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Arrhythmias in the Muscular Dystrophies

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Synopsis

In patients with muscular dystrophies, cardiac involvement leading to cardiomyopathy and arrhythmias occur with variable prevalence mirroring the phenotypic variability seen among and within the various hereditary myopathies. These patients are at risk for development for bradyarrhythmias and tachyarrhythmias including sudden cardiac death. Knowledge of the incidence of arrhythmias and predictors of sudden death in the various hereditary myopathies can help guide screening and appropriate management of these patients, thereby improving survival. The non-cardiac manifestations can lead to delayed recognition of symptoms (limited mobility and respiratory weakness masking cardiac manifestations), affect decision to implant prophylactic device (quantity vs. quality of life) and once a decision is made to proceed with device implant, increase peri-procedural respiratory and anesthesia-related complications.

Keywords

Muscular dystrophy; arrhythmia; sudden cardiac death; Genetics; Pacemaker; Implantable cardioverter-defibrillator

Introduction

The muscular dystrophies are a group of inherited disorders affecting skeletal muscle diseases and to variable degree, cardiac muscle, with manifestations including heart failure, conduction disease and heart block, atrial and ventricular arrhythmias, and sudden death. With improved multidisciplinary care and increase in the life span, the prevalence of later-onset cardiac involvement is increasingly being recognized. Electrophysiologists are typically part of the care team involved in the management of patients with muscular

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dystrophies due to associated atrial and ventricular arrhythmias and the risk of sudden cardiac death. The aim of this article is to familiarize the reader with the nature, prevalence, treatment and outcome of arrhythmias in muscular dystrophies and present the recent advances in this arena.

Classification of the muscular dystrophies is shown in Box 1.

Box 1

Classification of the muscular dystrophies

- Duchenne and Becker muscular dystrophies
- Type 1 and type 2 Myotonic dystrophies
- Emery-Dreifuss muscular dystrophies and associated disorders
- Limb-girdle muscular dystrophies
- Facioscapulohumeral muscular dystrophy

Duchenne and Becker Muscular Dystrophies

Genetics and cardiac pathology

Duchenne and Becker muscular dystrophy are X-linked recessive disorders caused by mutations in the dystrophin gene. Abnormalities in dystrophin and in dystrophin-associated glycoproteins underlie the degeneration of cardiac and skeletal muscle in several inherited myopathies including X-linked dilated cardiomyopathy. In Duchenne muscular dystrophy (DMD), dystrophin is nearly absent whereas in Becker muscular dystrophy (BMD), dystrophin is present but reduced in size or amount. This leads to the characteristic rapidly progressive skeletal muscle disease in DMD and the more benign course in BMD. Cardiac involvement is seen in both disorders, and the severity is not correlated with the severity of skeletal muscle involvement. Mutations in specific domains of the large dystrophin gene are associated with a higher risk for cardiomyopathy[1]. Most patients with DMD develop a cardiomyopathy with a predilection for involvement in the inferobasal and lateral left ventricle. In BMD, cardiac disease can even be more pronounced than skeletal muscle weakness[2].

Electrocardiography

The majority of DMD patients have an abnormal ECG with the classically described electrocardiographic pattern of distinctive tall R waves and increased R/S amplitude in V1[3] and deep narrow Q waves in the left precordial leads possibly related to the posterolateral left ventricular involvement [4]. Other common findings include short PR interval and right ventricular hypertrophy. No association between the presence of a dilated cardiomyopathy and electrocardiographic abnormalities has been established [5]. Left bundle branch block may be seen in patients with a dilated cardiomyopathy.

Arrhythmias

In patients with DMD, persistent or labile sinus tachycardia is the most common arrhythmia recognized. Atrial arrhythmias including atrial fibrillation and atrial flutter can occur, often in the setting of respiratory dysfunction with cor pulmonale and in those with a dilated cardiomyopathy. Abnormalities in atrioventricular conduction have been observed with both short and prolonged PR intervals recognized. Ventricular arrhythmias occur on monitoring in 30%, primarily as ventricular premature beats. Complex ventricular arrhythmias have been reported, more commonly in patients with severe skeletal muscle disease. The presence of systolic dysfunction was a powerful predictor of mortality but ECG abnormalities, late potentials or ventricular arrhythmias were not predictive [6]. In a cohort of DMD patients, QT dispersion was an independent risk factor for the occurrence of VT.[7]. Sudden death occurs in DMD, typically in patients with end-stage muscular disease. Whether the sudden death is caused by arrhythmias is unclear. Several follow-up studies have shown a correlation between sudden death and the presence of complex ventricular arrhythmias [8]. The presence of ventricular arrhythmias was not a predictor for all-cause mortality. Arrhythmia manifestations in BMD typically relate to the severity of the associated structural cardiomyopathy. Distal conduction system diseases with complete heart block and bundle branch reentry ventricular tachycardia have been observed.

Screening, Treatment and Prognosis

Clinical care guidelines recommend screening echocardiography at diagnosis or by the age 6 of years and subsequently every 2 years until the age of 10 and annually thereafter in boys with DMD [9]. In patients with DMD, with improvement in respiratory support, age at death has increased so that the majority of patients survive into their 30s[10]. Decision of implantation of an implantable cardioverter-defibrillator (ICD) should be considered individually based on patient status and wishes. Advanced heart failure therapy, including primary prevention ICDs, is appropriately considered in patients with cardiomyopathy. Patients with BMD often develop cardiac complications and death from congestive heart failure and arrhythmias is estimated to occur in up to 50% of cases [9]. BMD has a high heart transplantation rate in the first year after diagnosis of cardiomyopathy [11]. Female carriers of DMD and BMD do not develop a cardiomyopathy during childhood but can occur later in life. Screening echocardiography should be done in adults or with symptoms.

Myotonic Dystrophies

Genetics and cardiac pathology

The myotonic dystrophies are autosomal dominant disorders characterized by myotonia (delayed muscle relaxation after contraction), weakness and atrophy of skeletal muscles and systemic manifestations. Two distinct mutations are responsible for the myotonic dystrophies. In myotonic dystrophy type 1, the mutation is an amplified trinucleotide cytosine-thymine-guanine (CTG) repeat found on chromosome 19 [12]. It is typical for the CTG repeat to expand as it is passed from parents to offspring, resulting in the characteristic worsening clinical manifestations in subsequent generations termed anticipation [13]. Myotonic dystrophy type 2, also called proximal myotonic myopathy, has generally less severe skeletal muscle and cardiac involvement than in type 1 and is a tetranucleotide,

CCTG repeat expansion occurs on chromosome 3. A recent study suggests that cardiac pathology in both myotonic dystrophy type 1 and 2 is related to gap junction (GJA1) and calcium channel (CACNA1C) protein overexpression[14]. Cardiac pathology involves degeneration, fibrosis, and fatty infiltration preferentially targeting the specialized conduction tissue including the sinus node, atrioventricular node, and His-Purkinje system. Degenerative changes are observed in working atrial and ventricular tissue but only rarely progress to a symptomatic dilated cardiomyopathy. The primary cardiac manifestations of the myotonic dystrophies are arrhythmias and are age-dependent and although the pathology appears similar in types 1 and 2, type 1 typically has earlier and more severe cardiac involvement. No correlation has been established between spontaneous ventricular arrhythmia and the severity of muscular weakness [15], the size of CTG repetition[16], premature ventricular contractions on 24-hour ambulatory ECG [15], the presence of late ventricular potentials [17], or ventricular arrhythmia induced by programmed ventricular stimulation[15].

Electrocardiography

A majority of adult patients with myotonic dystrophy type 1 exhibit electrocardiographic abnormalities. In a large, unselected middle- aged U.S. myotonic population; abnormal electrocardiographic patterns were seen in 65% of the patients [18]. Abnormalities included first-degree atrioventricular block in 42%, right bundle branch block in 3%, left bundle branch block in 4%, and nonspecific intraventricular conduction delay in 12%. Q waves not associated with a known myocardial infarction are common. Conduction disease worsens with advancing age Electrocardiographic abnormalities are less common in myotonic dystrophy type 2, occurring in approximately 20% of middle-aged patients.

Arrhythmias

Patients with myotonic dystrophy type 1 demonstrate a wide range of arrhythmias. At cardiac electrophysiological study, the most commonly abnormality found is a prolonged His-ventricular (H-V) interval. Conduction system disease can progress to symptomatic atrioventricular block and necessitate pacemaker implantation. The prevalence of permanent cardiac pacing in patients with myotonic dystrophy type 1 varies widely between studies. Updated practice guidelines have recognized that asymptomatic conduction abnormalities in neuromuscular diseases such as myotonic dystrophy may warrant special consideration for pacing[19].

Atrial arrhythmias, primarily fibrillation and flutter, are common. Patients with atrial arrhythmias are often asymptomatic possibly because of a controlled ventricular response from concomitant conduction disease.

Up to one third of individuals with myotonic dystrophy type 1 die suddenly. The mechanisms leading to sudden death are not clear, but are believed to be related primarily to arrhythmia. Asystole, owing to complete heart block without an appropriate escape rhythm, has been considered a probable cause. Sudden death can occur despite pacemakers implicating ventricular arrhythmias.

Patients with myotonic dystrophy type 1 are at risk for bundle branch reentry tachycardia because of associated conduction disease. Arrhythmias are observed in patients with myotonic dystrophy type 2, but are less frequent and occur later in life. Patients with myotonic dystrophy type 1 are at a higher risk of sudden death if they have significant ECG conduction disease [18]. Up to 18% of patients with type 1 myotonic dystrophy and minor depolarization/repolarization at baseline present with Brugada ECG pattern after drug challenge[20]. This was not related to the occurrence of significant conduction disturbances or ventricular arrhythmias during follow-up. It may be useful to rule out Brugada ECG pattern myotonic patients with the idea of avoiding some medications (i.e., use of Class 1 drugs for decreasing myotonia in myotonic dystrophy) or in cases of unexplained syncope/palpitations. However, the role of drug challenge to unmask Brugada for purpose of risk stratification in these patients is uncertain. The prospective long-term multicenter RAMYD study is a large-scale clinical trial designed to investigate the course of cardiac disease in DM1 patients and to explore the value of noninvasive and invasive findings to predict the occurrence of sudden death, resuscitated cardiac arrest, ventricular fibrillation, sustained ventricular tachycardia, severe sinus node dysfunction or grade II or III atrioventricular block [21].

Emery-Dreifuss Muscular Dystrophies

Genetics and cardiac pathology

The X linked recessive Emery-Dreifuss muscular dystrophy (EDMD) disorder (EDMD1) is characterized by mild skeletal involvement but life threatening cardiac and arrhythmia manifestations. Mutations in the genes coding for the nuclear membrane protein Emerin [22] result in fibrotic replacement of cardiac muscle and conduction tissue and thought to be responsible for the abnormalities in impulse generation and conduction that are commonly encountered in this group. The autosomal dominant EDMD (EDMD2) and a rare autosomal-recessive form of EDMD are caused by a mutation in the lamin A/C gene. Lamin A/C mutations can cause several other phenotypes, including limb-girdle muscular dystrophy type 1B (LGMD1B). Because of the different implications of laminopathy and emerinopathy both from the point of view of management and genetic counseling, a precise diagnosis should be sought in all patients.

Arrhythmias

First degree atrioventricular block and atrial arrhythmias are among the early manifestations. Classically atrial standstill with junctional bradycardia may be seen. Pacing support is recommended once conduction disease is evident. Heart failure and ventricular arrhythmias seem to occur only in a minority of patient, but the risk may increase as patients with a pacemaker may survive longer [23]. In both XLEDMD and ADEDMD atrial fibrillation/flutter and atrial standstill occur frequently, even after pacemaker implantation, and this carries a substantial risk of thromboembolic events, including ischemic stroke and initiation of therapeutic anticoagulation should be strongly considered

Screening, treatment and prognosis

Sudden death is the most common cause of death and can be highly unpredictable [24]. Risk factors for sudden death and appropriate ICD therapy include nonsustained ventricular tachycardia, left ventricular ejection fraction less than 45%, male sex, and lamin A or C non-missense mutations [25]. Female carriers of X-linked Emery-Dreifuss muscular dystrophy are at risk of cardiac conduction disease and sudden death, typically occurring late in life. Affected patients should be monitored carefully for electrocardiographic conduction abnormalities and left ventricular dysfunction. Ambulatory monitoring can reveal asymptomatic ventricular arrhythmias that have prognostic significance. An ICD rather than bradycardia protection alone is the preferred prophylactic therapy.

Limb-Girdle Muscular Dystrophies

Genetics and cardiac pathology

The muscular dystrophies with a limb–shoulder and pelvic girdle distribution of weakness and heterogeneous inheritance are called limb-girdle muscular dystrophies (LGMD - autosomal recessive -subtypes 2A to 2P, dominant -subtypes 1A to 1H, sporadic inheritance). Genes involved include those encoding dystrophin-associated glycoproteins, sarcomeric proteins, sarcolemma proteins, nuclear membrane proteins, and cellular enzymes.

Arrhythmias

Occurrence of arrhythmias related to specific genetic subtypes with high incidence seen in subtype 1B (mutation in the gene coding Lamin-A/C akin to Emery-Dreifuss muscular dystrophy).

Screening, treatment and prognosis

The recommendations for cardiac surveillance in this group depend very much on the particular type of LGMD. LGMD2I patients are at risk of cardiomyopathy and should be assessed as for DMD/BMD. The severity of cardiomyopathy may be out of proportion to that of skeletal muscle involvement. Present perception is that the incidence of tachy- or brady-arrhythmias in sarcoglycanopathies (LGMD 2C, 2D, 2E, and 2F) is low but this issue is not fully resolved. Some arrhythmia surveillance with Holter ECG or similar recordings is still justified. In LGMD 1B, risk factors for sudden death and appropriate ICD therapy include non-sustained ventricular tachycardia, left ventricular ejection fraction less than 45%, male sex, and Lamin A or C non-missense mutations [26]. Prophylactic implantation of an ICD rather than pacemaker is recommended in patients with limb-girdle muscular dystrophy subtype 1B when cardiac conduction disease is present [27].

Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral muscular dystrophy is the third most common muscular dystrophy after the Duchenne and myotonic types inherited in an autosomal dominant fashion characterized by slowly progressive muscle weakness. Since significant clinical cardiac involvement is rather rare in this form of muscular dystrophy, specific monitoring or

treatment recommendations are not well defined. Discussion of arrhythmia related symptoms and yearly electrocardiograms have been recommended.

Conclusion

With progress in the respiratory management of patients and prolonged survival of muscular dystrophy patients, heart failure and arrhythmias contribute to a larger extent to premature death. Recognition of cardiac involvement requires active investigation and remains challenging since typical signs and symptoms of cardiac dysfunction may not be present and progression is unpredictable. Upon initial evaluation, the diagnostic workup for arrhythmias would depend on the type of muscular dystrophy, age of the patient, disease stage, symptoms attributable to cardiac involvement and previous cardiac events. Careful monitoring of cardiac symptoms, and surveillance using electrocardiogram, Holter and event monitoring and or implantable loop recorder as dictated by clinical situation would allow timely management of bradycardia and tachycardia rhythm disturbances with device implantation and can potentially improve prognosis. Because this clinical need frequently arises late in the life of many muscular dystrophy patients, kyphoscoliosis, and muscle wasting might complicate device implantation. Experimental therapy for muscular dystrophies include cell-based therapies are also being explored for the regeneration of skeletal and cardiac muscle; skeletal muscle stem cells, when delivered systemically, might also home to cardiac muscle and result in muscle regeneration, which would alter electrical properties and cardiac function.

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Key Points

- Duchenne, Becker, and limb-girdle 2C-2F and 2I muscular dystrophies frequently develop a dilated cardiomyopathy, which precedes arrhythmia and conduction disturbance. Decision for prophylactic device implant is based on current guidelines for non-ischemic cardiomyopathy.
- Myotonic dystrophy, Emery-Dreifuss and limb-girdle type 1B muscular dystrophies are variably associated with cardiomyopathy and frequently develop conduction disturbances requiring pacing. Recent studies support use of cardioverter defibrillator rather than pacemakers.
- Fascioscapulohumeral is a common muscular dystrophy, only variably associated with cardiac involvement and arrhythmias.