflazacort is a glucocorticoid derivative of prednisolone having both immunosuppressive and anti-inflammatory properties. The Food and Drug Administration approved deflazacort for treatment of Duchenne dystrophy in 2017 for patients 5 years of age or older and in 2019 expanded the start of treatment to the age of 2 years.[57] Deflazacort has almost immediate conversion into the active metabolite with peak concentrations in 1–2 hours; its plasma half-life is ~2 hours, which is shorter than that of methylprednisolone or prednisolone, with an adverse effect profile similar to that of most glucocorticoids.[57] Deflazacort may have more potent immunosuppressive activity with less osteoblastic depression and bone-sparing effect with resultant decreases in growth suppression or bone loss, and favorable behavioral adverse effect profile.[62]

Several key trials assessed clinical outcomes of deflazacort vs prednisone and prednisolone. The largest randomized trial published in 2016, a multicenter trial of 196 patients aged 5–15 years, examined the onset of weakness at various time points.[63] After a mean follow-up of 52 weeks, there appeared to be no statistically significant difference in outcomes in the deflazacort group and prednisolone group as assessed by muscle strength. Two observational studies comparing outcomes of deflazacort vs prednisone and prednisolone showed that deflazacort compared with prednisolone was significantly associated with longer time until loss of functional status by various metrics.[58,60] These observational studies are limited by cohort matching issues, making interpretation somewhat limited, but deflazacort has gained increased popularity in treating Duchenne dystrophy.

Angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, and angiotensin receptor–neprilysin inhibitor

In a randomized prospective trial, early treatment with the angiotensin-converting enzyme (ACE) inhibitor perindopril in boys with DMD delayed the onset and progression of left ventricular dysfunction.[64] A separate randomized prospective trial showed a similar benefit in the left ventricular systolic function for both lisinopril and the angiotensin receptor blocker losartan.[65] Evidence from CMR of muscular dystrophy patients with preserved ejection fraction shows that enalapril slows the progression of myocardial fibrosis, a strong predictor of LVEF and outcomes.[66] A small, randomized, double-blind study of DMD patients with mild cardiomyopathy demonstrated equivalent improvement in LVEF with either ACE inhibitor or angiotensin receptor blocker therapy.[65] On the basis of these studies, treatment with an ACE inhibitor or an angiotensin receptor blocker should be started before a reduction in left ventricular systolic function, no later than the age of 10 years. Adults have also been treated with angiotensin receptor–neprilysin inhibitors, with careful monitoring of hemodynamics, electrolytes, and renal function. Cautious use of these agents in the DMD population is necessary because of commonly encountered hypotension with initiation and titration.

β-Adrenergic blockers

Clear recommendations for the use of beta blockers in the DMD population have not been developed owing to a paucity of randomized prospective clinical trials. It is recommended that treatment with a beta blocker be initiated as soon as left ventricular dysfunction is diagnosed in accordance with the American College of Cardiology and American Heart Association guidelines.[67] Retrospective studies of nonambulatory patients with left ventricular dysfunction have also reported delayed cardiomyopathy progression and improved survival with early combined use of beta blockers and ACE inhibitors. The impact on survival was greater in asymptomatic patients than in patients with heart failure.[68] The cardioprotective mechanism of beta blockers in DMD may extend beyond cardiomyopathy and heart failure. In vitro and in vivo treatment of DMD human induced pluripotent stem

cell–derived cardiomyocytes with beta blockers decreased lethal arrhythmias and mitigated fibrotic remodeling response through reverse remodeling.[69]

Mineralocorticoid receptor antagonists

The role of mineralocorticoid receptor antagonists (MRAs) in heart failure with reduced ejection fraction is well established in both ischemic and nonischemic cardiomyopathy. Similarly, the evidence for clinical benefit is strong in DMD. In a randomized controlled trial of boys with DMD, the addition of eplerenone to background ACE inhibitor or angiotensin receptor blockade therapy slowed the progression of cardiomyopathy.[70] MRA therapy was associated with the attenuation in decline of left ventricular systolic function and delayed the onset of heart failure. Small studies have reported a protective effect of spironolactone and eplerenone in DMD started before the development of overt left ventricular dysfunction.[71,72] On the basis of these data, MRAs are part of guideline-directed medical therapy in the management of DMD patients with reduced ejection fraction. Consideration of their early use is warranted in this population at high risk of cardiac death, but impact on event-free survival in DMD has not been definitively studied.

Antiarrhythmic therapy

Whereas cardiac and electrophysiologic manifestations of DMD and BMD are well documented and well established in the medical literature, few articles address antiarrhythmic pharmacotherapy in patients with muscular dystrophies.[73] There is a small amount of literature to support the use of antiarrhythmic therapies for the treatment of generalized myotonia in DMD and BMD.[74,75] However, the literature is much more sparse in looking at the actual utility of antiarrhythmic agents for cardiac arrhythmia in DMD and BMD.

A 1996 case report documented the inefficacy of antiarrhythmic drugs in a patient with DMD who died of ventricular tachycardia.[76] In a 2016 case report, a young man with BMD and ventricular tachycardia was treated with amiodarone, but this was quickly discontinued when hemoptysis developed.[77] Beyond these isolated case reports, the literature is limited regarding the use of antiarrhythmic agents to treat electrophysiologic manifestations of muscular dystrophy and instead favors implantable pacemakers and defibrillators, as discussed later. This is an area that would benefit from increased study and consideration for clinical practice.

Gene therapies

Whereas medical therapies attempt to compensate for the dystrophin abnormalities, gene therapy is aimed at restoring dystrophin expression and mitigating disease severity. Therapies that restore dystrophin expression include cardiosphere-derived stem cells and exosome therapy, exon skipping, read-through therapy, vector-mediated gene transfer, and cell therapy. These genetic treatments attempt to convert DMD into a clinically milder disease; however, to date, genetic therapies have had only varying success.[72] Although DMD is an attractive candidate for gene therapy as it arises from a single-gene mutation, the estimation of how much dystrophin is necessary for function and the optimal way of gene delivery need to be optimized. As all dystrophic muscles lack dystrophin, efficient gene therapy should allow the expression of a new dystrophin gene not only in limb muscles but also in the diaphragm and the heart.

Cardiosphere-derived stem cells and exosome therapy

In patients with DMD, cardiomyocyte death and subsequent fibrosis may be reversed by a new therapy with a cardiac progenitor cell population called cardiosphere-derived cells.[78] These are proposed to secrete growth factors and microRNAs through exosomes and are thus thought to have anti-inflammatory, antifibrotic, and even cardiomyocyte regenerative processes. The Halt Cardiomyopathy Progression (HOPE)–Duchenne clinical trial was a phase 1/2 randomized, controlled, open-label clinical trial of allogeneic cardiosphere-derived cells (CAP-1002; Capricorn Therapeutics, Beverly Hills, CA) in 25 patients with advanced skeletal DMD and cardiac involvement.[78,79] Patients were randomized to intracoronary infusion of CAP-1002 (25 million cells in all 3 coronary branches) and usual care vs usual care alone at 3 sites in the United States, with outcomes of heart rhythm at 72 hours, humoral and cellular response assays at 6 weeks, cardiac MRI at 6 and 12 months, and functional assessment and quality of life at regular intervals throughout the 12-month follow-up. The early-phase HOPE-Duchenne trial showed cardiac and upper limb skeletal muscle benefit, with regional cardiac improvement in inferior, lateral, and anterior left ventricular segments that are affected early and severely in DMD-associated myocardial fibrosis.[79] The improvement in both cardiac and upper limb function with intracoronary CAP-1002 infusion is particularly compelling.

The HOPE-2 trial assessed the clinical safety and efficacy of sequential intravenous CAP-1002 injections.[78] This multicenter, randomized, double-blind, placebo-controlled phase 2 trial of 20 patients at 7 centers in the United States administered CAP-1002 or placebo every 3 months for a total of 4 total intravenous injections to DMD patients with advanced skeletal and cardiac dystrophy. Safety and clinical benefit were predetermined to be assessed by upper limb function, cardiac MRI, cardiac biomarkers, and spirometry measures of respiratory function. Intravenous CAP-1002 was well tolerated and importantly attenuated the upper limb and cardiac deterioration, reversed cardiac dysfunction, and improved upper limb function. There was, however, no impact on pulmonary function, possibly because of structural skeletal deformities like scoliosis that are unrelated to muscle loss of function.

Exon skipping

It is estimated that about 20.5% of DMD patients have deletion mutations. The nature of the deletion determines the severity of the disorder. Some *DMD* deletions lead to in-frame mutations that generate variants able to produce functional albeit truncated versions of dystrophin. These

mutations tend to accumulate between exons 45 and 55 in *DMD*. Exon skipping is a therapeutic approach aimed at correcting the disrupted reading frame through intramuscular or intravenous administration of a specific genetic sequence, hence inducing "skipping" of selected exons in the dystrophin pre-mRNA. Transfection with predesigned antisense oligonucleotides restores a shorter but largely functional dystrophin protein that is then translated. Currently, eteplirsen, golodirsen, and viltolarsen have been approved by the Food and Drug Administration to treat specific mutations in DMD.[80,81]

Read-through therapy

Approximately 10% of all patients with DMD carry nonsense mutations resulting in a premature stop codon in the dystrophin mRNA. This leads to the translation of a truncated, nonfunctional protein. Aminoglycoside antibiotics have been demonstrated to read through premature nonsense (stop) codons to restore dystrophin expression. Ataluren is a therapy that works by promoting ribosomal read-through of nonsense (stop) mutations. It was shown to slow disease progression based on patient registry data, yet it did not result in significant improvement in 6-minute walk test distance in a randomized placebo-controlled trial.[82]

Vector-mediated gene therapy

Delivery of normal *DMD* to replace the affected gene with a functional gene is a potential therapeutic approach that is hindered by the size of *DMD* (2.4 Mb) and its cDNA (14 kb) as well as the broad distribution of affected organs. Vector-mediated gene therapy for DMD consists of delivery of functional domains of dystrophin through viral or nonviral vectors to restore dystrophin. Several trials are underway to address immunity to preexisting antigenic epitopes in revertant dystrophin and to the viral capsid.[83] Gene therapies face multiple challenges and limitations as they are still in their early stages of development. Some of the limitations include observed immune-mediated toxic effects and development of neutralizing antibodies.[83] Theoretical challenges include risk of improper integration leading to disruption of other genes and loss of correction in the long run. Research and development are also blunted by the prohibitive cost of production relative to the small target population. Nevertheless, vector-mediated gene therapy offers a potentially revolutionary breakthrough in DMD, BMD, and similar pediatric conditions.

Advanced therapies

In DMD and BMD, the primary cardiac manifestation is dilated cardiomyopathy and subsequent heart failure. The guideline indications for pacing, cardiac resynchronization, and ICD placement are similar to those for patients without DMD or BMD, assuming they align with the patient's goals of care.[38] In rare situations, left ventricular assist devices have been considered with careful team-based decisions.[84]

As bradycardia is an uncommon manifestation of DMD, there are limited reports of the need for pacemakers in this population.[39,85] As such, there are no specific pacing recommendations for DMD and BMD. However, if pacemaker implantation is indicated, there are special considerations for device implantation in this population. There is an especially high risk of pulmonary complications with procedural sedation in nonambulatory patients and in those receiving respiratory support, with or without tracheostomy. It is estimated that early complications of pneumothorax are 16.6% and long-term infection risks are 8.3% after cardiovascular implantable electronic device implantation.[86] This highlights the unique challenges of cardiovascular implantable electronic device implantation in patients with muscular dystrophies and the need for particular caution in the management of these patients during invasive procedures. Prophylactic devices should be considered on the basis of long-term survival after a discussion about the benefits to quality of life and goals of long-term care. In addition, whereas cardiac resynchronization therapy may be appropriate in DMD and BMD when maximally tolerated guideline-directed therapy remains insufficient for symptomatic relief, large studies examining this in muscular dystrophies are lacking. Given this absence of data and lack of sufficient patient volume for clinical trials, data from other studies of cardiac resynchronization must be extrapolated on a patient-by-patient basis for DMD and BMD patients. Whereas DMD patients are generally not candidates for heart transplantation, in patients with BMD (especially those with milder skeletal muscle involvement), outcomes with cardiac transplantation are similar to those of age-matched patients with other forms of nonischemic cardiomyopathy.

Catheter ablation

Data on catheter ablation of patients with DMD and BMD are limited; most are case reports—3 case reports of young men with DMD or BMD with accessory pathways and reentrant tachyarrhythmias, 2 with Wolf-Parkinson-White reentrant tachycardia and 1 with bundle branch reentry ventricular tachycardia.[87–89] In the Wolf-Parkinson-White patients, 1 required repeated catheter ablation with the development of novel accessory pathways requiring recurrent catheter ablation.[88] Based on the incidence of Wolf-Parkinson-White in the general population, the accessory pathway is not likely to be related to the underlying DMD or BMD. Regardless, catheter ablation of the accessory pathway seems to be an effective strategy for reentrant tachyarrhythmias in this population.

Shared decision-making and end-of-life care

All classes of muscular dystrophy contain both arrhythmic and nonarrhythmic manifestations that can limit quality and quantity of life. This reality leads many patients and families to confront decisions about life-prolonging therapies including, among others, ICD implantation, setting adjustments and shocks, arrhythmia therapies, and intubation.[90] In conjunction with the patient's right to autonomy, every reasonable attempt should be made by physicians to respect a patient's desire to pursue, to discontinue, or even to withdraw care.

With DMD and BMD and the associated high rates of mortality, open and periodic discussions about diagnosis, treatments, and advanced therapies should occur between patients and, as appropriate, their families.

Particularly useful opportunities to have conversations to learn about a patient's long-term goals of care and preferences are before implantation of an ICD and when generator changes are indicated.[91,92] Owing to the progressive nature of muscular dystrophies, these conversations are likely to be recurrent as goals of care evolve over time. Notably, in patients who have had ICDs placed, studies have shown an escalation in shock frequency in the final weeks of life.[93,94] In many cases, patients no longer perceive these shocks as beneficial, and patients and families should be provided with education about options for reprogramming and deactivation in these situations.[93,95,96]

Inactivation of pacing is unique as it may precipitate immediate and life-threatening situations. As such, these decisions have distinct implications and ethical concerns. Whereas requests for inactivation of pacing are uncommon, if, after adequate patient education about cessation of cardiac pacing functions, patients continue to request termination of pacing devices, the patient's autonomy in medical decision-making remains the primary directive. When an individual physician has ethical concerns about fulfilling this request, referral to another physician is appropriate.[91]

Consulting experts in end-of-life care, such as palliative care and hospice care, is often useful in facilitating each of these evolving conversations about end-of-life care and muscular dystrophies.

Emery-Dreifuss

Emery-Dreifuss muscular dystrophy (EDMD) is another muscular dystrophy syndrome with some similarities to DMD and BMD; however, it has unique properties that warrant discussion. EDMD is a somewhat rare disorder with a prevalence estimated at <1/100,000 people.[97] It is a diverse muscular dystrophy with variable genetics including an X-linked recessive version, an autosomal dominant version, and an autosomal recessive version.[98] Most gene mutations result in abnormal nuclear membrane protein production; the most common are EDMD1 with a protein mutation coding for emerin and EDMD2 with a protein mutation coding for laminin A and C.[99,100]

The clinical manifestations usually involve upper extremity contractures with progressive humeral-peroneal muscle weakness and loss of muscle volume, with onset usually by the age of 20 years.[101] There is a significant amount of variability in the clinical progression and severity, but elbow involvement is 1 of the pathognomonic findings. Muscle weakness begins in the humeral-peroneal distribution, spreading to upper extremity, biceps, and triceps, yet spares the deltoid muscle distribution.[102] Additional clinical manifestations include contractures of the neck and thoracic spine with lower extremity involvement including Achilles tendon contractures, with progressive spine and lower extremity contractures. After the third decade of life, the clinical progression of these changes can occur quickly.

Cardiac involvement is common in patients with EDMD. Symptomatic onset usually begins in the third decade of life with presyncope, palpitations, syncope, and exercise intolerance.[101] Atrioventricular conduction defects, including first-degree heart block, sinus bradycardia, complete heart block, and atrial arrhythmias (atrial fibrillation and atrial flutter), occur in both EDMD1 and EDMD2.[103] However, the most severe cardiac manifestations, including dilated cardiomyopathy, hypertrophic cardiomyopathy, and lethal malignant ventricular arrhythmias, are more frequently seen in EDMD2.[104] Studies have called this dichotomy into question, suggesting that malignant ventricular arrhythmias are equally common in EDMD1 and EDMD2 despite that EDMD2 has high rates of left ventricular systolic dysfunction.[105] By the age of 50 years, the incidence of heart failure in EDMD2 exceeds 60%.[106]

Initial diagnostic testing with electrocardiography can detect the conduction abnormalities and associated arrhythmias. Baseline and surveillance echocardiography can initially detect dilated cardiomyopathy, hypertrophic cardiomyopathy, biatrial enlargement, or isolated right ventricular dysfunction.[101]

EDMD has little in the way of successful disease-modifying therapy; therefore, most care is supportive. This includes routine monitoring of LVEF, routine heart failure pharmacotherapy excluding beta blockers, consideration of implantable devices, and multidisciplinary management.[101] In cases of EDMD2, this includes implantation of an ICD irrespective of the need for pacing and skeletal muscle disease.[107] Advanced cardiomyopathy, congestive heart failure, and conduction abnormalities are the main cause of death in patients with EDMD.

Conclusion

DMD and BMD are severe illnesses of young males with historically predominant neurologic manifestations, yet with advancing therapies, there are increasing cardiac and arrhythmic complications. The cardiac and electrophysiologic manifestations of these conditions warrant close follow-up by both cardiologists and electrophysiologists. This includes timely use of electrocardiography, echocardiography, and cardiac MRI and arrhythmia-specific care that necessitates involvement of cardiac electrophysiologists. Effective diagnosis improves therapy with corticosteroids, ACE inhibitors/angiotensin receptor blockers, beta blockers, MRAs, devices, and, if indicated, antiarrhythmics; the progress in gene therapy holds promise for this X-linked condition. Similarly, EDMD has overlay with DMD and BMD, but specific clinical features and prognosis warrant a separate treatment strategy. In summary, DMD and BMD have rhythm disturbances necessitating close management by both cardiology and cardiac electrophysiology specialists to improve patient care.

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