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INVITED REVIEW

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Emery-Dreifuss muscular dystrophy

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Abstract

Emery-Dreifuss muscular dystrophy (EDMD) is a rare muscular dystrophy, but is particularly important to diagnose due to frequent life-threatening cardiac complications. EDMD classically presents with muscle weakness, early contractures, cardiac conduction abnormalities and cardiomyopathy, although the presence and severity of these manifestations vary by subtype and individual. Associated genes include *EMD*, *LMNA*, *SYNE1*, *SYNE2*, *FHL1*, *TMEM43*, *SUN1*, *SUN2*, and *TTN*, encoding emerin, lamin A/C, nesprin-1, nesprin-2, FHL1, LUMA, SUN1, SUN2, and titin, respectively. The Online Mendelian Inheritance in Man database recognizes subtypes 1 through 7, which captures most but not all of the associated genes. Genetic diagnosis is essential whenever available, but traditional diagnostic tools can help steer the evaluation toward EDMD and assist with interpretation of equivocal genetic test results. Management is primarily supportive, but it is important to monitor patients closely, especially for potential cardiac complications. There is a high potential for progress in the treatment of EDMD in the coming years.

KEYWORDS

cardiomyopathy, contractures, emerin, Emery-Dreifuss, laminopathy, muscular dystrophy

1 | HISTORY

Emery-Dreifuss muscular dystrophy (EDMD) has a distinct clinical presentation that led to its description as a classic clinical entity many years before the genetic etiologies were identified. An early description of a muscular dystrophy with early contractures was made by Cestan and Lejonne in 1902.[1] In 1955, Becker and Kiener described a slowly progressive X-linked muscular dystrophy with a later onset than Duchenne muscular dystrophy and a slightly reduced average lifespan.[2] It was not until 1966, however, when Emery and Dreifuss provided a more detailed description of the clinical features and typical progression of the disease that would later assume their names.[3] In 1979, this disease became officially known as Emery-Dreifuss muscular dystrophy (EDMD).[4]

Abbreviations: AAV, adeno-associated virus; ACE, angiotensin-converting enzyme; AV, atrioventricular; CK, creatine kinase; CMT, Charcot–Marie–Tooth disease; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; ECG, electrocardiogram; EDMD, Emery-Dreifuss muscular dystrophy; EF, ejection fraction; EMG, electromyography; ERK, extracellular-signal regulated kinase; FHL1, four-and-a-half LIM domains 1; FPLD, familial partial lipodystrophy; ICD, implantable cardioverter defibrillator; LAP2, lamina-associated polypeptide 2; LGMD, limb-girdle muscular dystrophy; LINC, linker of nucleoskeleton-and-cytoskeleton; LMNA, lamin A/C; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NAD+, nicotinamide adenine dinucleotide; Nup, nucleoporin; OMIM, Online Mendelian Inheritance in Man; SCD, sudden cardiac death; SUN1, SAD1 and UNC84 domain containing protein 1; SUN2, SAD1 and UNC84 domain containing protein 2; TMEM43, transmembrane protein 43.

2 | EPIDEMIOLOGY

A meta-analysis estimated that the pooled prevalence of EDMD in all age groups was 0.39 per 100,000.[5] However, this study noted significant heterogeneity of results in the four primary articles from which this estimate was derived. This is not surprising, as the studies

examined four diverse populations representing Northern Ireland,[6] Northern England,[7] Assuit, Egypt,[8] and Hong Kong.[9] Sporadic mutations are believed to be infrequent for *EMD*, but are becoming increasingly recognized for *LMNA*.[10] In the autosomal dominant and recessive forms of EDMD, males and females are equally affected, while the X-linked form primarily affects males, with some disease manifestations among female carriers.[11]

3 | CLINICAL PRESENTATION

Clinically, the classic form of EDMD can be thought of as a triad within a triad. The classic overall triad consists of early contractures, progressive muscle weakness and atrophy, and cardiac abnormalities. The second triad captures the pattern of contractures, most prominently involving neck extension, elbow flexion, and heel cord tightening.

The contractures frequently emerge in the first decade of life, but become more evident and bothersome during the growth spurt that often occurs in adolescence. They can affect the paraspinal ligaments and posterior cervical musculature so significantly that the patient's neck may become fixed in an extended position. The cervical spine rigidity may become prominent enough to alter neck anatomy, thereby leading to dysphagia.[12] It is important to remember that early contractures, including congenital contractures, may be associated with other diseases. Collagenopathies such as Ullrich congenital muscular dystrophy and Bethlem myopathy may present with early contractures, as may SEPN1-related myopathy.[13] Numerous underlying diseases have been found to cause arthrogryposis multiplex congenita, a pleiomorphic syndrome of congenital contractures.[14]

A common early motor symptom is difficulty with walking or running. Muscle weakness and atrophy become evident by the second or third decade. The weakness commonly presents in a "humeroperoneal" pattern, affecting the proximal arms (specifically the biceps and triceps, with relative sparing of the deltoids and infraspinatus) and distal legs (predominantly the peroneal muscles, with sparing of the thighs and intrinsic foot musculature). Neck weakness is almost universal and scapular winging is common, with sparing of facial muscles.[10]

Cardiac complications are found in the majority of EDMD patients. Atrial tachyarrhythmias, atrial standstill, ventricular tachyarrhythmias and cardiomyopathy are the most common manifestations. Symptoms usually start after the second decade of life with palpitations, presyncope and syncope, exercise intolerance, and heart failure symptoms. Frequently, cardiac manifestations precede the onset of significant skeletal muscle weakness. Compared with the background population, EDMD1 female carriers have an increased risk of developing cardiac complications, such as conduction abnormalities and sudden death, often in the absence of significant neuromuscular symptoms.[11]. The incidence of heart failure can exceed 60% in patients older than 50 years with *LMNA* mutations, including those with EDMD.[15]

4 | GENETICS

Several genes have been implicated in the pathogenesis of EDMD. Among them, *EMD*, *LMNA*, *SYNE1*, *SYNE2*, *FHL1*, and *TMEM43* have all been assigned to specific EDMD subtypes (EDMD1, EDMD2 and EDMD3, EDMD4, EDMD5, EDMD6, and EDMD7, respectively) (Table 1). These subtypes are recognized in the Online Mendelian Inheritance in Man (OMIM) database.[16] Other genes that have been associated with this disease are *SUN1* and *SUN2*, as well as *TTN*.[17–23] There are still more causative genes yet to be discovered, as over 60% of patients with EDMD do not have detectable mutations in *EMD* or *LMNA*, the two most common genes.[24]

In 1986, the molecular era began for EDMD when the first locus for this disease was mapped to the Xq27-28 region by Thomas and colleagues.[25] The gene was subsequently cloned and assigned the symbol *EMD*.[17,26,27] The encoded protein, emerin, is a 254 amino acid nuclear envelope protein found in both muscle as well as several other tissues.[28] A mutation in *EMD* leads to a complete cessation of emerin production and results in what is now called EDMD1.[17,27-29]

In 1999, Bonne et al. mapped the locus for EDMD2 to chromosome 1q11-q23, and the *LMNA* gene which lies within that interval was found to be the associated gene.[18,30] Mutations in *LMNA* result in disruption of the lamin A/C (LMNA) proteins, most typically with an autosomal dominant inheritance pattern, leading to EDMD2.[29] Missense mutations are frequently seen in EDMD2 as opposed to other laminopathies.[31] De novo mutations are common (76% in one study).[10] Autosomal recessive mutations in *LMNA* have also been associated with EDMD, and these have been assigned to the subtype EDMD3.[10,18,32,33]

Together, mutations in *LMNA* and *EMD* are the most common genetic causes of EDMD, accounting for around 40% of cases.[34,35]

The discovery of a pair of additional genes occurred in 2007, when the synaptic nuclear envelope genes *SYNE1* and *SYNE2*, encoding Nesprin-1 and Nesprin-2, respectively, were found to be associated with EDMD and subsequently assigned to the respective subtypes EDMD4 and EDMD5.[23] Nesprins contribute to nuclear envelope localization and structural integrity.[36,37]

In 2009, a fifth gene, *FHL1*, located on Xq26.3, was identified as causing an EDMD phenotype,[20] now known as EDMD6. The encoded protein, four and a half LIM domains 1 (FHL1), is unusual among EDMD-associated proteins in its cellular localization, which is at the sarcomere and sarcolemma rather than the nuclear envelope.[38,39]

Two years later, another EDMD gene, *TMEM43*, was discovered.[21,40] This gene encodes LUMA, another nuclear membrane protein that binds with both emerin and LMNA, and is involved with the structural organization of the nuclear membrane and maintenance of nuclear shape. Mutant LUMA can result in abnormally-shaped nuclei. LUMA may also play a role in the proper localization of emerin, and has an important interaction with SUN2 (see below), as there is evidence that mutant LUMAs may bind SUN2 to impede its nuclear localization and facilitate its destruction.[21] *TMEM43*-associated EDMD has been assigned to the subtype EDMD7.

TABLE 1 EDMD subtypes

Subtype	Gene	Protein	Inheritance	Age of onset	Muscle weakness	Contractures	Cardiac Involvement
1	*EMD*	Emerin	X-linked recessive	4–5 years	-Develops early in course -Usually slowly progressive -Often humeroperoneal distribution in early stages	-Typically the *initial* symptom -Most often involving the elbows, Achilles tendons, cervical spinal muscles	-Typically emerges *after* skeletal muscle weakness and contractures -Includes conduction defects, arrhythmias, *hypertrophic* cardiomyopathy
2	*LMNA*	LMNA	Autosomal Dominant	Usually 3–6 years, but rarely before age 3	-May be the *initial* symptom -Unpredictable severity, but frequently severe enough to result in loss of ambulation -Preferential involvement of biceps brachii may be a feature	Develop *after* muscle weakness	-Often the *initial* manifestation of disease -Includes conduction defects, arrhythmias, *dilated* cardiomyopathy
3	*LMNA*	LMNA	Autosomal Recessive	-Variable -Can range from 14 months to 24 years	-Variable pattern, including limb-girdle or diffuse muscle involvement -Variable severity, but can be severe enough to lead to immobilization	Present, with variable involvement of Achilles tendons, elbows, neck	-Variable -If present, can include supraventricular and/or ventricular arrhythmias
4	**SYNE1*	Nesprin-1	Autosomal Dominant	11 years old	Gradually progressive	Present	Variable
5	*SYNE2*	Nesprin-2	Autosomal Dominant	Childhood	Proximal muscle weakness	Usually *not* present	-Usually present -Includes arrhythmias, *dilated* cardiomyopathy, heart failure
6	*FHL1*	FHL1	X-linked recessive	Most range from 4 to 14 years, rarely in adulthood	-Variable pattern -Typically involves some combination of scapular, humeral, pelvic, peroneal, and/or axial regions -May have facial, bulbar, or respiratory involvement	-Usually present -May include rigid spine	-Usually present -Occurs *after* skeletal muscle manifestations -Includes conduction defects, arrhythmias, *hypertrophic* cardiomyopathy
7	*TMEM43*	LUMA	Autosomal Dominant	Adulthood	Proximal muscle weakness and atrophy	Not present in reported cases	Cardiac conduction defects
N/A	**SUN1*	SUN domain-containing protein 1	Autosomal Recessive	10 years old	Mild	Spine rigidity	None
N/A	***SUN2*	SUN domain-containing protein 2	NA	NA	NA	NA	NA
N/A	*TTN*	Titin	Autosomal Recessive	Infantile or childhood	-Limb-girdle pattern -Severe and progressive, leading to permanent loss of ambulation	Develop early in course	Variable

*Clinical features associated with a primary mutation of these genes causing an EDMD phenotype are based on a single reported case.
**Not well-established.

SUN1, encoded by a gene of the same name, was originally studied as a protein that accumulates in the setting of *LMNA* mutations,[41] but more recently variants in *SUN1* were reported to worsen cellular defects in the setting of primary EDMD mutations.[42] In 2014, a report showed both primary mutations and modifying variants for *SUN1* and *SUN2*, with potential primary mutations documented in one family for each gene.[43]

Mutations in *TTN* have been associated with various phenotypes, including distal tibial myopathy, limb-girdle muscular dystrophy (LGMD R10 titin-related, previously known as LGMD2J),[44,45] and dilated cardiomyopathy.[46,47] Recent reports indicate that the EDMD phenotype is also associated with *TTN* mutations, including recessive truncating mutations.[19,48] Some of these patients have been reported to have cardiomyopathy,[48] while others have not.[19]

5 | PATHOPHYSIOLOGY

EDMD typically results from a structural or functional defect of one or more proteins comprising the nuclear envelope (Figure 1), thus giving rise to the term "nuclear envelopathy".[49] A potential unifying disease mechanism may be loss of protein importation into the nucleus.[50,51] The nuclear envelope is composed of an inner and outer nuclear membrane as well as a nuclear lamina, which, collectively, form a structural framework for the nucleus. A deficiency or mutation affecting any of the proteins providing this framework can result in a loss of the structural integrity of the nucleus, which can be particularly problematic for tissues that are frequently under stress, including cardiac and skeletal muscle. Such proteins include emerin, LMNA, nesprin-1, nesprin-2, LUMA, SUN1, and SUN2, which are encoded by the *EMD*, *LMNA*, *SYNE1*, *SYNE2*, *TMEM43*, *SUN1*, and *SUN2* genes, respectively.[17,18,20-23,43,52-66] Specifically, the linker of nucleoskeleton-and-cytoskeleton (LINC) bridging complex located at the nuclear envelope is believed to tether the nucleo and cyto-skeletons, and is composed of emerin, LMNA, nesprin-1 and nesprin-2, SUN1 and SUN2.[35,67] An exception is FHL1, a protein encoded by the gene of the same name, which localizes to the sarcomere and the sarcolemma; at the former, it contributes to sarcomere assembly.[38,39]

Mutant forms of emerin show diminished transport to the inner nuclear membrane,[68] and have been associated with decreased nuclear invagination and abnormalities in nuclear Ca^{++} transients.[69]

In the case of *LMNA* mutations, and the associated effects on LMNA, there also appears to be an effect on myocytes and muscle regeneration, as these proteins are expressed in mature myocytes, skeletal muscle stem cells, and satellite cells.[70] Thus, mutations in *LMNA* can lead to impaired muscle regeneration, and ultimately a progressive muscular dystrophy.[71] There is evidence for apoptosis in the atrioventricular (AV) nodal cells and cardiac conduction defects in mice heterozygous for mutations in *LMNA*.[72]

A defect in some of these nuclear proteins can lead to mislocalization of one of its binding partners. For example, overexpression of mutant LUMA can disrupt the nuclear localization of emerin and SUN2, leading to downstream effects that are similar to those seen in emerin deficiency. Similarly, nesprin deficiency has been shown to result in altered localization of emerin and lamins,[73,74] while a deficiency in A-type lamins or overexpression of their mutant form can lead to mislocalization of lamina-associated polypeptide 2 (LAP2), Nup (Nucleoporin) 153, and lamin B.[21] Mutant forms of SUN1 show impaired interactions with both LMNA and emerin.[42]

6 | GENOTYPE–PHENOTYPE CORRELATIONS

The cellular localization of proteins associated with EDMD at the nuclear envelope is a distinct biological feature of this class of diseases, distinguishing EDMD from other categories of muscular dystrophies. However, our knowledge of how various defects at the nuclear envelope lead to widespread destruction of myofibers, merging into the classic clinical features as well as clinical features distinct for specific EDMD subtypes, is unclear. Some genotype–phenotype correlations have been observed that may help with diagnosis and patient counseling. Key phenotypic patterns distinct for each subtype are noted in Table 1. A list of known mutations is provided in Supplemental Table 1.

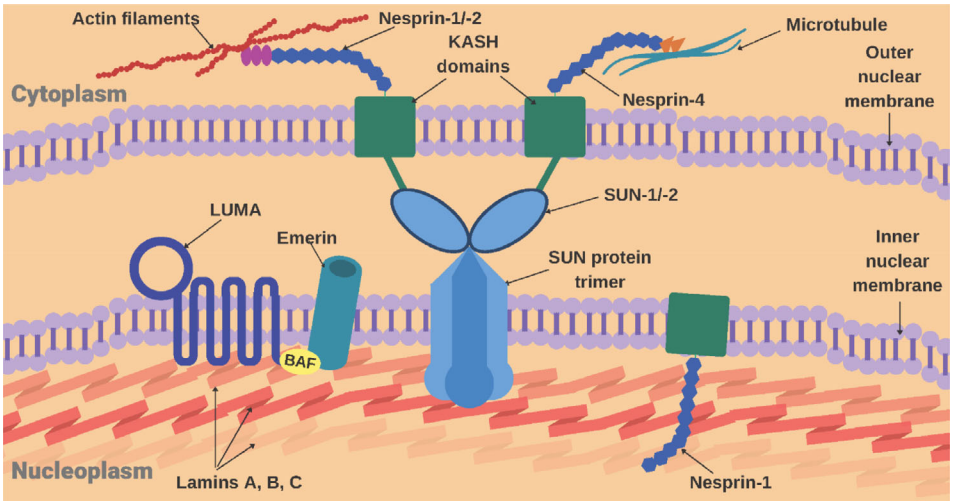

FIGURE 1 Schematic diagram of nuclear membrane indicating locations of proteins known to be associated with EDMD. Known protein interactions are shown (Courtesy Raghav Kalra)

6.1 | EDMD1 and EDMD2

There is significant overlap in the phenotypes resulting from mutations in the two most common genes associated with EDMD, *EMD* (EDMD1) and *LMNA* (EDMD2), suggesting a functional relationship between their protein products (emerin and LMNA, respectively).[29] However, there are also clear clinical distinctions between the two subtypes. On the whole, patients with EDMD2 have a more severe disease course than those with EDMD1, including more severe and progressive wasting of the biceps brachii.[10,75]. Hypertrophy of the quadriceps and extensor digitorum brevis musculature has also been reported in EDMD2, but not in EDMD1; this appears to be true hypertrophy rather than pseudohypertrophy as connective tissue infiltration is not prominent on muscle biopsy.[3,10] In EDMD1, skeletal muscle symptoms usually occur before cardiac involvement, while cardiac symptoms are more likely to be an initial manifestation in EDMD2. Additionally, as in most X-linked conditions, the full clinical spectrum of EDMD1, with skeletal muscle symptoms and cardiac involvement, is only seen in men. Female carriers do not typically present with muscle signs or symptoms, although approximately 20% of them may develop cardiac abnormalities, sometimes requiring treatments such as pacemaker implantation.[76] The cardiac complications of EDMD1 consist most prominently of AV conduction defects, including complete heart block, atrial paralysis, and atrial flutter.[77] Autopsy studies of EDMD1 showed gradual replacement of myocardium by fibrous and adipose tissue, most prominently in the atria and AV node, and affecting the ventricles at later stages.[78,79]

A notable distinguishing feature of EDMD2 is the much broader, more diverse spectrum of disease compared with that seen in EDMD1, to the point where several patients with *LMNA* mutations are assigned to non-EDMD disease categories. These alternate phenotypes include a congenital muscular dystrophy with a distinct "dropped head" syndrome caused by severe neck muscle weakness,[80] autosomal dominant dilated cardiomyopathy with conduction defect,[81] familial partial lipodystrophy (FPLD),[82,83] an autosomal recessive axonal Charcot–Marie-Tooth (CMT) neuropathy phenotype,[84] and Hutchinson-Gilford progeria.[85,86] Of note, a subtype of autosomal dominant LGMD, LGMD1B, was previously associated with *LMNA* mutations.[87] However, a recent reclassification of the LGMDs recognizes laminopathy as a separate category of muscle disease.[88]

The two subtypes also differ in that the severity of skeletal muscle symptoms in EDMD2 is less predictable than in EDMD1. In general, most patients with EDMD2 have a slowly progressive course during the first 3 decades of life with more rapid progression thereafter. However, in some cases, symptoms present very early (before the age of 3) and muscle weakness and contractures can progress more rapidly. Most patients experience difficulties walking and require ambulatory support, occasionally losing ambulation by the fourth decade.[10] In one study, three of five patients with the early and rapidly progressive phenotype became nonambulatory between the ages of 8 and 13 years.[10,89,90]

The phenotypic variability seen with *LMNA* mutations does not appear to be directly associated with the type of mutation, evidenced by the significant inconsistency in severity between families, as well as among members of the same family, with identical mutations.[10] For example, a single nucleotide deletion (c.959Tdel in exon 6) shared by members of the same family has been shown to lead to diverse clinical phenotypes, including pure dilated cardiomyopathy (DCM) with conduction defects, DCM with EDMD-like skeletal muscle abnormalities, and DCM with LGMD-like skeletal muscular dystrophy.[91]

7 | EDMD3

EDMD3, associated with an *LMNA* mutation but a recessive trait of inheritance, is much less common than its autosomal dominant counterpart. The first described case manifested a very severe muscle disease with onset at 14 months of age, characterized by marked contractures, prominent and progressive muscle weakness and atrophy, loss of ambulation, normal intellect, and no cardiac involvement.[33] However, four members of a family with EDMD3 did in fact develop cardiac sequelae, including supraventricular and/or ventricular arrhythmias.[92]

7.1 | EDMD4 and EDMD5

The clinical phenotypes related to *SYNE1* or *SYNE2* mutations can be quite variable, ranging from nearly asymptomatic hyperCKemia to a muscular dystrophy with severe DCM requiring heart transplantation.[37] Within this spectrum, most patients with EDMD4, associated with *SYNE1* mutations, manifest with gradually progressive muscle weakness and atrophy, joint contractures, and no significant cardiac involvement.[93,94] EDMD5, on the other hand, classically presents with muscle weakness and cardiac features (eg, arrhythmia, DCM, heart failure) but no notable contractures.[12]

8 | EDMD6

EDMD6 is caused by mutations in *FHL1*. Skeletal muscle hypertrophy has been observed for EDMD6; this appears to be a true hypertrophy rather than a pseudohypertrophy, although interstitial tissue was present on some muscle biopsies.[20] Other potential symptoms include vocal cord paresis with dysphonia, facial weakness, ptosis, dysphagia, and respiratory compromise. Female carriers may have cardiac defects, either in isolation or along with mild skeletal muscle involvement.[12,20,76] Mutations in *FHL1* have also been associated with other myopathies, including reducing body myopathy, scapuloperoneal myopathy, X-linked myopathy with postural muscle atrophy, and hypertrophic cardiomyopathy.[95,96]

9 | EDMD7

EDMD7, caused by a heterozygous mutation in *TMEM43*, is an autosomal dominant subtype that was initially described in 2011.[21] Two

Japanese individuals with this mutation were identified, both of whom manifested with adult-onset disease. Only one of these patients had a clearly defined clinical phenotype, characterized by proximal muscle weakness and atrophy, as well as cardiac involvement (atrial fibrillation and bradycardia, requiring pacemaker implantation).[21]

9.1 | EDMD due to SUN1 and SUN2 mutations

Only a single case each of primary mutation(s) causing EDMD has been described for *SUN1* and *SUN2*.[43] The putative *SUN1* patient had onset at age 10 of mild muscle weakness, spine rigidity, moderate serum CK elevations, and sparing of cardiac involvement early in the course. Detailed phenotype information is not available for the *SUN2* patient.

9.2 | EDMD due to TTN mutations

The EDMD phenotype associated with mutations in *TTN* has generally consisted of progressive limb-girdle weakness, early-onset contractures, and sparing of the facial, bulbar, and oculomotor musculature. As noted above, the presence of cardiomyopathy appears to be variable.[19,48] The disease process tends to begin in infancy or childhood, and ultimately results in permanent loss of ambulation between 13 and 36 years of age.[19]

10 | DIAGNOSTIC TESTING

Due to its rarity and the phenotypic overlap with other forms of muscular dystrophy such as congenital muscular dystrophy and LGMD, diagnosing EDMD may be challenging.[97] Clinical clues include neck extensor weakness, the classic pattern of contractures, a cardiomyopathy, bradyarrhythmias, and tachyarrhythmias.[97]

10.1 | Creatine kinase levels

In patients with skeletal muscle involvement, creatine kinase (CK) levels can range from normal to 15 times the upper limit of normal. In those with exclusive cardiac involvement, CK levels are generally normal.[10] Thus, elevated CK levels may be helpful in the diagnostic evaluation but normal CK levels do not exclude the diagnosis of EDMD.

10.2 | Electrodiagnosis

Overall, electromyography (EMG) findings in EDMD are similar to those seen in other myopathies, including low amplitude, short duration motor unit action potentials and early recruitment patterns.[98] However, the needle examination may also reveal "irregular" motor unit action potentials consisting of high amplitudes, increased polyphasia, and normal or long durations; this can cause confusion as these are generally regarded to be neurogenic features.[98] This range of EMG findings likely reflects the muscle fiber changes (such as hypertrophy and splitting) and overall fiber size variability (with both hypertrophy and atrophy) that can occur in a slowly progressive myopathy.[98-100] Abnormal spontaneous activity tends to be abundant[101,102] with myotonic discharges reported in one case,[102] although abnormal spontaneous activity is not universally present[103] or may be present only in selected muscles.[104]

No systematic studies have been published regarding the use of electrical impedance myography in the diagnostic evaluation of EDMD.

10.3 | Muscle imaging studies

Skeletal muscle imaging can be a helpful adjunctive tool to be used alongside other diagnostic modalities. A handful of articles indicate that distinct patterns of muscle involvement may be seen on muscle imaging studies in the setting of EDMD, sometimes suggesting specific disease subtypes.

A muscle MRI study of 22 patients with laminopathies, including 5 with EDMD2, showed fatty infiltration of the semimembranosus, long and short heads of the biceps femoris, adductor magnus, and vasti muscles, with relative sparing of the rectus femoris. Only one of these patients showed a similar pattern of fatty infiltration in the calf muscles.[105]

With regard to distinguishing EDMD from other muscle diseases, one study showed that muscle CT imaging can differentiate EDMD from collagen VI-related myopathies. This can be especially useful for clinicians, as both of these myopathies can present with significant contractures. In Bethlem or Ullrich myopathy, fatty infiltration was more likely to be seen in the rectus femoris, while posterior thigh muscles were more prominently infiltrated in EDMD. The patients with EDMD also displayed more severe involvement of the posterior calf muscles.[106]

Two studies examined the question of whether skeletal muscle imaging can distinguish among different subtypes of EDMD. One study examined patterns of muscle abnormalities in 42 patients with EDMD, 10 with EDMD1 and 32 with EDMD2. In both subtypes, paraspinal muscles, adductors, glutei, quadriceps, biceps femoris, semitendinosus, semimembranosus, soleus, and gastrocnemius were affected. The peroneal muscles were more frequently involved in patients with EDMD1 compared with EDMD2, suggesting that these muscles may help distinguish the two.[107] The second study suggests that patterns of gastrocnemius involvement may help distinguish patients with EDMD2 from other subtypes. Sixteen patients (9 with EDMD2, 4 with EDMD1, and 3 who appeared to have other subtypes) underwent MRI imaging of the leg muscles. All patients with EDMD2 had involvement of the medial gastrocnemius, with relative sparing of the lateral head. In contrast, none of the patients with EDMD1 or other subtypes showed this pattern.[108]

The imaging literature is thus intriguing but sparse to date. No systematic studies have been published regarding the use of

ultrasound in the diagnostic evaluation of EDMD. Further studies are needed to define fully the role of skeletal muscle imaging in the diagnostic evaluation of EDMD.

10.4 | Muscle pathology

Traditionally, muscle biopsy was used in the diagnostic evaluation of patients suspected of having EDMD. In those patients with skeletal muscle involvement, muscle biopsies typically demonstrate dystrophic or other myopathic features, including a variation in muscle fiber size, a marked increase in internal nuclei, and, occasionally, a mild increase in endomysial connective tissue and necrotic fibers.[10] Disruption of myofibrillar architecture has been reported, particularly in EDMD 1,[49] EDMD 2,[49] and EDMD 6.[109] Abnormally shaped nuclei can be seen as well.[21] However, these structural findings are not specific to EDMD, and thus muscle biopsy has limitations with regard to diagnosing EDMD.

Immunohistochemistry can yield useful diagnostic findings in some EDMD subtypes. In EDMD1, for example, the anti-emerin antibody shows absence of staining of the inner nuclear membrane.[27,28] This finding can be seen not only in muscle, but also in peripheral leukocytes, skin fibroblasts, and buccal cells.[110] In the skeletal muscle of female carriers, emerin protein levels are variable, ranging from <5% of normal to normal levels.[111]

Immunohistochemistry is not as useful in EDMD2, as staining for LMNA is normal in these patients. Of note, however, reduced LUMA staining has been demonstrated in these patients, in addition to those with EDMD7.[21]

In EDMD7 due to *TMEM43* mutations, there may be reduced nuclear staining not only of LUMA, but also of emerin and SUN2, presumably due to the interaction that LUMA has with these other nuclear membrane proteins.[21]

Distinct, clinically useful immunohistochemistry findings have not been established in the other EDMD subtypes.[112]

10.5 | Genetic Testing

The gold standard for establishing a subtype-specific diagnosis for EDMD is genetic testing. Genetic testing is commercially available for the genes associated with this condition: *EMD*, *LMNA*, *FHL1*, *SYNE1*, *SYNE2*, *TMEM43*, *SUN1*, *SUN2*, and *TTN*. Specific genes and associated phenotypes are described above. Most disease-focused genetic tests are currently designed as targeted sequence capture panels, based on next generation sequencing technology.[113,114] To capture slightly larger mutations such as exon-level deletions, the sequencing panel is often supplemented by specific deletion-duplication testing as well.[115] The older Sanger sequencing technology is currently used only for selected applications such as verification of a specific single nucleotide mutation. Exome sequencing will capture many pathogenic mutations also, but does not consistently detect larger deletions and duplications.

11 | MANAGEMENT

As there are currently no disease modifying therapies available for EDMD, management consists of appropriate clinical monitoring and symptomatic treatment. There are currently no systematic articles on the use of exercise, creatine, or coenzyme Q10 in EDMD. Given the complex, multi-organ system complications seen in EDMD, patients should ideally be monitored in either a multidisciplinary clinic or in a setting in which coordination and communication among different specialists is seamless.

11.1 | Genetic counseling

Genetic counseling should be offered to all patients and their families to help them better understand the recurrence risks for future children as well as potential risks for other individuals in the extended family. Genetic counselors can also guide families regarding family planning options to curtail the risk of recurrence, such as preimplantation genetic diagnosis. Genetic counseling also allows for carriers to pursue appropriate monitoring for potentially life-threatening cardiac complications.[89]

11.2 | Contractures

Physical therapy with an emphasis on stretching is the initial management strategy for this symptom; however, severe contractures may require surgical interventions, such as elongation of the Achilles tendon for ankle contractures. Procedures often need to be repeated to achieve a sustained benefit. However, the therapeutic effects of surgical procedures appear to last longer if the surgery is done after the adolescent growth spurt.[10,76,89] Overall, outcomes for ankle contractures seem to be the most favorable, while surgical treatment for elbow contractures is more complex and results are frequently not long-lasting. Surgical intervention for neck contractures, typically requiring internal fixation with rods, can be considered, although the potential risks (including loss of ambulation) should be weighed against the benefits before pursuing this option.

11.3 | Cardiac screening

All EDMD patients should have thorough cardiac evaluations at diagnosis, including a physical examination, electrocardiogram (ECG), echocardiogram, and Holter monitor.[116,117] For *LMNA* mutations in particular, the high penetrance, especially with regard to cardiac symptoms (nearly complete by the age of 60 years), and potential severity (initial manifestation can be sudden cardiac death [SCD]) must be appreciated; therefore, everyone who harbors these mutations requires a comprehensive cardiac assessment and ongoing monitoring.[118,119]

ECG abnormalities include low amplitude P waves with prolonged PR intervals. Tachyarrhythmias, such as atrial fibrillation, atrial flutter, as well as supraventricular and ventricular arrhythmias, are commonly seen, most likely due to progressive atrial, ventricular, and AV node fibrosis.[120] There is a high risk of progression of these electrocardiographic abnormalities to complete heart block and/or atrial standstill/paralysis[121-123]; the latter may be associated with junctional escape rhythms.[120]

Echocardiograms are particularly useful to screen for dilated or hypertrophic cardiomyopathy. The severity of cardiac complications does not correlate with the degree of skeletal muscle weakness. Signs of cardiac fibrosis are not typically seen early in the course of LMNA-associated EDMD, but subtle signs of ventricular dysfunction may be seen on echocardiogram and cardiac MRI.[124] Cardiac MRI is particularly useful for the detection of cardiac fibrosis; however, many children will require sedation for such studies.[124]

Female carriers of X-linked EDMD, either confirmed or those at risk, should be informed about the risk of cardiomyopathy and the symptoms of cardiac failure. In those without cardiac symptoms, cardiac evaluations should begin at diagnosis, with periodic monitoring thereafter. If any cardiac symptoms arise, a complete baseline cardiac evaluation, including a clinical examination, ECG, echocardiogram, and Holter monitor should be performed, followed by annual follow-up evaluations.[76]

11.4 | Cardiac pharmacotherapy

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are recommended for all patients with decreased ejection fractions (EFs).[117] Other medications commonly used to treat heart failure should also be considered in the appropriate clinical setting of progressive cardiac dysfunction; however, beta blockers should be used with caution due to the high prevalence of AV block.

11.5 | Pacemaker/implantable cardioverter defibrillator placement

National guidelines recommend pacemaker placement on EDMD patients with any degree of AV block, including first-degree block, due to known progression to complete AV block over time.[125,126] A newer approach, cardiac resynchronization therapy (CRT), also known as a biventricular pacemaker, is worth considering in certain situations due to the potential for ventricular dysfunction[116]; however, this device has not been studied extensively in EDMD. Cardiac complications of *LMNA* mutations have been examined in greater depth than those of *EMD* mutations; there is a 30% risk of sudden death in patients with the former. Several reports recommend placement of an implantable cardioverter defibrillator (ICD) concurrently with a pacemaker in the setting of *LMNA* mutations due to the high risk of fatal tachyarrhythmias.[15,127,128] Another source recommends ICD placement as soon as ventricular tachycardia is detected.[129]

11.6 | Antithromboembolic prophylaxis

The efficacy of antiplatelet or anticoagulation prophylaxis for atrial fibrillation and atrial flutter has not been studied in the context of EDMD; however, due to the risk of cerebral thromboembolism and myocardial infarction, prophylaxis is recommended barring contraindication.[11,129]

11.7 | Heart transplantation

Heart transplantations have been performed on patients with EDMD who experience progressive heart failure.[11,130-133] Thus, this therapeutic option should be considered under the appropriate circumstances in patients with EDMD.

11.8 | Respiratory management

Respiratory dysfunction is generally not a prominent component of EDMD, but can become a factor during the disease course; therefore, respiratory monitoring and periodic pulmonary function testing should be performed. In those patients with respiratory failure, respiratory support can be used, particularly at night, preferably with noninvasive devices.

11.9 | Investigational therapies

Investigational therapies for EDMD have been largely directed at the laminopathy subtype (EDMD2), due in part to the larger proportion of patients represented by this subtype, but also due to the availability of a robust mouse model for laminopathy[134]; in contrast, a mouse model that was developed for emerin deficiency has a more subtle phenotype.[135]

For laminopathies, several preclinical studies have shown promising results, some focusing primarily on the cardiac phenotype. One therapeutic strategy targets the activation of the mitogen-activated protein kinase (MAPK) pathway, particularly the extracellular-signal regulated kinase (ERK) branch.[136] Candidate therapies that inhibit MAPK/ERK activity have included PD98059,[137] selumetinib,[138] "molecule 8",[139] and the ACE inhibitor benazepril.[140] ARRY-371797 targets a different branch of the MAPK cascade, p38α, and prevented cardiac complications in a mouse model of laminopathy.[141] Another strategy used temsirolimus to inhibit the mammalian target of rapamycin (mTOR) pathway, which also appears to be involved in the pathogenesis of laminopathies.[142] Alleviation of oxidative stress in laminopathies has been achieved with N-acetyl cysteine.[143] Lastly, nicotinamide riboside, a natural precursor of nicotinamide adenine dinucleotide (NAD+), improved cardiac function in a laminopathy mouse model.[144] Among these candidates, ARRY-371797 is currently under investigation in a Phase 3 study focusing on patients with cardiomyopathy caused by *LMNA* mutations.[145]

As in many other hereditary neuromuscular diseases, genetically sophisticated treatments are under investigation for EDMD. A recent study showed that, at least in cell culture, antisense oligonucleotide-mediated skipping of exon 5 of LMNA can be successfully used, and, therefore, shows promise as a potential therapeutic approach for patients with dominant mutations in this exon.[146,147] Other molecular strategies that have a possible role in EDMD, such as adeno-associated virus (AAV)-based gene replacement and gene-editing techniques, have not been formally studied in this disease thus far.[146]

12 | CONFLICT OF INTEREST

Scott A. Heller has no conflicts of interest to disclose. Peter B. Kang has served as a consultant for AveXis and ChromaDex. He has served on an advisory board for Sarepta Therapeutics. He has received honoraria from Wiley for serving as an associate editor for *Muscle & Nerve* and from Wolters Kluwer for contributing material to UpToDate.

13 | ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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