Life-threatening Arrhythmias in a Becker Muscular Dystrophy Family due to the Duplication of Exons 3-4 of the Dystrophin Gene

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Abstract

We herein present a report of three patients with Becker muscular dystrophy in the same family who developed complete atrioventricular block or ventricular tachycardia with severe cardiomyopathy. Our cases became unable to walk in their teens, and were introduced to mechanical ventilation due to respiratory muscle weakness in their twenties and thirties. In all three cases, a medical device such as a permanent cardiac pace-maker or an implantable cardiac defibrillator was considered to be necessary. The duplication of exons 3-4 in the dystrophin gene was detected in two of the patients. In patients with Becker muscular dystrophy, complete atrioventricular block or ventricular tachycardia within a family has rarely been reported. Thus attention should be paid to the possibility of severe arrhythmias in the severe phenotype of Becker muscular dystrophy.

Key words: life-threatening arrhythmias, Becker muscular dystrophy, cardiomyopathy

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Introduction

Becker muscular dystrophy (BMD) occurs due to a deletion, duplication, or point mutation in the dystrophin gene on chromosome Xp21.1, which leads to a reduced amount or abnormal size of the muscle dystrophin isoform (1-3). In typical BMD patients, the clinical course is more benign than in Duchenne muscular dystrophy. The age at onset is around 12 years, and ambulation difficulty varies from adolescence and onwards (4). Cardiac involvement is well documented in patients with BMD (5), and heart failure is the primary cause of death. Cardiac involvement in BMD may also manifest as either electrocardiography (ECG) abnormalities or arrhythmias including atrial fibrillation, right bundle branch block, left bundle branch block, intraventricular conduction delay or ventricular tachycardia (6-8). Complete atrioventricular (AV) block, however, is unusual. Moreover, Diegoli et al. reported that dystrophinopathy is associated with a low risk of life-threatening arrhythmias, and a high risk of severe heart failure (9). In this report, we present three cases of BMD in the same family who exhibited life-threatening arrhythmias, including complete AV block.

Case Reports

The family pedigree of the patients is shown in Fig. 1. The clinical features of our patients are shown in Table.

Patient 1

A 57-year-old man with an abnormal gait since 10 years of age was diagnosed with BMD by muscle biopsy and through his clinical manifestations. He became unable to walk at 13 years of age. He developed cardiomyopathy, which was diagnosed via ECG and echocardiography at 34 years of age. At 57 years of age, he was bed-bound with artificial respiration with tracheotomy due to respiratory muscle weakness. He was placed on oral digoxin (0.125 mg/
and Holter electrocardiography revealed almost ventricular arrhythmias, and incomplete/complete left bundle branch block (5). Complete AV block is unusual in BMD patients; however, a few cases have been reported (11-13). In two cases (11, 12), complete AV block occurred secondarily to severe cardiomyopathy a few decades after skeletal muscle involvement. The other case (13) was a patient with the deletion of exons 45-48 of the dystrophin gene, who had cardiomyopathy and dilated cardiomyopathy requiring the insertion of a permanent cardiac pacemaker. The patient died from heart failure 5 months after surgery.

**The analysis of the dystrophin gene and protein**

In Patients 1 and 2, multiplex ligation-dependent probe amplification of the dystrophin gene from peripheral blood (10) showed a duplication of exons 3 and 4 (data not shown). The biceps brachii muscles in Patient 2 were biopsied when he was at 16 years of age, and dystrophin immunostaining of this tissue revealed a patchy or discontinuous staining pattern, with decreased staining intensity compatible with BMD. A Western blot analysis of the biopsied muscle demonstrated a low molecular mass (390 kDa) and a reduced quantity of the dystrophin protein (data not shown).

**Discussion**

We report a family with BMD presenting with complete atrioventricular block or ventricular tachycardia. BMD patients occasionally develop dilated cardiomyopathy with concomitant heart failure. Patients with BMD also exhibit various ECG abnormalities, including sinus tachycardia at rest, atrial fibrillation, intraventricular conduction delay, ventricular arrhythmias, and incomplete/complete left bundle branch block (5). Complete AV block is unusual in BMD patients; however, a few cases have been reported (11-13). In two cases (11, 12), complete AV block occurred secondarily to severe cardiomyopathy a few decades after skeletal muscle involvement. The other case (13) was a patient with the deletion of exons 45-48 of the dystrophin gene, who had cardiomyopathy and dilated cardiomyopathy requiring the insertion of a permanent cardiac pacemaker. The patient died from heart failure 5 months after surgery.

**Patient 3**

This patient was the older brother of Patient 1. He was diagnosed with BMD as a result of his clinical manifestations and his family history. He became unable to walk in his teens. At 43 years of age, he was bed-bound with artificial respiration and tracheotomy due to respiratory muscle weakness. At 53 years of age, he developed complete AV block with dilated cardiomyopathy requiring the insertion of a permanent cardiac pacemaker. The patient died from heart failure 5 months after surgery.

**The family pedigree.** Females and males are presented as circles and squares, respectively. Females were asymptomatic and muscle biopsy or gene analysis was not performed for carrier diagnosis. The filled symbols indicate affected males. The slashed symbols indicate deceased family members. The number shows the age at death (in years).
3 syncopal episodes and who developed complete AV block before the onset of muscle weakness and cardiomyopathy. Moreover, Wakefield et al. reported that a 34-year-old man with dystrophinopathy was found to have a paradoxical arrhythmia without cardiac and skeletal muscle symptoms (14). These previous cases had no family history of BMD, while our family had at least three members who presented with life-threatening arrhythmias including complete AV block. Moreover, the uncle of Patient 2 was diagnosed with BMD and died at 23 years of age from an unknown cause. We speculate that life-threatening arrhythmias may be related to his cause of death (Fig. 1).

There is no correlation between the progression of cardiomyopathy and skeletal muscle involvement in BMD patients (15, 16), and its etiology remains obscure. There are several reports on the relationship between cardiomyopathy and the type of dystrophin gene mutation (17, 18). In 1991, Beggs et al. suggested that deletions within the amino-terminal domain result in low levels of dystrophin and a more severe phenotype (17). In 2009, Kaspar et al. suggested that analysis of dystrophin mutations predicted the age of onset of cardiomyopathy in cases of BMD (18). They reported that patients with deletions affecting exons 2-9, which encode the actin-binding amino-terminal domain of dystrophin, exhibited severe cardiomyopathy. Compatible with the report of Kaspar et al. (18), the family of the present cases also exhibited abnormalities among exons 2-9 (exons 3-4). Therefore, the life-threatening arrhythmias in the family cases may have been secondary to the occurrence, due to genetic factors, of the dysfunction of the myocardium and the electrical conduction system. It possibility cannot be denied that the life-threatening arrhythmias of our patients may have resulted from insufficient medical management before the implanting of a permanent cardiac pacemaker or an implantable cardiac defibrillator. In general, complete AV block and VT due to idiopathic dilated cardiomyopathy are not considered rare. However, the inability to walk and the early initiation of treatment for cardiomyopa-

**Figure 2.** Electrocardiograms of our patients. (a) An electrocardiogram of Patient 1 showing a complete atrioventricular block. (b) A Holter electrocardiogram of Patient 1 after onset showing sporadic ventricular tachycardia. (c) An electrocardiogram of Patient 2 showing ventricular tachycardia-caused syncpe.

| Table. The Clinical Features of Our Patients. |
|---------------------------------------------|
| Age (years) | Age at walking difficulty (years) | Activities of daily living | Age at introducing mechanical ventilation (years) | Use of a ventilator | Arrhythmias | Mechanical devices |
| Patient 1 | 57 | 13 | Bed-bound | 34 | TPPV | Complete AV block | Permanent pacemaker |
| Patient 2 | 31 | 19 | Wheelchair-bound | 27 | NPPV | Ventricular tachycardia | Implantable cardiac defibrillator |
| Patient 3 | 53 | Teens | Bed-bound | unknown | TPPV | Complete AV block | Permanent pacemaker |

TPPV: tracheostomy positive pressure ventilation, NPPV: non-invasive positive pressure ventilation

**Figure 3.** M-mode echocardiography of Patient 1 showed dilated cardiomyopathy.
thy may result in the lower incidence of complications due to arrhythmias in BMD patients. To our knowledge, no previous reports have described clusters of life-threatening arrhythmias, including advanced AV block, within a family.

The pathologic consequences of cardiomyopathy in dystrophinopathy are the infiltration of inflammatory cells and fibroblasts causing myocardial cell death and fibrosis (which also occurs in skeletal muscle) (19). There are previous reports on pathological abnormalities of the impulse conduction system (the sinoatrial node, the atrioventricular node, and the bundle of His) caused by fibrous tissue or fat infiltration in Duchenne muscular dystrophy (19, 20). In our family, it is possible that the life-threatening arrhythmias were not only caused by severe cardiomyopathy, but were also the result of a pathological abnormality of the impulse conduction system due to the dystrophin abnormality itself.

In conclusion, we herein reported a familial case of BMD with a duplication of exons 3-4 of the dystrophin gene. This report has important implications for clinical practice, because BMD patients with life-threatening arrhythmias may be clustered within a family and because sudden cardiac death can be prevented by the use of mechanical devices.

The authors state that they have no Conflict of Interest (COI).

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