Neuromuscular Disease
Cardiac Manifestations and Sudden Death Risk

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KEYWORDS

• Muscular dystrophy • Arrhythmia • Conduction block • Sudden death • Pacemaker • Implantable cardioverter-defibrillator (ICD)

KEY POINTS

- Neuromuscular diseases, including the most common muscular dystrophies, affect the heart.
- Conduction system disease is common when the heart is involved.
- Pacemakers and defibrillators can be life-saving in selected patients.

INTRODUCTION AND GENERAL PRINCIPLES

Neurologic diseases often affect the heart and vascular system, and in many cases cardiovascular disease limits life expectancy in these patients. Many neuromuscular diseases (NMD) have been associated with myocardial impairment, significant arrhythmia, and sudden cardiac death (SCD). This review focuses on the muscular dystrophies exhibiting prominent cardiac manifestations, including myotonic dystrophy, Duchenne (DMD), Becker (BMD), Emery-Dreifuss (EDMD), and limb-girdle (LGMD) muscular dystrophies. In each disease, recognition and treatment of cardiac involvement can prolong and improve the quality of life.

Muscular dystrophies are a group of complex multisystem disorders that commonly and prominently affect striated muscle. Several NMDs significantly impact function of the heart and in some cases cardiac disease is the cause of mortality. The spectrum of cardiovascular manifestations of NMDs range from asymptomatic incidental findings to life-threatening arrhythmias. NMDs often produce conduction system disorders[1] with resulting bradyarrhythmias and tachyarrhythmias, cardiac dilation, hypertrophy, hypertrabeculation, and cardiomyopathy (Table 1).

The cardiovascular presentation and management of patients with an NMD is dependent on the specific type of disease. To optimize the care of these patients, a team of practitioners is required, often with the neurologist or internist taking the lead. The treatment of patients with NMDs is likely to require input from neurologists, pulmonary specialists, gastroenterologists, cardiologists, endocrinologists, orthopedists, and general surgeons.[2] The treatment of cardiac manifestations occurs in the context of other potentially life-limiting comorbidities. Often the main concern is the risk of a serious cardiac arrhythmia.[3]

MUSCULAR DYSTROPHIES, CARDIAC ARRHYTHMIAS, AND SUDDEN CARDIAC DEATH

The NMDs may be classified on the basis of their clinical features, molecular genetics, or pathophysiological consequences. In this group of

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Table 1
Cardiovascular complications of muscular dystrophies

Disease	DCM	Conduction Abnormality	Ventricular Arrhythmia	Atrial Arrhythmia
DM1	Rare	+++	+	++
DM2	Rare	+	+	+
DMD	++	+	+	+
BMD	++	+	+	+
FSHMD (AD)	Rare	Rare	Rare	Rare
EDMD	++	+++	Rare	Rare
KSS	+	+++	Rare	+

Abbreviations: AD, autosomal dominant; BMD, Becker muscular dystrophy; DCM, dilated cardiomyopathy; DMD, Duchenne muscular dystrophy; EDMD, Emery-Dreifuss muscular dystrophy; FSHMD, facioscapulohumeral muscular dystrophy; KSS, Kearns-Sayre Syndrome.

disorders are nucleotide repeat diseases (myotonic dystrophies, Friedrich ataxia), laminopathies, desminopathies, dystrophinopathies, sarcoglycanopathies, and mitochondrial disorders. The latter includes mitochondrial encephalomyopathy lactic acidosis and strokelike episodes, myoclonic epilepsy with ragged-red fibers, Kearns-Sayre syndrome, beta oxidation defects, primary carnitine deficiency, carnitine-palmitoyl-transferase deficiency, medium chain acyl CoA deficiency, and Barth syndrome.

Mutations in cytoskeletal proteins that link to the extracellular matrix with the structural muscle proteins are associated with skeletal and cardiac myopathies. For example, the dystrophin-glycoprotein membrane complex is composed of laminin-2, dystroglycans, sarcoglycans, syntrophins, and dystrophins. Mutations in dystrophin cause DMD and BMD, sarcoglycan mutations have been associated with LGMD, and mutations in lamins have been demonstrated in EDMD, LGMD, and dilated cardiomyopathy (DCM) (Table 2).

Myotonic Dystrophy

Myotonic dystrophy is the most common neuromuscular disorder presenting in adulthood and often affects the heart. These are multisystem disorders with protean manifestations, but 2 prominent features: myotonia and muscular dystrophy. The cardiac manifestations include conduction system disorders, atrial fibrillation (AF), and cardiomyopathy.[1,4,5]

Genetics and molecular pathogenesis

There are 2 major genetic types of myotonic dystrophy that are transmitted in autosomal dominant fashion. Dystrophia myotonia type 1 (DM1, Steiner disease, Online Mendelian Inheritance in Man [OMIM]#160900) is due to a triplet nucleotide (CTG) expansion in the 3' untranslated region *DMPK* and immediately upstream to the promoter region of the transcription factor SIX5 on chromosome 19. DM type 2 (DM2, proximal myotonic myopathy) is due to a tetranucleotide repeat (CCTG, OMIM #602668) in intron 1 of ZNF9 (CNBP) on chromosome 3.[6]

Genetic anticipation, which is an increase in the number of repeats in subsequent generations, was first described in DM1.[7] Short tandem repeats are found in healthy individuals (up to 37 in the DM1 locus in healthy individuals); however, when the expansion size gets too long, it becomes unstable and prone to further expansion because of wobble in the DNA replication machinery. The increase in expansion size leads to earlier onset and increased severity of disease in subsequent generations. In addition to vertical (through generations) instability in the nucleotide repeat expansion size, there is somatic instability with different tissues exhibiting differences in repeat expansion. Studies have shown that skeletal muscle and neurons harbor more repeats than white blood cells (WBCs).[8] Somatic instability has a prominent role in disease severity and age of onset of symptoms in DM1. This instability is a heritable trait suggesting a role for transcriptional disease modifiers that may be therapeutic targets.[9] There is a maternal transmission bias, particularly in congenital forms of DM1, disproportionately affected infants are born to mothers with disease or repeat expansions in the premutation (38–50 CTG) range. The mechanism of the gender bias is unknown; speculation includes unstable repeat expansion during oogenesis or failure of sperm with large repeat expansions to survive.

There is a general association between disease onset and severity with repeat expansion size; however, it is not an exact correlation and it is

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