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Review

Myotonic dystrophy and the heart: A systematic review of evaluation and management

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ABSTRACT

Myotonic dystrophy (MD) is a multisystem, autosomal dominant disorder best known for its skeletal muscle manifestations. Cardiac manifestations arise as a result of myocardial fatty infiltration, degeneration and fibrosis and present most commonly as arrhythmias or conduction disturbances. Guidelines regarding the optimal cardiac management of patients with MD are lacking. The present article provides a summary of the pathophysiology of cardiac problems in patients with MD and provides a practical approach to contemporary cardiac monitoring and management of these patients with a focus on the prevention of complications related to conduction disturbances and arrhythmias.

Methods: A literature search was performed using PubMed and Medline. The keywords used in the search included "myotonic dystrophy", "cardiac manifestations", "heart", "arrhythmia", "pacemaker" and "defibrillator", all terms were used in combination. In addition, "myotonic dystrophy" was searched in conjunction with "electrophysiology", "electrocardiogram", "echocardiograph", "signal averaged electrocardiograph", "magnetic resonance imaging" and "exercise stress testing". The titles of all the articles revealed by the search were screened for relevance. The abstracts of relevant titles were read and those articles which concerned the cardiac manifestations of myotonic dystrophy or the investigation and management of cardiac manifestations underwent a full manuscript review.

1. Introduction

Myotonic dystrophy (MD) is the most common inherited muscular dystrophy in adulthood with an incidence of 1 in 8000 [1]. Cardiac involvement is an important cause of premature death in these patients. Despite being relatively common, guidelines regarding optimal investigation, management and follow-up of cardiac issues, particularly in asymptomatic patients with MD are lacking. The aim of this study was to comprehensively review the literature regarding cardiac manifestations of MD and to propose an evidence-based protocol for investigation, management and follow-up of asymptomatic cardiac abnormalities with a focus on arrhythmic manifestations.

2. Pathophysiology

2.1. Genetic basis

The genetic basis of MD type 1 is a mutational expansion of cytosine, thymine, guanine (CTG) repeats in the 3′ untranslated region of the Myotonic Dystrophy Protein Kinase (MDPK) gene, a serine–threonine protein kinase on chromosome 19. A normal allele contains between 5 and 35 repeats whereas alleles in patients with MD type 1 may contain up to 4000 CTG repeats. The disease is transmitted across generations in an autosomal dominant fashion with incomplete penetrance, variable phenotypic expression and somatic mosaicism. Anticipation, where increased number of CTG repeats in subsequent generations is associated with earlier onset and increased severity of disease, is well recognised [2] and more marked with maternal transmission. The disease is divided into two types based on both genetic and clinical criteria, with type 1 being most common. MD 2 arises from mutations affecting a CCTG repeat on the zinc finger protein 9 gene on chromosome 3 and is milder than MD 1. This review will focus on MD type 1.

The CTG expansion size may increase with age, vary between tissues and correlate with the extent and rate of progression of cardiac disease [2–5], however, the correlation with clinical cardiac disease has not

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been universally observed [6–10]. There appears to be a more consistent association between cardiac conduction disturbances and age, duration of neurological disease and male gender than with CTG repeats [11]. Peripheral blood leucocyte DNA can underestimate CTG repeat lengths relative to skeletal and cardiac muscle DNA where expansion lengths may be up to 13-fold longer [1,12,13].

2.2. Mechanisms

The expanded CTG repeat sequences are transcribed into RNA but not translated, accumulating in the nucleus and disrupting the splicing of pre-messenger RNA into mature mRNA of a number of genes including those coding for the muscle specific chloride channel and also the insulin receptor [14]. Impairment of intercellular impulse propagation has been implicated in the cardiac conduction manifestations of the disease. MDPK in the myocardium is localised to the intercalated discs and animal models of MDPK deficiency demonstrate compromised conduction at the level of the atrioventricular node and of the His–Purkinje system [1].

2.3. Clinical presentation and pathology

In its classical form, most patients with MD type 1 present in the 2nd to 4th decades with skeletal myotonia, progressive muscle weakness and wasting. Axial, distal limb and facial muscles are predominantly affected. However, MD is a multi-system disorder involving the endocrine (diabetes, thyroid disease, hypogonadism), central nervous (cognitive impairment, attention disorders), respiratory (hypoventilation, obstructive sleep apnoea), gastrointestinal (dysphagia, gall stones, pseudo bowel obstruction), ophthalmologic (cataracts), genitourinary (micturition disturbances) and cardiovascular systems [15,16].

Muscle biopsy is not necessary for the diagnosis but histopathological changes include a marked increased variation in fibre diameter, severely atrophic fibres with pyknotic nuclei, minimal contractile elements and ring fibres with a sarcolemmal band of cytoplasm with or without a sarcoplasmic mass [17]. A variety of nonspecific histopathological findings have been reported in MD-related cardiac disease. These include interstitial fibrosis, degeneration, fatty infiltration, myocyte hypertrophy, variation in myocyte size and focal myocarditis with lymphocyte infiltration. In addition, muscle fibre re-arrangement and focal vacuolar myocyte degeneration may be seen [13,18–22]. Early and extensive involvement of the conduction system is a common finding.

Patients with MD have higher tumour necrosis factor alpha (TNF-α) levels than do healthy controls and the level of TNF-α correlates with disease severity, CTG repeat expansion size, PR intervals and the presence of ventricular late potentials on the signal averaged ECG [23]. It remains unclear whether TNF-α plays a role in the pathogenesis of MD or is a marker of disease activity [23]. Higher levels of TNF-α have also been found in Becker and Duchenne muscular dystrophy and may prove to be a useful marker of disease stage and activity if correlations with clinical endpoints are demonstrated.

3. Clinical cardiac manifestations

The early stages of cardiac involvement in MD are typically clinically silent. Phenotypic variability results in a wide spectrum of clinical manifestations even amongst members of the same family [24].

3.1. Cardiac contributions to reduced life expectancy

Patients with MD have a reduced life expectancy with a mean age at death of 53 years and a mortality rate approximately 7.3 times that of an age-matched general population [25]. The cause of death is respiratory failure in approximately 40% of cases and cardiac in origin in approximately 30% of cases [25–27]. Predictors of mortality include older age, male gender and ECG conduction defects [28], while conduction disease on a surface ECG and a past history of atrial fibrillation are predictors of sudden death [29].

3.2. Arrhythmias

The most common cardiac manifestations of MD are arrhythmic. Cardiac fibrosis and fatty infiltration most commonly affect the His–Purkinje system but may also involve the sino-atrial and atrioventricular (AV) nodes. These provide a substrate for conduction block, ectopic activity and re-entrant arrhythmias and can present with palpitations, syncope and sudden cardiac death (0.56% per year of follow-up) [24,30]. A meta-analysis of 1828 patients with MD revealed 1st degree AV block in 28.2%, QTc >440 ms in 22.0%, QRS >120 ms in 19.9%, frequent premature ventricular contractions in 14.6%, atrial fibrillation/flutter in 5.0%, right bundle branch block in 4.4%, left bundle branch block in 5.7% and non-sustained ventricular tachycardia in 4.1% [30].

Traditionally bradyarrhythmias, with asystole or bradycardia-induced ventricular fibrillation [15], were thought to be the main mechanisms of sudden death in patients with MD. Primary ventricular tachyarrhythmias are increasingly recognised in these patients, possibly responsible for a proportion of cases of sudden death in patients with pacemakers [1,31,32]. Male patients with MD are at higher risk of both atrial and ventricular tachyarrhythmias as well as bradyarrhythmias, as are those patients who are older and who have greater muscular disability and symptoms [33]. There is also a positive association between age and the need for device implantation.

3.2.1. Tachyarrhythmia

The most common tachyarrhythmias are atrial (atrial tachycardia, atrial fibrillation and atrial flutter) and the predisposition is probably due to regions of atrial fibrosis [15]. Monomorphic and polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) due to classic re-entry circuits are promoted by fibrotic foci, fatty infiltration as well as triggered activity [31,34]. Delayed conduction in the His–Purkinje system also predisposes patients to bundle branch re-entry tachycardia, an unusual form of ventricular tachycardia due to re-entry occurring exclusively within the bundle branch system [1,35]. This requires specific pacing and pharmacological protocols during EP study for identification and may be cured by catheter ablation of either the right or left bundle [31,35]. Ventricular tachycardia arising from the left anterior or posterior fascicles has also been reported [36] as has QT interval prolongation and torsade de pointes [37]. Sudden cardiac death may result from ventricular tachycardia or ventricular fibrillation [9].

3.2.2. Sleep and arrhythmia in MD

While most cases of arrhythmias are not precipitated by sleep apnoea, episodes of apnoea and desaturation can be a precipitant for both atrial and ventricular tachyarrhythmias [38]. There have been studies suggesting reduction in arrhythmias with the use of continuous positive airway pressure in the obstructive sleep apnoea syndrome [39].

Bradycardia during sleep is well described in the healthy population, particularly in younger patients and athletes. Holter monitors during sleep may identify higher grades of conduction disturbance than an ECG while awake. Specifying the degree of conduction disturbance during sleep at which intervention is required in this population is challenging.

3.3. Left ventricular dysfunction and other structural abnormalities

MD may also be associated with left ventricular hypertrophy (LVH), left ventricular (LV) dilatation, left ventricular systolic dysfunction and mitral valve prolapse [40,41]. Similar to other patient populations, left ventricular impairment and heart failure impacts on patient prognosis.