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DIAGNOSIS AND MANAGEMENT OF DUCHENNE MUSCULAR DYSTROPHY (DMD) CARDIOMYOPATHY

Pediatrics

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ABSTRACT

Duchenne muscular dystrophy (DMD) is a severe X-linked neuromuscular disorder that affects one in 3500 live born males. The total absence of Dystrophin protein due to mutation that disrupt the reading frame of DMD gene and about 95% of cases are due to gene deletions and duplications. The life expectancy in patients with DMD is early 20s. The leading cause of morbidity and mortality in DMD patient is cardiomyopathy associated heart failure. To improve life expectancy together with enhancing quality of life in DMD patients, cardiac care is important with goal of slowing the onset and progression of heart failure complications. The purpose of this article is to update with recent non-invasive diagnostic modalities and managements (supportive as well as emerging therapies like new Food and Drug Administration (FDA) approved heart failure medication, Heart transplantation, mechanical circulatory support with left ventricular assist devices (LVADs) and implantable cardioverter defibrillator (ICD) and most recent FDA approved medication that directly target absence of dystrophin in DMD) because with increased DMD cases worldwide and with supportive management, patients are living longer which increasing the cardiomyopathy cases overall leading to need of early diagnosis and management concern for DMD patients as they age. Therefore, there is need for more knowledge and clinical researches/trials to improve the diagnosis and management in DMD cardiomyopathy.**SUMMARY:** There is increased prevalence of DMD patients in Indian population, because of increased overall cases and longer life expectancy, i.e. increased DMD cardiomyopathy. Therefore, there is need for early diagnosis and treatment of cardiomyopathy leading to heart failure. Early diagnosis with higher sensitive and specific test is required like CMRI than echocardiography which leads to early start of management to increase the quality of life in DMD patients.

KEYWORDS

Duchenne Muscular Dystrophy, Neuromuscular disorder, Dystrophin protein, Cardiomyopathy, Heart failure, Non-invasive diagnosis, Heart transplantation, Mechanical circulatory support, Left ventricular assist devices, Implantable cardioverter defibrillator, Cardiac magnetic resonance imaging, Echocardiography.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a fatal X-lined neuromuscular disorder characterized by progressive muscular deterioration, caused by loss-of-function mutations in the DMD gene coding for dystrophin protein, a cytoskeletal protein that stabilizes the plasma membrane of muscle fibers. DMD is characterized by muscle weakness usually begins around the age of two years in boys and worsens quickly. Typically, muscle loss occurs first in the thighs and pelvis followed by arms. This can result in trouble standing up. Most are unable to walk by the age of 12 years. Affected muscles may appear hypertrophied due to increased fat content. Females with a single copy of the defective gene may show mild symptoms. The life expectancy in patients with DMD is early 20s. Previously, most common cause of death was respiratory failure but with improved respiratory support, cardiomyopathy leading to heart failure is important cause of morbidity and mortality. About 30% patients with DMD are symptomatic at the time of diagnosis of disease. For cardiac function assessment in DMD cardiomyopathy, echocardiography considered as primary investigation but has known limitations; that is why with advancement over time and better understanding of DMD cardiomyopathy, cardiac magnetic resonance imaging (CMRI) is preferred for cardiac function monitoring. In recent studies, DMD cardiomyopathy is underdiagnosed and undertreated [1]. However, there is requirement of highly sensitive and specific diagnostic modality and advanced treatment of DMD cardiomyopathy. With increased DMD cases worldwide and with supportive management, patients are living longer which increasing the cardiomyopathy cases overall leading to need of early diagnosis and management concern for DMD patients as they age.

DIAGNOSTIC MODALITY FOR CARDIOMYOPATHY IN DMD PATIENTS

In DMD patients, traditional heart failure symptoms are difficult to diagnose, especially in non-ambulatory patients and also there is large delay in onset of cardiac functional changes and mortality; that is why baseline cardiac functional assessment is done regularly by non-invasive imaging techniques, Echocardiography and CMRI [2]. Previously, echocardiography used as primary imaging but today CMRI is preferred non-invasive imaging. Echocardiography has significant limitation with inadequate acoustic imaging windows, which especially gets affected by body habitus in DMD patients. CMRI has better imaging quality and minimally affected by body habitus.

For diagnosis of DMD related ventricular dysfunction, CMRI is considered superior than echocardiography, which is supported by multiple studies done by Soslow et al (found suboptimal image quality of echocardiography which frequently causes significant over/under estimate the left ventricular systolic function in half of the patients with DMD) and Buddhe et al (found that ventricular functional assessment via echocardiography had a weak correlation than CMRI measurements, even in patients with better image quality by echocardiography) [3-5].

Histo-pathological cardiac changes are sub-epicardial myocardial fibrosis, degeneration and fatty infiltration; detected by CMRI before changes appear in standard functional measurements (i.e. Ejection fraction (EF) and/or fractional shortening). Gadolinium contrast enhanced CMRI used for non-invasive assessment of pathologic myocardial fibrosis by extent of late gadolinium enhancement (LGE) (assess focal fibrotic lesion in myocardium), can be an important clinical biomarker in management of DMD associated cardiac disease and also determine benefit of early medical management in preventing the progression of ventricular dysfunction. CMRI positive myocardial fibrosis can be used as independent predictor of adverse cardiac remodeling, ventricular arrhythmias, death or need for heart transplantation [6].

Fibrotic changes in myocardium have heterogeneous distribution leading to regional cardiac wall motion abnormality which is detected by new technique called Strain imaging. CMRI strain has a better correlation with CMRI left ventricular ejection faction (LVEF) than echocardiographic strain due to inadequate image quality [7]. Thus, strain analysis with standard echocardiography, CMRI and LGE imaging can provide risk associated cardiac assessment in DMD cardiomyopathy.

Emerging imaging technique in DMD related cardiomyopathy is T_1 mapping by CMRI which assess extracellular volume and diffuse fibrosis in myocardium [8].

MANAGEMENT OF CARDIOMYOPATHY IN DMD PATIENTS

First line therapy in DMD patients with heart failure is angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). The age of starting ACEI or ARBs in DMD patients despite normal cardiac evaluation is 10 years. According to recent studies, combination therapy with mineralocorticoids receptor antagonists eplerenone and ACEI, leads to decline in left ventricular functions after 2 years compared to use of ACEI alone [9]. Beta-

adrenergic blockers are added if ventricular dysfunction continue or increased heart rates. Diuretics or digoxin, considered when addition heart failure therapy is required.

The Food and Drug Administration (FDA) recently approved two new drugs for heart failure [10]. First, Sacubitril (neprilysin inhibitor) and valsartan (ARB) combination for decreasing heart failure hospitalization. Second, Ivabradine which acts on sinoatrial node to decrease heart rate (recommended if heart rates > 70 beats per minute despite optimal use of beta-adrenergic blockers).

Advanced therapies in DMD patients are heart transplantation and mechanical support via Left Ventricular Assist Devices (LVADs). Heart transplantation is done in case of refractory end stage heart failure but not considered in irreversible dysfunction of other organ systems. In DMD patients, respiratory insufficiency and muscular weakness already present thus, heart transplantation is avoided due to post-transplant mortality. Mechanical devices like LVADs use is very limited due to slower adoption of the concept but some cases showed favorable outcomes. LVADs adverse outcomes are due to bleeding, infection and stroke which increases morbidity and mortality.

Arrhythmias like atrial premature beats, ventricular premature beats, atrial tachycardia, non-sustained and sustained ventricular tachycardia (VT) are common cause of sudden cardiac death in DMD patients. Arrhythmia is not considered as predictor of mortality in DMD but only LVEF is considered. The benefit of Implantable Cardioverter Defibrillator (ICD) is not established in DMD patients. There is increased risk with ICD placement in DMD patients due to anesthesia risks, respiratory compromise and contractures.

In 2016, FDA approved first drug which directly target dystrophin deficiency by exon skipping method is Eteplirsen. Studies show that eteplirsen is relatively less efficacious in heart muscles compared to skeletal muscles, so severity of skeletal myopathy can be decreased but not mortality unless cardiac treatment discovered. Also drugs Drisapersen and Vyondys 53 (Golodirsen) have been approved. Exondys 51 (Eteplirsen) is targeted to skip exon 51. Vyondys 53 (Golodirsen) is targeted to skip exon 53. Another drug Ataluren (Translarna), which was also known as PTC124, is used in patients with DMD who have non sense mutation in dystrophin gene, can walk and are more than 5 years old. Ataluren make ribosomes less sensitive to premature stop codons by promoting insertion of near-cognate tRNA at the site of nonsense codons with no apparent effects on downstream transcription, mRNA processing, stability of the mRNA or the resultant protein, thereby making a functional protein. It seems to work particularly well for the stop codon 'UGA'. Another drug Morpholino (Phosphorodiamidate Morpholino Oligomer (PMO) is used in patients with DMD and is been approved. Morpholino is the safest Anti Sense Oligonucleotides (ASOs) for therapy in DMD patients using synthetic DNA like molecules for exon skipping therapy. Morpholino treatment involves splicing out the frame-disrupting segment of the dystrophin mRNA, which restores the reading frame and produces a truncated yet functional dystrophin protein. Another therapy is Gene Therapy for DMD, which is currently in experimental phase. Gene therapy includes the gene editing method to correct a mutation that leads to DMD. The technique is called CRISPR/Cas9-mediated genome editing, which can precisely remove a mutation in the dystrophin gene in DNA, allowing the body's DNA repair mechanisms to replace it with a normal copy of the gene. The benefit of this over other gene therapy techniques is that it can permanently correct the defect in a gene rather than just transiently adding a functional gene. Biostrophin is a delivery vector for gene therapy in the treatment of DMD. [11]

SUMMARY AND CONCLUSION

There is increased prevalence of DMD patients in Indian population, because of increased overall cases and longer life expectancy, i.e. increased DMD cardiomyopathy. Therefore, there is need for early diagnosis and treatment of cardiomyopathy leading to heart failure. Early diagnosis with higher sensitive and specific test is required like CMRI than echocardiography which leads to early start of management to increase the quality of life in DMD patients.

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