MANAGEMENT OF CARDIAC COMPLICATIONS IN NEUROMUSCULAR DISEASE

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In the past decade major advances have been made in understanding the genetics and pathophysiology of neuromuscular diseases. These advances have led to many diseases being subtyped and distinguished from similar disorders. Most of our understanding of cardiovascular complications of the neuromuscular diseases comes from observational data. This understanding is complicated by older studies that grouped together disorders now known to be distinct. One example of this is found in literature dealing with facioscapulohumeral muscular dystrophy and its association with atrial paralysis. These studies probably included patients with Emery-Dreifuss muscular dystrophy, and it is these patients who manifest the atrial paralysis, not the patients with facioscapulohumeral muscular dystrophy. These limitations can impair our understanding of neuromuscular diseases.

Neuromuscular diseases vary widely in their degree of cardiac involvement. In many cases, such as Charcot-Marie-Tooth disease, cardiac involvement is minimal and rarely causes significant morbidity. In others, such as Duchenne muscular dystrophy, cardiac involvement is a source of considerable morbidity and mortality. Since so little is known about the mechanisms involved in most neuromuscular diseases, this article will concentrate on detailing the observed abnormalities for the major neuromuscular diseases and will not speculate on the mechanisms involved.

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Management of cardiac complications of neuromuscular diseases is based primarily on experiences from other diseases. When available, experiences with the specific diseases will be discussed.

DUCHENNE MUSCULAR DYSTROPHY

Of the muscular dystrophies, Duchenne muscular dystrophy (DMD) is the one most commonly associated with significant cardiac involvement. Death may result from heart failure in 40% to 50% of patients[28, 53, 81] or from sudden death in about 5% of patients.[169] Abnormalities of the heart may be detected by numerous methodologies, appearing first on the electrocardiogram, followed by chest radiography and echocardiography.[8] Physical examination is notable for the point of maximal impulse palpable at the left sternal border due to the marked reduction in anteroposterior chest dimension common in DMD. A mitral regurgitation murmur frequently can be auscultated and is thought to be secondary to dystrophic involvement of the posterobasal left ventricular wall and adjoining posterolateral papillary muscle leading to dysfunction of the mitral valve.[134] A loud pulmonic component of the second heart sound suggests pulmonary hypertension in patients with respiratory failure.

Nearly all patients over the age of 13 demonstrate abnormalities of the electrocardiogram (Table 1).[5, 35, 47, 58, 61, 81, 82, 91, 93, 136, 143] Q waves in the lateral leads are the first abnormalities to appear, followed by elevated ST segments and poor R wave progression, then increased R/S ratio, and finally resting tachycardia and conduction defects. Electrocardiographic abnormalities have been demonstrated to be predictive for cardiomyopathic death with the major determinants being: R wave in lead V1 less than 0.6 mV; R wave in lead V5 less than 1.1 mV; R wave in lead V6 less than 1.0 mV; abnormal T waves in leads II, III, AVF, V5, and V6; cardiac conduction disturbances; premature ventricular contraction; and sinus tachycardia.[1] Sinus tachycardia may be gradual in onset due to progressive cardiomyopathy, or sudden in onset and labile, suggesting autonomic disturbance or direct involvement of the sinus node by the dystrophic process.[98, 119] Short PR intervals have been reported in varying frequency, with some authors reporting a 50% prevalence (Table 1).[119, 120] Neither delta waves nor reciprocating tachycardias have been reported suggesting that bypass tracts are not the cause of the short PR intervals.

Necropsy studies[135] and thallium-201 SPECT imaging have demonstrated left ventricular lateral and posterior wall defects that may explain the lateral Q waves[151] and the increased R/S ratio in V1 seen on electrocardiography.[168] Localized posterior wall fibrosis was found to be peculiar to DMD and was not found in other types of muscular dystrophy. Pulmonary hypertension leading to right ventricular enlargement also is known to effect prominent R waves in V1 and has been demonstrated in patients with DMD.[174] Improvement of the pulmonary hypertension

Table 1. PERCENTAGE OF PATIENTS WITH ELECTROCARDIOGRAPHIC ABNORMALITIES ASSOCIATED WITH NEUROMUSCULAR DISEASES

	Duchenne			Myotonic			Limb-Girdle			SMA			
ECG Abnormality	Age <13	Age >13	Becker	C-MD	NC-MD	Pelvi	ARMDC	ADLO	FSHMD	SMA-II	SMA-III	HMSN	FA
Q Waves	52	74	60	31	36	23	16	18	25	16	23	32	13
Abnormal axis	4	16	7	19	17	4	11	0	3			2	40
Right ventricular hypertrophy			20	20	4	19	11	36	6			0	
Left ventricular hypertrophy			40	7	16	15	22	9	12	33	0	2	16
Left atrial abnormality			13	0	0	8	22	9	16	25	7	9	
Increased R/S ratio V1	7	45	20	6	11	27	24	46	25			11	20
Resting tachycardia	4	47	0	13	3	4	6	18	0	17	7	0	6
Resting bradycardia						23	11	0	38				
Prolonged QRS	4	9	13	19	37	4	17	36	13			2	
Prolonged QTc	78	61											
Short PR interval	2	7	0	0	1	0	0	9	0			2	24
Prolonged PR interval		4	0	0	31	33	0	6	0			9	
Intranodal conduction defects	9	31	15	56	57	15	37	18	22	17	7	4	
Any ECG abnormality	67	91	73	81	75	73	62	73	72	75	57	30	92
Number studied (n)	(46)	(45)	(15)	(16)	(75)	(29)	(19)	(11)	(32)	(12)	(14)	(47)	(78)

C-MD = Congenital Myotonic Dystrophy
NC-MD = Non-Congenital Myotonic Dystrophy
Pelvi = Pelvifemoral Myotonic Dystrophy
FSHMD = Facioscapulohumeral Muscular Dystrophy
SMA = Spinal Muscular Atrophy
ARMDC = Autosomal Recessive Muscular Dystrophy of Childhood
ADLO = Autosomal Dominant Late Onset
HMSN = Hereditary Motor Sensory Neuropathy
FA = Friedreich's Ataxia
From references 2, 23, 24, 65, 70, 92, 93, 94

with supplemental oxygen suggests the pulmonary hypertension is due to pulmonary artery constriction secondary to hypoxia.

Dystrophin is the muscle protein affected in DMD. This protein also has been isolated in cardiac muscle and on the membrane surface of cardiac Purkinje fibers.[13] Involvement of Purkinje fibers likely contributes to the known infranodal conduction disturbances (Table 1), but whether this contributes to the occurrence of sudden death remains speculative. Ventricular ectopy and sudden death are known complications of cardiomyopathy, and this association is the most likely explanation for the observed cases of sudden death. Corroboration of this speculation has come from studies reporting high-grade ventricular ectopy in DMD associated with left ventricular dysfunction[105] and sudden death.[29]

Cardiomyopathy is a common clinical problem in older patients.[15, 53, 81, 82] Preclinical involvement has been seen in 25% of patients under 6 years of age, increasing to over 50% by age 10. Clinically evident cardiomyopathy is usually first noted after age 10 and is apparent in nearly all patients over age 18.[109, 110] Development of cardiomyopathy is a predictor of poor prognosis, with death occurring within a few years.[108] Controversy exists over whether the severity of cardiomyopathy correlates with extent of skeletal muscle disease.[5, 150] More severe cardiomyopathy has been demonstrated in patients with deletion of the dystrophin gene than in patients without gene deletion.[66]

Echocardiography has been used extensively to follow the development of cardiomyopathy and to attempt to predict prognosis in patients with DMD. The onset of systolic dysfunction is associated with a poor short-term prognosis.[108] Stress echocardiography with angiotensin A has demonstrated inducible posterior wall defects in six of nine patients with normal resting echocardiograms.[3] Latent systolic dysfunction can be detected by abnormalities in the time interval between the onset of electrical activity and the onset of ventricular ejection (preejection period) and in the duration of ventricular ejection (left ventricular ejection period). In cardiomyopathy, the preejection period increases and the left ventricular ejection period decreases. Abnormalities in these intervals can be detected before age 10 and increase rapidly during the teen years.[5, 28, 90]

Diastolic dysfunction generally is thought to predate systolic dysfunction in most forms of cardiomyopathy. Studies of diastolic dysfunction utilizing mitral valve blood flow have not shown abnormalities in peak atrial velocity or time-velocity integrals. The lack of abnormal diastolic mitral valve blood flow suggests that either diastolic dysfunction does not exist in DMD or that there may be disease in the atria equal to that in the ventricle, leading to normalization of mitral valve diastolic blood flow.

Clinical cardiomyopathy has also been found in 17% of 210 women with a close relationship to patients with DMD. Forty-three percent of the women studied showed minor signs of myocardial involvement.[34] Significant cardiomyopathy was associated with serum creatine kinase greater than 80 U/L or a genetic risk higher than 70%. In another report, cardiomyopathy was described in two women with elevated serum creatine kinase and absent dystrophin in many fibers of myocardial biopsy specimens.[99] These authors suggest that, because 30% of cases of DMD are due to spontaneous mutations, cardiomyopathies in young men without obvious clinical causes should be investigated for dystrophin abnormalities, and cardiomyopathies in young women should raise suspicion for a carrier state of DMD. This may be reasonable in young patients with no other obvious cause for their cardiomyopathies, but overzealous and indiscriminate analysis for DMD of all patients with cardiomyopathy is not warranted. One study of 27 cardiomyopathy patients average aged 50 years and no skeletal muscle weakness, dystrophin gene analysis showed no defects.[97]

Duchenne muscular dystrophy also has been associated with clinically silent mitral valve prolapse in patients with severe skeletal muscle disease.[127] These patients did not have significant cardiomyopathies that might explain the valve abnormality. Some investigators speculate that the thoracic cage abnormalities associated with severe DMD might be involved in developing mitral valve prolapse. This theory is supported by the association of mitral valve prolapse with decreased anteroposterior chest wall diameters in individuals without muscular dystrophy.

There have been no large randomized treatment trials of cardiomyopathy in DMD, but there have been several small studies suggesting that therapy is possible. Atrial natriuretic peptide (ANP) is a protein produced by the myocardium and is elevated in heart failure. In patients with DMD, ANP is markedly elevated (35.5 pg/mL vs 19.3 for normals)[71] and correlates with increased cardiothoracic ratio on chest radiography, abnormal preejection and ejection periods on echocardiography, but not with respiratory failure. A subsequent study demonstrated a decrease in ANP and clinical improvement in nine patients treated with digitalis, beta blockers, and angiotensin converting enzyme inhibitors.[100] Another study reported clinical improvement in three patients treated initially with angiotensin converting enzyme inhibitors and subsequently with beta blockers.[62] Another study reported improved physical well-being in 12 patients treated with coenzyme Q10 in a double-blind and open crossover trial.[50]

Supplemental oxygen has been demonstrated to improve survival in patients with cor pulmonale,[107, 111] but no studies have been performed in patients with neuromuscular diseases to date. Most investigators believe that the benefit from oxygen therapy demonstrated in patients with COPD also applies to patients with reversible pulmonary hypertension from other etiologies. Because the pulmonary artery hypertension in DMD has been demonstrated to reverse with supplemental oxygen, this therapy may be beneficial in patients with respiratory failure and increased R/S ratios in lead V1 of the electrocardiogram suggestive of pulmonary hypertension.

Duchenne muscular dystrophy is characterized by significant cardiomyopathy leading to death in approximately 40% of patients. Electrocardiography is the first test to become abnormal in these patients

HEREDITARY MOTOR AND SENSORY NEUROPATHY

Charcot-Marie-Tooth (CMT), a disease of the lower legs, rarely is associated with cardiac abnormalities. Approximately one third of patients will have an abnormality of the electrocardiogram. Abnormal Q waves are the most common abnormalities[23] but do not correlate with postmortem abnormalities.

There have been case reports of dilated cardiomyopathy,[137, 172] but studies of patients and their families have not shown an increased prevalence in patients with CMT.[44] Similarly, conduction system disease has been reported,[17, 83, 84, 124, 129] but a prospective study of patients demonstrated a prevalence of conduction defects similar to the general population.[63]

Central autonomic control of heart rate and blood pressure is normal in patients with CMT.[59] Peripheral abnormalities in sweating and vascular reaction to cold stress have been documented, consistent with demyelination of peripheral nerves.[59, 164] Possibly because of these peripheral nerve abnormalities, some patients complain of cold intolerance. Protection against cold exposure is warranted in these patients.

FRIEDREICH'S ATAXIA

Cardiac involvement has been found in more than 90% of subjects from a homogeneous group of patients with Friedreich's ataxia (FA) who meet strict neurologic and genetic criteria for the disease.[31] With longitudinal follow-up the incidence may be as high as a 100%. The locus of the genetic defect has been mapped to chromosome 9.[26] This *Frataxin* gene, encoding a protein with unknown function, has a number of mutations with expansions of a GAA repeat in the first intron.[21] Hypertrophic cardiomyopathy increases in prevalence with the size of the GAA expansion.[39] The GAA expansion may become an important prognosticator, since complications of cardiomyopathy are a frequent cause of death in FA.

Heart disease in FA is often silent, since the neuromuscular disorder curtails physical activity. Symptoms normally are seen only with advanced involvement of the myocardium, and cardiomyopathy is a frequent cause of death.[7, 54] There appears to be no relationship between the degree of neurologic deficit and the degree of cardiac involvement.[31] Electrocardiography and echocardiography may assist in identifying the presence, severity, and type of heart disease.

The electrocardiogram is a sensitive (92%) but nonspecific means of diagnosing myocardial involvement in Friedreich's ataxia, with most patients demonstrating an electrocardiographic abnormality (Table 1).[2, 31] Right axis deviation and Q waves in inferior leads are believed to represent areas of regional ventricular dystrophy, which if sufficiently widespread may result in systolic dysfunction.[31, 54]

Cardiomyopathy occurs in FA in two forms.[31] The hypertrophic form is more common, and in one echocardiographic screening study was characterized by concentric left ventricular hypertrophy in 11% of patients and asymmetric left ventricular hypertrophy in 9% of patients. Ventricular dysrhythmias are common in most forms of hypertrophic cardiomyopathy but have not been reported in FA. The septal cellular disarray, the histologic hallmark of genetic hypertrophic cardiomyopathy, has not been identified on autopsy in FA.[19, 64, 118] This may explain why potentially malignant arrhythmias are rare in FA. Patients with FA were found to have a distinct correlation of left ventricular hypertrophy with diastolic filling abnormalities when compared with normal age-matched subjects.[106] Diastolic dysfunction is common in other forms of cardiomyopathy.

The dilated form of cardiomyopathy presents with predominant electrocardiographic abnormalities and global left ventricular systolic dysfunction. On screening echocardiography, dilated cardiomyopathy was detected in 9% of patients.[31] Serial echocardiography in a small cohort of patients showed no change in the pattern of echo abnormalities over time and no progression of hypertrophic cardiomyopathy to dystrophic cardiomyopathy.[2] This suggests that the hypertrophic and dilated cardiomyopathies are distinct genetic entities. Atrial fibrillation/flutter and ventricular arrhythmias are common features of the dilated cardiomyopathy.[31, 177] Mitral valve prolapse was seen in 14% of patients.

Symptomatic dilated cardiomyopathy should be treated with angiotensin converting enzyme inhibitors, digitalis, and diuretics according to generally accepted guidelines. Asymptomatic patients with ejection fractions less than 35% should be started on therapy with angiotensin converting enzyme inhibitors as well.[144] Atrial dysrhythmias need to be anticoagulated to prevent stroke[121, 142, 155] or converted to normal sinus rhythm. There is considerable debate as to which of these two management strategies is better, but we favor cardioversion and maintenance of sinus rhythm with low-dose amiodarone (200 mg/day).[40] Symptomatic ventricular dysrhythmias also should be treated. Possible therapies include antiarrhythmic therapy or implantable cardiac defibrillators, and the help of a cardiac electrophysiologist should be sought. There are currently few data to suggest that this course of action improves survival, but it can decrease symptoms and improve the quality of life. Hypertrophic cardiomyopathy can be treated with beta blockers or calcium channel blockers if symptomatic dynamic outflow tract obstruction is present. This therapy can decrease the gradient and attenuate symptoms.[27, 87]

GENERAL MANAGEMENT PRINCIPLES

Management of the cardiac complications requires specific knowledge about the type of complications commonly seen in the various