Cardiomyopathy in becker muscular dystrophy: Overview

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Becker muscular dystrophy (BMD) is an X-linked recessive disorder involving mutations of the dystrophin gene. Cardiac involvement in BMD has been described and cardiomyopathy represents the number one cause of death in these patients. In this paper, the pathophysiology, clinical evaluations and management of cardiomyopathy in patients with BMD will be discussed.

INTRODUCTION

Becker muscular dystrophy (BMD), first described by Doctor Peter Emil Becker in 1955, is an X-linked recessive disorder involving mutations of the dystrophin gene. The dystrophin gene located on chromosome Xp21.1, codes for a large protein that serves as a scaffolding protein in both skeletal and cardiac muscle. In BMD, the mutations allow for expression of truncated but functional dystrophin or a reduced amount of dystrophin protein. BMD is characterized by progressive skeletal muscle weakness. It affects one in 18450 males with the prevalence of at least 2.4/100000[1]. Researchers started correlating BMD with cardiac involvement in 1960s[2]. BMD patients may live until the fifth or sixth decade of life and cardiomyopathy represents the number one cause of death.

Key words: Becker muscular dystrophy; Cardiomyopathy; X-linked recessive disorder; Dystrophin

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cause of death in these patients\textsuperscript{[1,3]}

**CARDIOMYOPATHY IN BMD**

The frequency of cardiac involvement in BMD is 60% to 75\%\textsuperscript{[4]}\textsuperscript{[4]}. The average age of onset of cardiac involvement is 28.7 ± 7.1 years\textsuperscript{[5]}. Severe dilated cardiomyopathy (DCM) in patients less than 20-year-old is rare. The primary pathology of cardiomyopathy in BMD is thought to be due to diffuse degeneration and fibrosis in the ventricles especially the inferolateral region and the conduction tissue\textsuperscript{[4]}. Myocardial damage preferentially in the inferolateral wall is presumed to be due to exaggerated mechanical stress and not due to limited distribution of dystrophin in this region.

There are different cardiac manifestations in BMD ranging from very subtle signs to severe cardiomyopathy requiring cardiac transplant\textsuperscript{[6]}. Most of BMD patients have asymptomatic cardiac involvement. Only up to one third of patients develop DCM with symptoms of heart failure. Studies have shown that there appears to be no correlation between skeletal muscle involvement and the severity or time of onset of myocardial involvement\textsuperscript{[1,5]}\textsuperscript{[1,5]}. Myocardial damage preferentially in the inferolateral wall is presumed to be due to exaggerated mechanical stress and not due to limited distribution of dystrophin in this region.

PATHOPHYSIOLOGY OF CARDIOMYOPATHY

The detailed molecular mechanism of the development of cardiomyopathy in BMD has not been well established. Currently, the mechanism is thought to be secondary to increase in intracellular calcium influx. Elevation of intracellular calcium results in mitochondrial deregulation, protease calpain-mediated necrosis and NF-κB activation. This leads to degradation of troponin I compromises the contraction of the cardiomyocyte and eventually results in cardiomyocyte death. The exact mechanism causing an increased intracellular calcium influx is subject to a debate. One proposed mechanism is that dysfunction of the sarcolemmal stretch activated channels causes an increased influx of calcium. Others believe that the absence of dystrophin causes cells to have a fragile membrane that is leaky and thus allowing intracellular calcium influx\textsuperscript{[8,9]} (Figure 1).

**GENOTYPE AND CARDIOMYOPATHY CORRELATION**

The wide phenotypic variation in the severity of cardiomyopathy in BMD patients may be due to different mutations in the dystrophin gene. Deletions affecting the amino terminal domain or mutations resulting in disruption of spectin repeat in the rod domain of the dystrophin protein, and mutations involving exons 12 and 14 to 17 or 31 to 42 are associated with early onset of cardiomyopathy\textsuperscript{[1,10]}\textsuperscript{[1,10]}. People with deletion mutations of exons 2 to 9 or exons 45 to 49 are at risk of developing DCM in the second and third decades of life respectively\textsuperscript{[11]}\textsuperscript{[11]}. Specifically, deletion of the intron located between exon 48 and 49 is associated with cardiomyopathy. Deletion around exon 1 damages the expression and or function of dystrophin selectively in cardiac muscle. On the other hand, no cardiac abnormality is seen in patients with deletions on the 5’ side\textsuperscript{[12]}\textsuperscript{[12]}. Further studies are needed to unify these findings. However, these findings suggest that BMD patients with certain mutations may have significant cardiac involvement and need more careful and regular cardiac evaluation.
Previous studies have shown that there is no correlation between the extent of cardiac and skeletal muscle disease in patients with BMD. A possible, straightforward explanation is that different genetic mutations lead to different phenotypes. However, recent findings suggest that there may be another explanation. Cardiac dystrophin may interact with proteins that are different from those of skeletal dystrophin. Johnson et al[13] using antibody-based immunoprecipitation, discovered that there is a different interaction between members of the dystrophin-associated protein complex (neuronal nitric oxide synthase and β2-syntrophin) with cardiac and skeletal dystrophin. Neuronal nitric oxide synthase does not interact with cardiac dystrophin while β2-syntrophin interacts with cardiac but not skeletal dystrophin. They also found that there is a unique interaction between cardiac dystrophin and Cavin-1 (polymerase I and transcript release factor), Ahnak1 (neuroblast differentiation-associated protein), Cypher (a PDZ-LIM domain Z-line protein), and CRYAB (crystalline, alpha B). The significance of these interactions remains to be determined.

**CARDOIOMYOPATHY IN FEMALE CARRIERS**

Female carriers of dystrophin mutations may develop cardiomyopathy even without skeletal muscle disease. There are reports of electrocardiographic and echocardiographic evidence of cardiomyopathy among BMD carriers. However, the significance of cardiomyopathy in female carriers has been a source of debate, since it does not appear to affect life expectancy[14]. Hence, the benefit of routine cardiac surveillance in BMD carriers is unclear. Currently, there is no consensus on the need for regular cardiac surveillance in BMD carriers.

**EKG FINDINGS**

Typical EKG changes in BMD include an R:S ratio ≥ 1 in lead V1, tall R waves in the right precordial leads, deep Q waves in the inferolateral leads, short PR, and longer QTc interval. There are also conduction abnormalities including incomplete and complete right bundle branch block, incomplete and complete left bundle branch block, and infra-hisian block[1,2,12].

**DEVICE THERAPY**

BMD patients with cardiomyopathy can develop atrial and ventricular arrhythmias. The degree of arrhythmia is proportional to the severity of left ventricular dysfunction. The benefit of an implantable cardioverter-defibrillator (ICD) in BMD patients has not been established. Therefore, the same criteria is used for prophylactic ICD implantation in BMD patients as in other forms of nonischemic DCM[4,15]. Resynchronization therapy with biventricular pacing may also be considered to reduce heart failure symptoms[15-18].

**CARDDIAC TRANSPLANT**

Although there were case reports dated back to the 1990s of patients with BMD who successfully underwent cardiac transplantation[19], inherited myopathies remained as a relative contraindication for heart transplant for a number of reasons. First, immunosuppression after transplant may cause progression of muscle impairment. Secondly, respiratory muscle dysfunction may make it difficult to wean off the ventilator post-operatively.

Wu et al[20] challenged these traditional concerns in a study comparing patients with muscular dystrophy to a matched cohort of patients with idiopathic DCM after heart transplant. The results showed that survival, rate of infection, cardiac rejection, and transplant vasculopathy post heart transplant were similar between the two groups. The limitation of this study was its small sample size and the possibility of selection bias. Nonetheless, the findings of this study suggest that BMD patients who have only mild muscular disability and no involvement of respiratory muscles may successfully undergo cardiac transplantation[7,20]. Patients with BMD may have a small additional risk of rhabdomyolysis and malignant hyperthermia reaction[21].

Cardiac rehabilitation after heart transplant in a patient with BMD has also been shown in a case report to improve cardiac function[6].

**FUTURE THERAPEUTIC PERSPECTIVES**

There are ongoing investigations looking at the introduction of a modified functional dystrophin gene via gene transfer as well as molecular correction of the mutated dystrophin gene. There are adeno-associated virus capsids that target cardiomyocytes specifically which allow gene expression in the heart even when the capsid is delivered via a peripheral vein. There are two types of synthetic dystrophin genes: Mini-dystrophin and micro-dystrophin. In mini-dystrophin, part of the rod domain is removed, while in micro-dystrophin, a significant portion of the rod and the C-terminal domain are removed. Mini-dystrophin transferred in a mouse model showed normalization of EKG and improved myocardial fibrosis and ejection fraction. Similarly, micro-dystrophin was able to restore normal heart rate, PR and QT interval, and cardiomyocyte integrity. The challenge of this gene therapy is the immune rejection of the viral vector or the newly expressed dystrophin protein[17].

Another gene therapy is exon skipping. In this method, antisense oligonucleotides (AONs) are used to remove mutated exons resulting in a truncated but functional protein. Applying this method in a mouse model with mutated dystrophin showed favorable echocardiographic changes[17,22-27]. Mendell et al[28] showed that AONs increased functional dystrophin-positive fibers in an open-labeled human study. Unfor-
Evaluating for wall motion abnormalities and cardiac function.

Contrast enhanced cardiovascular magnetic resonance
Evaluating for early tissue fibrosis.

Spatial mapping cardiovascular magnetic resonance
Evaluating for early tissue fibrosis.

IMAGING FINDINGS

The echocardiogram shows a dilated left ventricle with wall motion abnormality and cardiac function, and detecting regional myocardial deformation. Contrast enhanced CMR (ceCMR), using late gadolinium enhancement as an indication of myocardial damage, allows for detection of even small areas of myocardial deformation[24]. Using ceCMR, Yilmaz et al[1] showed that myocardial damage in BMD begins in the subepicardium of the inferolateral wall. However, Soslow et al[22] showed recently that spatial mapping of the longitudinal relaxation time constant (T1) CMR might be superior to ceCMR in detecting early myocardial fibrosis. As such, more research is warranted to ascertain the best modality for detecting early fibrosis in BMD.

Previously, it has been recommended that BMD patients undergo a screening ECG and echocardiogram at the time of diagnosis and every five years thereafter if the findings are normal. However, as CMR becomes widely accepted, it is recommended it be initiated at diagnosis and then at least every two years even in the case of normal findings. This rigorous screening procedure is proposed with the hope of early cardiomyopathy detection so that effective treatment can be initiated to slow the progression of cardiac dysfunction (Table 1).

OTHER ASSESSMENT METHODS

There are other methods that can either support the diagnosis or monitor left ventricular function. Chest X-ray may show cardiomegaly, pleural effusion, and pulmonary congestion. Cardiac troponin I is a marker for myocardial damage. Brain natriuretic peptide, released following ventricular overload and increased wall stress, has been proposed as a marker for monitoring of left ventricular dysfunction[26].

PHARMACOTHERAPY

Angiotensin-converting enzyme inhibitors (ACEIs) have been shown to delay the progression of LV dysfunction, improve left ventricular function, and confer a mortality benefit. However, there is no universal guideline on the best time for the initiation of ACEI in patients with BMD. Suggestions have been made for ACEI to be given when left ventricular ejection fraction is less than 55%[31,32].

β blockers are beneficial in patients with DCM. Therefore, β blockers may have positive effects on BMD patients with cardiomyopathy. A Japanese study comparing patients with different types of muscular dystrophies on ACEI alone vs ACEI plus β blocker showed that the combination of ACEI and β blocker provided a significant improvement on left ventricular fractional shortening[23]. Therefore, β blockers are recommended to be used in accordance with current heart failure guidelines. Clinically, hypotension may limit the use of a β-blocker.

Corticosteroids have been shown to improve muscle strength and function. Numerous studies implicated the role of steroid in prolonging ambulation and stabilization of pulmonary function. However, corticosteroids have many adverse effects, which include Cushing’s, hypertension, osteoporosis and hyperglycemia[9].

There has been no large trial examining the mortality benefit of angiotensin receptor blockers (ARBs) in BMD patients with cardiomyopathy. It is possible that ARBs are efficacious based on studies showing their benefit in other causes of heart failure. Diuretics and digoxin can be used as adjuncts for symptom reduction although no mortality benefit has been demonstrated. Aldosterone blockade can be added for patients with NYHA Class III or IV who are already on optimal doses of an ACEI and β blocker[15]. Calcium channel blockers such as diltiazem, flunarizine, and nifedipine have not been shown to be beneficial[34].

Current data suggested that there might be a role of eplerenone in treating BMD. Raman et al[23] showed that eplerenone in addition to ACEIs slow down the

Table 1: Summary of current diagnostic modalities

| Imaging modalities                  | Description                                      |
|-----------------------------------|-------------------------------------------------|
| Echocardiogram                    | Evaluating for wall motion abnormality and cardiac function |
| Contrast enhanced cardiovascular magnetic resonance | Evaluating for early tissue fibrosis |
| Spatial mapping cardiovascular magnetic resonance | Evaluating for early tissue fibrosis |
progression of left ventricular systolic function decline. The exact mechanism is unknown. But evidence from ceCMR suggested that it is likely secondary to eplerenone anti-inflammatory effect.

Ivabradine is a medication that selectively blocks the I(f) current in sinoatrial cells and slows heart rate. Unlike β blockers, ivabradine does not cause hypotension. Ivabradine may reverse cardiac remodeling thus providing a mortality benefit. A case report on Ivabradine in BMD cardiomyopathy has shown benefits.

Randomized controlled trials are needed for further evaluation. Currently, this medication is not available in the United States[146].

CONCLUSION

There are still many unknowns regarding BMD cardiomyopathy. Imaging techniques need to be optimized further to allow for early diagnosis of CM. Different pharmacological and gene therapies currently being developed offer hope for patients with BMD cardiomyopathy.

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