Cardiac Involvement in a Family with Becker Muscular Dystrophy

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We report a family with Becker muscular dystrophy (BMD) presenting with cardiac involvement. The proband was a 41-year-old Japanese man who was hospitalized with exertional dyspnea and muscle weakness. Cardiac examination showed findings consistent with dilated cardiomyopathy. Dystrophin immunohistochemical analysis showed a discontinuous patchy staining pattern in cardiac and skeletal muscles biopsied from the proband. His brothers had high creatine kinase (CK) activity and abnormal electrocardiogram. Dystrophin gene analysis revealed that the proband and his brothers had G-to-T transversion at the terminal nucleotide of exon13. We conclude that the mutated dystrophin gene may cause cardiac involvement as a symptom precedent to skeletal muscle involvement.

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Introduction

The severe Duchenne muscular dystrophy (DMD) and the more benign Becker muscular dystrophy (BMD) are allelic disorders of the dystrophin gene located at Xp21 (1, 2). The dystrophin gene consists of 79 exons spread over more than 2,500 kb of the chromosome (3). Approximately two-thirds of DMD or BMD patients carry deletions in their dystrophin gene (4). The dystrophin immunohistochemistry of the skeletal muscle shows a negative staining pattern in DMD. In BMD, discontinuous patchy staining pattern was thought to be characteristic (5, 6). However, it has been proved that the staining pattern varies from negative to nearly normal according to the specificity of the antibodies used (7).

BMD is marked by late onset and slowly progressive muscular degeneration, compared with DMD. However, BMD is known to show a wide clinical spectrum (8). BMD patients with dilated cardiomyopathy, albeit rarely, have been reported (9-13). These observations led to speculation that a genetic abnormality of dystrophin may be present in patients with X-linked cardiomyopathy (XLCM). XLCM is a rapidly progressive primary myocardial disorder presenting as congestive heart failure in teenage males without clinical signs of skeletal myopathy (14).

We had the opportunity to examine a family with BMD

presenting with cardiac involvement. While the proband manifested dilated cardiomyopathy and muscle weakness, one of his brothers showed only an electrocardiographical abnormality and did not show muscle weakness, despite carrying the same mutation in the dystrophin gene as the proband.

Case Report

A pedigree was constructed for the family (Fig. 1). The proband (Subject IV-3) was a 41-year-old Japanese man with normal intelligence. He was a greengrocer and had experienced difficulty in running and lifting a load weighing more than 20 kg for past three years prior to the current hospitalization. He also noted atrophy of the thighs since 1990 (40 years of age). Exertional dyspnea developed in September 1991 (41 years of age). In November 1991, he consulted our hospital complaining of exertional dyspnea and muscle weakness.

On admission, blood pressure was 110/74 mmHg, and the pulse rate was regular and 78 beats/min. A third cardiac sound was audible. Hepatomegaly with slight tenderness was also noted. Muscle strength in the extremities was decreased, with predilection in the proximal area. The thighs were atrophic and calves were hypertrophic. Deep tendon reflexes were normal. There was no sensory disturbance, pathologic reflex or ataxia. Waddling gait and Gowers' sign were negative.

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Figure 1. Pedigree of a family with BMD. The proband is indicated by a black square. The proband's mother (Subject III-2), the fourth (Subject IV-4) and the fifth brothers (Subject IV-6) revealed elevated serum muscular enzyme activities. Serum CK activities (IU/l) of the subjects are shown below the ages.

Figure 2. ECGs of the proband, his fourth and fifth brothers. The proband's ECG (A) suggested left ventricular hypertrophy. The fourth brother's ECG (B) suggested a posterior myocardial lesion of the left ventricle. The fifth brother's ECG (C) suggested a lateral myocardial lesion of the left ventricle.

Serum muscular enzyme activities were elevated; creatine kinase (CK) 1903 IU/l, lactate dehydrogenase (LDH) 742 IU/l, and aldolase 6.1 IU/l (normal ranges are 35 to 169 IU/l, 227 to 416 IU/l, and 2.5 to 5.5 IU/l, respectively). Regarding CK isozyme, the MM type was dominant (98%), suggesting that elevated CK activity was derived mainly from skeletal muscle. Electromyogram revealed short duration and polyphasic waves, indicating myogenic change.

Cardiomegaly was noted on chest roentgenogram (CTR of 56%). Electrocardiogram (ECG) of the proband is shown in Fig. 2A. High voltage (SV1+RV5=50 mm) and ST depression in leads I, V4, V5 and V6 indicated left ventricular hypertrophy. The R/S ratio in lead V1 exceeded 1.0, suggesting the presence of a myocardial lesion in the posterior wall. Figure 3 shows the B-mode echocardiogram of the proband. Left ventricular diastolic dimension was 71 mm and systolic dimension 69 mm. Two-dimensional echocardiogram revealed dilated and diffuse hypokinetic left ventricle with a mural thrombus, quite similar to the findings of severely progressed idiopathic dilated cardiomyopathy. Findings of contrast left ventriculography were consistent with those of echocardiography, indicating dilated and diffuse hypokinetic left ventricle. End-diastolic volume

was 229 ml/m², end-systolic volume was 197 ml/m² and ejection fraction was 14%. Coronary angiography did not demonstrate any abnormalities of the coronary arteries. Left ventricular pressure was 80/9–22 mmHg. Cardiac index was 2.84 l/min/m².

Biopsies of the skeletal muscle (quadriceps femoris) and cardiac muscles were examined. Skeletal muscle specimens showed dystrophic changes such as large variation in fiber size and a small number of necrotic fibers. The cardiac muscle showed marked myocyte hypertrophy with little increased fibrous connective tissue. Immunoperoxidase staining of the skeletal and cardiac muscles was done according to the method described by Arahata et al, using three monoclonal antidystrophin antibodies (NCL-DYS1, NCL-DYS2, NCL-DYS3; Novocastra Laboratories Ltd, UK) specific for the rod, carboxyl-terminal and amino-terminal domains, respectively. Dystrophin immunostaining of the skeletal muscle, with each of the antibodies employed, showed a positive staining at the cell membrane of muscle fibers, although there was variation in labeling intensity between muscle fibers (discontinuous patchy staining pattern) (Fig. 4B). Dystrophin immunostaining of the cardiac muscle also showed discontinuous patchy staining with each of

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Figure 3. M-mode echocardiogram of the proband. Severely dilated left ventricle and diffuse hypokinesis were found. End-diastolic and end-systolic dimensions were 71 mm and 69 mm, respectively.

Figure 4. Immunoperoxidase staining of skeletal muscle (quadriceps femoris) and cardiac muscle with anti-dystrophin antibody (DYS-2). Panels A, B, C and D are skeletal muscle (patient with polymyositis as a control), skeletal muscle (proband), cardiac muscle (patient with idiopathic hypertrophic cardiomyopathy as a disease control) and cardiac muscle (proband), respectively. Skeletal muscle and cardiac muscle of the proband showed discontinuous patchy staining pattern (panels A and B $\times 50$, panels C and D $\times 100$).

the antibodies employed, but the overall intensity was more severely decreased than that of the skeletal muscle (Fig. 4D).

Physical examination, blood chemical analysis, ECG and echocardiogram studies of the family members were also performed. The proband had five brothers and two sisters (Fig. 1). His mother and two brothers (Subjects III-2, IV-4 and IV-6 in Fig. 1) demonstrated elevated serum muscular enzyme activities (CK, LDH and aldolase). These two brothers also showed abnormal ECG findings. The fourth brother (39 years of age, Subject IV-4), showing muscle weakness, and had been diagnosed with BMD at another hospital. Figure 2B shows his electrocardiogram. The R/S ratio in lead V1 exceeded 1.0 and the amplitude of R decreased in leads V4, V5 and V6, suggesting the presence of a myocardial lesion in the posterior wall. Echocardiogram revealed diffuse hypokinesis of the left ventricle. The fifth brother (35 years of age, Subject IV-6) did not show muscle weakness. He demonstrated only an abnormal ECG as a presenting symptom (Fig. 2C). Negative T waves were seen in the leads I, V5 and V6, and the amplitude of R in lead V5 suddenly decreased. These findings suggested the presence of a myocardial lesion in the lateral wall. His

echocardiogram did not demonstrate abnormal wall motion.

Dystrophin gene analysis was performed using peripheral blood cells from the family members (15). The proband and the two brothers with abnormal ECGs (Subjects IV-4, IV-6 in Fig. 1) were proved to have G-to-T transversion at the terminal nucleotide of exon13 of the dystrophin gene, resulting in complete skipping of exon13 during the processing of dystrophin pre-mRNA. The mother proved to be a heterozygote having the indicated mutation.

Discussion

Cardiac involvement is a frequent occurrence in DMD and BMD (16, 17). The known manifestations of cardiac lesion in BMD vary: right-axis deviation and posterobasal or anterior wall ^{201}Tl perfusion defect (18), an echocardiographic configuration of hypertrophic cardiomyopathy (19), dilated cardiomyopathy (9-12), etc. Anan et al examined a cardiac biopsy specimen from a patient with BMD presenting cardiomyopathy and evidenced the same dystrophic lesion in the cardiac muscle as in skeletal muscle, suggesting that cardiac involvement in

BMD might be directly linked to the expression of an altered dystrophin (12). The proband in our family with BMD showed very severe global left ventricular dysfunction closely compatible with the end stage of idiopathic dilated cardiomyopathy. Examination of skeletal and cardiac muscles obtained by biopsy showed a discontinuous patchy immunostaining pattern of dystrophin in the cell membrane, which is compatible with the findings reported by Anan et al (12).

DMD/BMD with cardiomyopathy is considered caused by intragenic deletions of the dystrophin gene. Melacini et al suggested that intron48 includes sequences relevant to the function of dystrophin in the cardiac muscle (20). Yoshida et al also suggested that a deletion around exon1 (muscle type) may severely damage the expression and/or the function of dystrophin selectively in cardiac muscle, but not in skeletal muscle (13). In our case, as Hagiwara et al reported previously, a G-to-T transversion was located at the end of exon13, resulting in skipping of exon13 during the processing of dystrophin pre-mRNA (15). Involving exon13 might also be associated with cardiac involvement in DMD/BMD.

The relationship between Becker muscular dystrophy (BMD) with dilated cardiomyopathy and X-linked cardiomyopathy (XLCM) has been controversial (21). Recently, in two families with XLCM, linkage to the dystrophin gene located at Xp21 was demonstrated by Towbin et al (22). They reported that abnormal cardiac dystrophin was shown by Western blotting with N-terminal dystrophin antibody, suggesting a genetic abnormality in dystrophin. Muntoni et al also demonstrated that one familial form of dilated cardiomyopathy linked to the X-chromosome was due to a deletion in the promoter region and the first exon of the dystrophin gene (23). The patient reported by Muntoni was found to have elevated activity of serum CK, type MM and less intense immunostaining pattern of dystrophin in skeletal muscle, suggesting that he had very mild skeletal muscle involvement. It has become very difficult to distinguish XLCM with a mutated dystrophin gene from BMD with dilated cardiomyopathy. Muntoni et al categorized a proportion of XLCM cases as dystrophinopathy, as well as DMD and BMD.

Our case provided a link in understanding the relationship between BMD and XLCM. Three males in this family carried the same mutation in the dystrophin gene; G-to-T transversion at the terminal nucleotide of exon13. However, muscle weakness was not found in the youngest brother (Subject IV-6 in Fig. 1), although cardiac involvement was detected in all three brothers. In addition, clinically and pathologically, the degree of cardiac involvement was more advanced than skeletal muscle impairment in the proband. Therefore, we can say that the mutated dystrophin gene may cause cardiac involvement as a symptom precedent to skeletal muscle involvement. Our results strongly support that at least a portion of XLCM cases are caused by a genetic abnormality of dystrophin.

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