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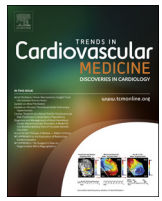

Diagnosis and management of adult hereditary cardio-neuromuscular disorders: A model for the multidisciplinary care of complex genetic disorders

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ABSTRACT

Genetic disorders that disrupt the structure and function of the cardiovascular system and the peripheral nervous system are common enough to be encountered in routine cardiovascular practice. Although often these patients are diagnosed in childhood and come to the cardiologist fully characterized, some patients with hereditary neuromuscular disease may not manifest until adulthood and will present initially to the adult cardiologist for an evaluation of an abnormal ECG, unexplained syncope, LV hypertrophy, and or a dilated cardiomyopathy of unknown cause. Cardiologists are often ill-equipped to manage these patients due to lack of training and exposure as well as the complete absence of practice guidelines to aid in the diagnosis and management of these disorders. Here, we review three key neuromuscular diseases that affect the cardiovascular system in adults (myotonic dystrophy type 1, Friedreich ataxia, and Emery–Dreifuss muscular dystrophy), with an emphasis on their clinical presentation, genetic and molecular pathogenesis, and recent important research on medical and interventional treatments. We also advocate the development of interdisciplinary cardio-neuromuscular clinics to optimize the care for these patients.

Key words: Neuromuscular disease, Heart failure, Heart disease, Multidisciplinary care.

Introduction

Cardiologists and neurologists have long been involved in the collaborative care of patients with diseases that primarily affect the central nervous system and secondarily affect the cardiovascular system (e.g., intracerebral hemorrhage leading to myocardial damage), as well as primary cardiovascular disorders that lead secondarily to neurological impairments (e.g., embolic stroke from atrial fibrillation). Certain genetic disorders disrupt the function of both the heart and elements of the peripheral nervous system, such as skeletal muscle and nerve. Although neurologists are frequently exposed to patients with muscular dystrophy, mitochondrial disorders, muscle channelopathies, and lysosomal storage diseases, cardiologists have virtually no training or exposure to patients with neuromuscular diseases that affect cardiac muscle and the cardiac conduction system. In the case of neuromuscular disorders that are diagnosed in childhood by

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pediatric neurologists, these patients are often referred to cardiologists with an established diagnosis (e.g., Duchenne muscular dystrophy). However, many patients with neuromuscular disease do not present until adulthood, and some may initially present to an adult cardiologist because of asymptomatic left ventricular (LV) dysfunction or elevated biomarkers reflecting myocardial dysfunction (e.g., creatine kinase, troponin, and B-type natriuretic peptides). In this instance, cardiologists are ill-equipped to manage these patients because of lack of training/exposure and the absence of practice guidelines to aid in the diagnosis and management of these patients.

Many careful reviews have been published regarding cardiomyopathy associated with Duchenne and Becker muscular dystrophy [1–3]. Rather than reduplicate these reviews, here we focus on three other relatively common disorders that may present undiagnosed in adult patients who are referred to cardiologists because of an abnormal ECG, unexplained syncope, and/or left ventricular (LV) hypertrophy or LV dysfunction of unknown cause. These hereditary neuromuscular diseases may manifest in adolescence or adulthood with progressive muscle weakness or ataxia, and include myotonic dystrophy type 1 (DM1), Friedreich ataxia (FRDA), and Emery–Dreifuss muscular dystrophy (EDMD). All of these disorders may lead to cardiomyopathy and/or conduction system disease that may shorten life span and worsen quality of life, and were chosen to illustrate the genetic and phenotypic breadth of this unique disease category. The intent of this review is to provide the cardiologist with a working knowledge of these diseases as well as propose an algorithm for the evaluation and management of these patients and, where possible, emphasize an evidence-based approach to their cardiovascular management wherever possible. Finally, we propose a new model of care for these complex disorders by outlining a multidisciplinary clinic approach such as is being developed at Washington University School of Medicine.

Myotonic dystrophy type 1

Genetics and pathogenesis

Myotonic dystrophy type 1 (DM1) is the most common adult-onset hereditary muscle disease, with an estimated prevalence of around 1:9000 [4], and is among the most common lethal monogenic disorders in persons of European descent. DM1 is an autosomal dominantly inherited, slowly progressive, multisystem disease with a striking range of clinical severity, from severe prenatal disease to asymptomatic disease diagnosed in the sixth decade or later. The classic and most common form has symptomatic onset in the second or third decade. The cause of DM1 is unstable expansion of a CTG trinucleotide repeat sequence within the 3′ untranslated region of the *DMPK* gene encoding the myotonic dystrophy kinase protein. Whereas the normal *DMPK* allele contains 5–35 CTG repeats, this allele is expanded to hundreds or even thousands of copies in DM1 patients. A CTG repeat number of 50 or greater is sufficient for the diagnosis of DM1, but expansions can be as high as 4000 repeats in congenital DM1. There is a modest positive correlation between repeat size and disease severity and age of onset. As with other trinucleotide repeat diseases, intergenerational expansions of the repeat number are common and may lead to more severe phenotypes in successive generations.

DM1 is the prototype of the new category of RNA-mediated disease [5]. The molecular pathways for DM1 have not been completely elucidated at the time of this writing. The pathologically expanded *DMPK* mRNA transcript has a polyadenylated (CUG) tail that confers a toxic gain-of-function via sequestration of RNA-binding proteins and interference with the alternative splicing of numerous other genes, as well as RNA processing [6]. However, muscle wasting cannot be explained by the splicing changes that have been identified thus far. Unlike other forms of muscular dystrophy (e.g., Duchenne muscular dystrophy), muscle wasting in DM1 is characterized by muscle atrophy rather than of muscle necrosis suggesting defects in muscle protein metabolism.

Neuromuscular manifestations

DM1 is named for what is usually its most prominent feature, a progressive myopathy characterized by both distal and facial weakness and muscle atrophy (Table) (http://neuromuscular.wustl.edu/musdist/pe-eom.html), along with myotonia, a peculiar slowness of muscle relaxation following activation (e.g., slow release of grip after turning a doorknob). This phenomenon results from the aberrant splicing of the muscle-specific chloride channel gene *CLCN1*, resulting in a hyperexcitable sarcolemma [7]. Patients classically have a narrow, droopy-appearing face with temporal wasting, frontal balding, and ptosis, and often go on to develop dysarthria, dysphagia, and diaphragmatic weakness in addition to early foot drop and hand weakness. Other important systemic features of DM1, though often variable and incomplete in their appearance, include intellectual impairment, early cataracts,

Table – Summary of neurologic manifestations of cardio-neuromuscular disorders that can present in adulthood.

	Age of onset (years)	Localization of neurologic disease	Major neurologic symptoms	Other noncardiac features
Myotonic dystrophy type 1	Infancy—late life	Muscle	Weakness (distal and facial) and myotonia	Cataracts and diabetes
Friedreich ataxia	10–20	Spinal cord, cerebellum, and peripheral nerve	Limb and truncal ataxia	Diabetes and scoliosis
Emery–Dreifuss muscular dystrophy	10–40	Muscle	Weakness (proximal)	Joint contractures, especially at elbows and ankles