Cardiac Involvement in Emery-Dreifuss Muscular Dystrophy and Related Management Strategies

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Summary

Emery-Dreifuss muscular dystrophy (EDMD) is a group of hereditary muscular dystrophy syndrome caused by deficiency of genes encoding nuclear envelope proteins. Patients having EDMD show the triad of muscle dystrophy, joint contracture, and cardiac disease. In almost all patients, cardiac involvement is prevalent and is the most severe aspect of EDMD. Cardiac disease is predominantly shown by conduction defects, atrial fibrillation/flutter, and atrial standstill. Sudden death and heart failure because of left ventricular dysfunction are important causes of mortality, particularly in those patients that have the LMNA mutation. Medical treatment of EDMD is limited to addressing symptoms and ambulation support; moreover, pacemaker implantation is necessary when there are severe conduction defects and bradycardia occurs. Note that automated defibrillation devices may be considered for those patients who have a high risk of sudden death, rate, or rhythm control. Also, anticoagulation should be initiated in those patients who have atrial fibrillation/flutter. Thus, for optimal management, a multidisciplinary approach is required.

Key words: Skeletal muscle disease, Arrhythmia

In the 1960s, two neurologists, Emery and Dreifuss, identified a unique group of hereditary muscle-joint-cardio syndrome.13 Compared with Duchenne and Becker muscular dystrophy (DMD and BMD), the clinical course for its treatment is benign.2-4 The syndrome was named as Emery-Dreifuss muscular dystrophy (EDMD), which is characterized by the following triad. First, a gradual progressive wasting and weakness in the scapulohumero-peroneal muscles, for which symptoms in most cases can appear in early childhood (< 15 years); however, the progress in muscle wasting is slow with loss of ambulation being reported only for exceptional cases. Second, early contractures of elbows, achilles tendons, and post-cervical muscles is observed. Third, cardiac involvement, which usually becomes evident when affected individuals reach the second or third decade of life, is predominantly seen in the form of atrial cardiomyopathy (conduction disturbance, atrial fibrillation/flutter, and atrial standstill); moreover, it is occasionally accompanied by left ventricular systolic dysfunction (Figure 1).5 Although a skeletal muscle disease such as EDMD is relatively benign compared to other muscular dystrophies, the cardiac involvement can be severe and is the most serious and important aspect of EDMD.60

Inheritance and Genes of EDMD

Although there is a defining group of clinical findings, the proteins and underlying gene defects responsible for EDMD are different. Among the affected families, different inheritance patterns have been observed (Table). EDMD was first recognized as a different form of muscular dystrophy from DMD/BMD in a family that had an X-linked recessive inheritance pattern.7,8 Defects in EMD (alternately known as STA), which encode nuclear envelope protein emerin, were identified to be the cause of disease (EDMD1).9

Similarly, another inheritance type of EDMD is autosomal dominant (AD-EDMD). Although AD-EDMD’s prevalence is unknown, it appears to be more common compared to X-linked EDMD (X-EDMD).10 For autosomal dominant EDMD (EDMD2), mutation in LMNA is the most common cause.7,9 LMNA encodes lamins A and C, both of which are components of nuclear envelope and located in the lamina. Moreover, autosomal recessive inheritance of LMNA has been described (EDMD3).11 Actually, in addition to EDMD, mutations in LMNA have been associated with various phenotypes, including limb-girdle muscular dystrophy type 1B, autosomal recessive axonal neuropathy (CMT2B), and Hutchinson-Gilford progeria syndrome. Furthermore, for dilated cardiomyopathy (DCM), LMNA is being listed as one of the most common
Figure 1. Clinical presentation and management strategy for EDMD.

Table. Genes and Inheritance for EDMD

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Location of protein</th>
<th>Inheritance pattern</th>
<th>Type of EDMD</th>
<th>Proportion of EDMD attributed to this gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDM (STA)</td>
<td>Emerin</td>
<td>Inner nuclear membrane (ubiquitously expressed) intercalated disc (cardiac muscle)</td>
<td>X-linked recessive</td>
<td>EDMD1</td>
<td>~61% of X-linked EDMD</td>
</tr>
<tr>
<td>LMNA</td>
<td>Lamins A/C</td>
<td>Inner nuclear membrane (ubiquitously expressed)</td>
<td>Autosomal dominant</td>
<td>EDMD2</td>
<td>~45% of AD-EDMD</td>
</tr>
<tr>
<td>SYNE1</td>
<td>Nesprin-1</td>
<td>Nuclear envelope (ubiquitously expressed)</td>
<td>Autosomal dominant</td>
<td>EDMD3</td>
<td>unknown for AR-EDMD</td>
</tr>
<tr>
<td>STNE2</td>
<td>Nesprin-2</td>
<td>Nuclear envelope (ubiquitously expressed)</td>
<td>Autosomal dominant</td>
<td>EDMD4</td>
<td>Rare</td>
</tr>
<tr>
<td>FHL1</td>
<td>FHL1A</td>
<td>Sarcomere I-band and Z-line, costamere (predominant in skeletal muscle and intermediate level in the heart)</td>
<td>X-linked recessive</td>
<td>EDMD5</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>FHL1B</td>
<td>Shuttling between the nucleus and the cytoplasm (brain, skeletal muscle, cardiac muscle)</td>
<td></td>
<td>EDMD6</td>
<td>~10% of X-linked EDMD</td>
</tr>
<tr>
<td></td>
<td>FHL1C</td>
<td>Nuclear (testis, skeletal muscle and cardiac muscle)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMEM43</td>
<td>LUMA</td>
<td>Nuclear envelope</td>
<td>Autosomal dominant</td>
<td>EDMD7</td>
<td>Rare</td>
</tr>
</tbody>
</table>

causative genes. Between the clinical phenotype and type or localization of mutations within the gene, there has been no clear correlation. Moreover, in the clinical expression of LMNA mutations, inter- and intra-familial variability exist, ranging from patients expressing EDMD’s full clinical picture to those characterized by only cardiac involvement. This suggests that modifier genes may also be involved during the course of EDMD.

Less common causative genes of EDMD are SYNE1, which encodes nesprin-1 (autosomal dominant EDMD4), and SYNE2, which encodes nesprin-2 (autosomal dominant EDMD5). Moreover, mutations in TMEM43 and FHL1 have been reported to be responsible for EDMD myopathy (EDMD7) and 10% of X-EDMD (EDMD 6). Except for FHL1, all these genes encode linkers of nucleoskeleton and cytoskeleton complex of the inner nuclear membrane.

Pathogenesis

LMNA and EMD are the two most common mutant genes that have been identified in EDMD. Lamins A/C and emerin are the nuclear membrane proteins and components of a proteinaceous meshwork (the nuclear lamina), which plays an important role for maintaining the architecture and serves as a scaffold for various other nuclear factors involved in DNA replication, chromatin organization, and transcription. Muscle biopsies for both affected X-EDMD and AD-EDMD patients revealed that myonuclei display an aberrant nuclear architecture, breakdown of fragile nuclear membrane, and chromatin reorganization. In addition to specific localization at the inner nuclear membrane, in heart, and cultured rat cardiomyopathy, emerin was found to localize on the intercalated disc, which may account for characteristic conduction defects in EDMD. However, although mouse models have been created and several working hypotheses have been developed, the pathogenic processes by
which mutations in genes encoding nuclear envelope proteins cause striated muscle abnormalities in EDMD remain unclear.

Noncardiac Findings

Typically, muscle weakness occurs during adolescence and leads to the onset of EDMD symptoms. The affected skeletal muscles follow a scapulohumeroperoneal distribution with the serum creatine kinase (CK) levels being elevated in the affected family members. Compared with other muscular dystrophy, skeletal muscle involvement of EDMD is benign. Moreover, muscle weakness has a mild to moderate tendency to progress over years for a majority of X-EDMD patients. Severe disease course leading to loss of ambulation has only been reported for exceptional cases. Patients having AD-EDMD are prone to have a more severe disease course. During a long-term longitudinal study that included 53 AD-EDMD patients, 17% of them had markedly elevated serum CK and lost the ability to walk unsupported early in life. Joint contracture is another common presentation after muscle weakness. Flexion contractures of elbows, shortening of achilles tendon and tightening of spinal extensor muscle lead to a lordotic stance, a waddling gait, and absence of the deep tendon reflexes for the affected adults.

Cardiac Involvement

In EDMD, cardiac involvement is quite common and usually is less evident after the third decade. The normal myocardium is gradually replaced by the fibrous and adipose tissue. It is a process that usually starts in the atria, often involves the atrioventricular node, and eventually affects the ventricles (Figure 2). Therefore, patients with EDMD may have atrial arrhythmias, conduction abnormalities, progressive dilation, and systolic failure. The severity of cardiac involvement does not correspond to the progression of muscular weakness. In patients who only have a mild skeletal muscle disorder, many suffer severe conduction defects and require implantation of pacemakers. Note that severe dilated cardiomyopathy has been reported for either EMD or LMNA mutation carriers. Moreover, sudden death can even happen for a few of them, which is probably attributable to malignant ventricular arrhythmia because it could not be prevented by implantation of pacemakers. Therefore, it is recommended that patients diagnosed with EDMD should be referred for cardiology evaluation.

Arrhythmia: In EDMD, conduction disturbances are the predominant cardiac involvement. The initial cardiac result is often accidental identification of a prolonged PR interval and reduced amplitude of P wave in the ECG (Figure 3). Furthermore, various degrees of heart block may occur.

Longitudinal studies related to EDMD suggested that atrial fibrillation and flutter, which can occur at various stages of EDMD, are the most frequent cardiac incidents. A prolonged P-wave duration and increased P-wave dispersion (measures differences between the short-
The longest P-wave durations recorded from differential leads can serve as a marker to identify the risk of paroxysmal atrial fibrillation.

In EDMD, electrical silence of atrium is typically observed, which is noticed by the P wave’s absence and the junctional or ventricular escape rhythm in the surface ECG. However, to verify true atrial silence, additional electrophysiological examination is required because sinus node dysfunction shares the same trace in the surface ECG. Although patients who develop third-degree heart blocks or atrial standstills are prone to suffer from symptoms such as fatigue and syncope, it is better tolerated by EDMD, which may be a result of patients adapting to a slower rhythm and significant decreased physical activity compared to their peers.

In EDMD patients who require a pacemaker for significant bradycardia, introduction of the dual-chamber (DDD) pacing mode is practically limited because a chronic AF is developed. In a longitudinal study, 18 patients with genetically confirmed X-linked or autosomal dominant EDMD were followed for a period ranging from 1 to 30 years. It was found that pacemakers were required by 10 of 18 patients (56%). In 11 of 18 patients (61%), atrial fibrillation/flutter developed, with atrial standstill subsequently occurring for 5 of 11 (45%) cases. During another retrospective study, 75% of those who received a DDD pacemaker had the mode changed to VVI. This was requested 3-7 years after the first procedure because of the development of chronic AF.

In the presence of either atrial standstill or atrial fibrillation/flutter, there is risk of cerebral thromboembolism because of emboli of cardiac origin. Note that a stroke can be the first clinical manifestation of EDMD in young adults and can be disabling. Therefore, for antithromboembolic prophylaxis, administration of anticoagulants is probably required in EDMD patients affected by atrial fibrillation/flutter or standstill.

Cardiomyopathy and heart failure: While atrial cardiomyopathy is the predominant cardiac effect, heart failure because of dilated cardiomyopathy (DCM) occurs only in a minority of patients having EDMD, which is different from other X-linked muscular dystrophy such as DMD/BMD. In longitudinal studies reported by Boriani, et al., heart failure requiring transplantation only occurred for 1 of 18 patients, whereas asymptomatic left ventricular dysfunction occurred only for 3 patients. To date, although > 200 different EMD mutations have been reported, only a few of them have been reported to be associated with DCM.

Sudden death: In EDMD, cardiac involvement is unpredictable and can be possibly life threatening, present with arrhythmias, and heart block-causing syncope or sudden death. For X-EDMD, syncope and sudden death may be the first symptom in rare cases. Sudden death in X-EDMD is primarily caused by complete heart block and can be possibly averted by pacemaker implantation. In longitudinal studies, no case of sudden death was observed at long-term follow-up after pacemaker implantation. However, pooled clinical data demonstrated that patients carrying mutation in LMNA gene had an unexpected high risk of premature sudden death. This risk was not related to heart failure and seems to have been caused by lathy ventricular tachyarrhythmia because it cannot be prevented by pacemaker therapy. It is unclear which clinical factors predicted the increased risk of sudden death. In a European cohort study, nonsustained ventricular tachycardia, left ventricular ejection fraction of < 45%, male sex, and non-missense mutations were identified to be risk factors for malignant ventricular arrhythmias.

Although female carriers of EMD mutation are not affected by musculoskeletal manifestation, they are at risk of cardiac arrhythmia and sudden death. Systemic studies on the natural history of cardiac involvement in EMD mutation carriers are not available; however, it seems appropriate to consider continuous ECG surveillance.

Diagnosis

EDMD-related diagnosis is based on a clinical trial...
of joint contractures, proximal muscle weakness, and cardiac involvement. For this diagnosis, some tests could be pursued. Electrocardiography and echocardiography can help detect rhythm abnormalities or cardiomyopathy. Note that CK levels may be elevated and computed tomography can reveal the muscle involved.

Usage of cardiac magnetic resonance (CMR) to evaluate patients with EDMD is limited because of the frequent requirement for pacemaker implantation. Moreover, although histological study confirmed that widespread atrial fibrosis underlies EDMD’s pathogenesis, a study that included 8 patients with AD-EDMD demonstrated absence of significant replacement fibrosis by late-gadolinium enhanced (LGR) CMR.40) This is different from other muscular dystrophy such as DMD/BMD, in which CMR is recommended for mutation carriers to detect myocardial fibrosis, which is also an early sign of myocardial injury even before systolic dysfunction occurs.41,42) Such differences may imply different pathogenesis of cardiac involvement in EDMD. Moreover, although LGE-CME is generally used for ventricular imaging, it is not being widely employed for atrial imaging because of technical challenges faced in achieving adequate image resolution in thin-walled atriums.43)

Emerin and lamin A/C are ubiquitously expressed at the nuclear membrane and can be assayed using exfoliative buccal cells, skin biopsy, or blood samples rather than muscle biopsy.44) Consider that ~90% of EMD mutations result in the complete absence of proteins by immunohistochemical staining, immunocytochemistry may be informative if defects are found in emerin.45) However, immunocytochemistry has not been proven to be useful for establishing a diagnosis with defects in lamin A/C because of the isoform’s redundancy.46) Thus, to establish the genetic diagnosis of EDMD, next-generation sequencing and gene panels are commonly used.

Management Strategies

At present, there is no cure for any of the subtypes of EDMD. All patients diagnosed with EDMD should be referred to cardiologists for a careful cardiological evaluation. Treatment strategy is largely based on addressing these symptoms. For patients with muscular dystrophy, gentle aerobic exercise combined with supervised submaximal strength training program as well as assistive devices that are adapted to the patient’s deficiencies should be prescribed to preserve mobility and function.29,47,48) For certain patients, tendon release and corrective spinal surgery may be considered to assist mobility and optimize quality of life.11 As heart diseases may be progressive, it is imperative to screen patients with EDMD for evidence of cardiac involvement. To decrease the risk of potentially life-threatening bradycardia, when symptomatic bradycardia or conduction disease is identified, it is essential to implant a cardiac pacemaker.5,33) However, a pacemaker does not eliminate the risk of sudden death, particularly in those carrying LMNA mutation. Considering the high risk of malignant ventricular arrhythmia, ICD may be considered when AD-EDMD patients require pacemakers.35) In the presence of either atrial standstill or atrial fibrillation/flutter, there is a risk of cerebral thromboembolism because of emboli of cardiac origin. Strokes can be the first clinical manifestation of EDMD in young adults and can be disabling; therefore, administration of anticoagulants for antithromboembolic prophylaxis is probably required in EDMD patients affected by atrial fibrillation/flutter or standstill.31) ACEIs, angiotensin receptor blocker (ARBs), and mineralocorticoid receptor antagonist are the cornerstone of neurohormonal modulation in heart failure and were shown to be effective for reduction of cardiovascular mortality in patients with heart failure and reduced LV function. Although there is a lack of evidence in this special circumstance, it may be reasonable to prescribe neurohormonal therapy to EDMD patients who have LV dysfunction. In those who do not have pacemaker, use of beta-adrenergic receptor blockers should be very cautious because of the concern of conduction defect and bradycardia.

Future Consideration and Unanswered Questions

Cardiac diseases are a major cause of morbidity and mortality in patients with EDMD. Currently, there is no cure and treatment strategy is largely based on addressing symptoms. Furthermore, EDMD is defined by a group of clinical manifestation. Although now it is known that it could be caused by mutations in a group of genes encoding nuclear envelope proteins, the mechanism and the genotype-phenotype relationship is unclear. Moreover, at present, there is only limited clinical data available from several longitudinal studies because it was not until 1960s that EDMD was separated from DMD/BMD and was recognized to be a unique syndrome. Because of its relatively lower incidence, maintaining the global database collected from multiple registry center is important for us to better understand EDMD and answer related questions. Furthermore, a multidisciplinary team, including a neurologist, a cardiologist, and an orthopedic spine surgeon is required for better management.

Disclosures

Conflicts of interest: None declared.

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