Familial Skeletal Myopathy with Atrioventricular Block

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Objective We studied familial cases of skeletal myopathy with atrial fibrillation (Af) and atrioventricular (AV) block to compare the clinical features to other myopathies associated with cardiac abnormalities. Methods Neurologic, cardiologic, electrophysiologic, muscle pathology, and genetic studies were performed on the patients showing muscle weakness. Patients Four patients (a 63-year-old mother, 30 and 32-year-old sisters, and their maternal grandmother) and three healthy family members from three generations were studied. The mode of inheritance was suspected as autosomal dominant. Results Two sisters with congenital myopathy without rigid spine developed Af and AV block at the age of 28 and 18, respectively. The mother showed AV block, and underwent pacemaker implantation at the age of 63. The maternal grandmother had dilated cardiomyopathy, Af and severe lordosis. She died of stroke attacks and congestive heart failure at the age of 78. Muscle biopsy obtained from the mother and sisters showed myopathic changes without characteristic abnormalities. No mitochondrial DNA mutations were found. Other inherited myopathies with cardiac complications were not suspected in this family. Conclusion This Japanese family appears to belong to a new genetically heterogeneous group of autosomal dominant skeletal myopathy with severe AV block and Af.

(Keywords: congenital, cardiac complications, atrial fibrillation, cardiomyopathy, desmin)

Introduction

Patients with skeletal muscle diseases show a variety of cardiac involvements. Cardiomyopathy and congestive heart failure are characteristics of Duchenne and Becker muscular dystrophies (1) and X-linked dilated cardiomyopathy (2), whereas conduction system abnormalities such as heart block, arrhythmia, and sudden death are more commonly seen in limb-girdle type (3, 4), myotonic (5) and Emery-Dreifuss muscular dystrophies (6, 7), Kearns-Sayre syndrome (8), and desmin myopathy (9, 10). Recent genetic analyses have identified the causative genes or gene loci in these inherited muscular disorders with cardiac involvement. However, the etiologies in many of the other familial patients with inherited muscular disorders and cardiac involvement are still unknown. We report here a Japanese family with myopathy, severe atrioventricular (AV) block, and atrial fibrillation (Af) without desmin accumulation.

Patients and Methods

Patient evaluation and family study

Seven family members from three generations including 4 affected individuals were studied (Fig. 1). Detailed neurologic and cardiologic examinations were performed in family members III-2, III-4, IV-1, IV-2 and IV-3. Family members II-6 and II-7 were evaluated based on their medical records. Blood samples were obtained from 4 family members (III-2, III-4, IV-2 and IV-3). Nerve conduction study and electromyography were performed according to standard protocols.

Muscle pathology

Muscle biopsy specimens were obtained from the rectus femoris at the age of 13 years old in patient 1, biceps brachii at the age of 18 in patient 2 and biceps brachii at the age of 62 in patient 3. Frozen thin sections of the biopsy specimens were stained with hematoxylin and eosin, modified Gomori trichrome, reduced nicotinamide adenine dinucleotide-tetrazolium reductase, cytochrome c oxidase, acid phosphatase, and myosin ATPase with preincubation at pH 4.2, 4.6 and 10.3.

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Myopathy and Atrioventricular Block

Figure 1. Pedigree of family with skeletal myopathy and conduction block. Subjects fully examined clinically and cardiologically are indicated by a double horizontal bar, and those evaluated from medical records are indicated by a single horizontal bar. Filled symbols indicate patients with myopathy, atrioventricular block and atrial fibrillation; the shaded symbol indicates a patient with dilated cardiomyopathy and atrial fibrillation without myopathy; open symbols, healthy subjects; lower right, age at examination; oblique slash, deceased; squares represent men; circles, women; arrow, proband.

Immunohistochemical analysis was performed using monoclonal antibodies to adhalin (1:50 dilution), dystrophin C-terminus (1:50 dilution), emerin (1:100 dilution), and desmin (1:100 dilution) purchased from Novocastra. The monoclonal antibodies to laminin molecules comprised a 1:1,000 dilution of anti-merosin (Gibco, Rockville), a 1:5,000 dilution of anti-lamininβ1 (Chemicon, Temecula), and a 1:500 dilution of anti-lamininβ2 antibodies (Chemicon). Biotinylated anti-mouse IgG was used as a second antibody, and the ABC method was used for signal detection (ABC kit; Vector, Burlingame).

Mitochondrial DNA analysis

Southern blotting analysis was performed using DNA extracted from biopsied muscle obtained from patient 3. The DNA was digested with SnaBI, PstI, EcoRI, HindIII, XbaI, Apal and PvuII by the method reported previously (11). Using DNA obtained from peripheral blood of patients 1, 2 and 3 and the father of patient 1, the following point mutations were studied by PCR amplification followed by specific restriction enzyme digestion; 1555(A→G), 3243(A→G), 3271(T→C), 3250(T→C), 3260(A→G), 4317(A→G), 8344(A→G), 8993 (T→G), 11778(G→A) (11). All studies were performed after informed consent had been obtained from all participants.

Results

Case reports

Patient 1 was a 32-year-old woman (IV-2 in Fig. 1) born by normal vaginal delivery at 40 weeks of gestation. Her early motor and intellectual milestones were normal. She experienced difficulty in walking and running at the age of 2 years old. Contracture in elbow and ankle joints appeared at the age of 10. Muscle atrophy became marked at the age of 12. On initial examination at the age of 13, she weighed 28 kg and was 149 cm tall. She had diffuse and proximal dominant muscle weakness, scoliosis and contracture of the elbow and ankle joints but not rigid spine. She had iron-deficiency anemia and was treated with iron supplementation. Systolic murmurs were audible but chest X-ray and electrocardiogram (ECG) were normal at that time (Fig. 2A). She underwent an Achilles tendon extension operation at the age of 13. Since graduating from high school, she never required any help in her daily life and has maintained a desk job, despite the mild muscle weakness and iron-deficiency anemia that occasionally required iron supplementation. At the age of 28, first degree AV block was detected by ECG analysis. Af in addition to AV block was noted at the age of 31 (Fig. 2B). She experienced episodes of loss of consciousness lasting for a few seconds, and therefore Adams-Stokes syndrome was suspected. She was admitted to our hospital for treatment of Af at the age of 32. On admission, she weighed 39 kg and was 155 cm tall. Intellectual function and cranial nerves were normal. She had diffuse mild proximal dominant muscle weakness and atrophy, high arched palate, scoliosis, contracture of the elbows and ankle joints, and areflexia. Rigid spine was not observed. Her serum creatine kinase (CK) level was 66 IU/l (normal: 43–146) and electromyography showed a myogenic pattern. A long pause of cardiac contraction, with a maximum of 4.9 seconds, was detected by 24-hour ECG Holter monitoring (Fig. 2C). Echocardiography showed disturbed left ventricular function, and the ejection fraction was 48% (normal: 50–80). She was treated with denopamine and pilsicainide hydrochloride.

Patient 2 was a 30-year-old woman (IV-3 in Fig. 1), the younger sister of patient 1, born by normal vaginal delivery at 40 weeks of gestation. Her early motor and intellectual milestones were normal. She showed mild gait disturbance at the
Figure 2. Electrocardiograms of patient 1 (A, B and C recorded at the ages of 13, 31 and 32 years old, respectively), patient 2 (D), patient 3 (E) and patient 4 (F) showing atrial fibrillation and atrioventricular block.

Patient 1 was a 2-year-old girl with normal neurological and ECG findings. She had no difficulties in her daily life. She experienced an episode of loss of consciousness with vomiting and urinary incontinence at the age of 12. Electroencephalography showed no abnormalities. She again experienced an episode of loss of consciousness at the age of 18. She could not run but could walk unaided. Her serum CK level was 56 IU/l (normal: 43–146) and electromyography showed a myogenic pattern. Twenty-four hour ECG Holter monitoring revealed a long pause of cardiac contraction, with a maximum of 2.9 seconds.

Patient 2 was a 63-year-old woman (III-4 in Fig. 1), the mother of patients 1 and 2. She experienced difficulty in climbing stairs at the age of 55. On examination at the age of 62, she weighed 33 kg and was 145 cm tall. Her intelligence and cranial nerve system were normal. She showed mild proximal dominant muscle weakness and atrophy, but no joint contracture or rigid spine. Chest-thoracic ratio was 56% on chest X-ray film. ECG showed AF and AV block (Fig. 2E). Her serum CK level was 33 IU/l (normal: 43–146) and electromyography showed a myogenic pattern. Twenty-four hour ECG Holter monitoring revealed a long pause of cardiac contraction, with a maximum of 4.3 seconds. Echocardiography showed decreased ejection fraction (48%) and dilatation of the left atrium. Her conductive block was becoming more severe and she underwent pacemaker implantation at the age of 63.

Patient 3 was a 63-year-old woman (III-4 in Fig. 1), the mother of patients 1 and 2. She experienced difficulty in climbing stairs at the age of 55. On examination at the age of 62, she weighed 33 kg and was 145 cm tall. Her intelligence and cranial nerve system were normal. She showed mild proximal dominant muscle weakness and atrophy, but no joint contracture or rigid spine. Chest-thoracic ratio was 56% on chest X-ray film. ECG showed AF and AV block (Fig. 2E). Her serum CK level was 33 IU/l (normal: 43–146) and electromyography showed a myogenic pattern. Twenty-four hour ECG Holter monitoring revealed a long pause of cardiac contraction, with a maximum of 4.3 seconds. Echocardiography showed decreased ejection fraction (48%) and dilatation of the left atrium. Her conductive block was becoming more severe and she underwent pacemaker implantation at the age of 63.

Patient 4 (II-6 in Fig. 1), the maternal grandmother of patients 1 and 2, noticed dyspnea on effort at the age of 64 years old. On admission at the age of 74, she weighed 44 kg and was 155 cm tall. She had dilated cardiomyopathy, congestive heart failure (CHF) and AF (Fig. 2F). She showed severe lordosis but could walk unaided. Chest X-ray showed 62% cardiothoracic ratio. Her ejection fraction was 42% (normal: 50–80) on echocardiography. She had repeated stroke attacks, probably due to cerebral embolism, and died of CHF at the age of 78.

**Family study**

The elder sister of patients 1 and 2 and their father showed normal neurological and ECG findings. Other family members did not show muscle or cardiac disorders. Therefore, autosomal dominant or maternal inheritance of the disease was suspected from the family pedigree (Fig. 1).

**Muscle pathology**

The muscle biopsy findings demonstrated mild to moderate myogenic changes in patients 1, 2 and 3. In addition to the myogenic changes, rimmed vacuoles were seen in only a few muscle fibers in patient 2 and a single ragged-red fiber was detected in patient 3. Immunohistochemical studies for dystrophin, α-sarcoglycan, laminin M, lamininβ1, lamininβ2, desmin and emerin showed normal findings in the muscle biopsy specimens from patient 3.

**Mitochondrial DNA analysis**

Neither mitochondrial DNA large deletion nor point mutations were detected in these patients.
Discussion

These familial patients were characterized by slowly progressive mild proximal dominant muscle weakness and atrophy, cardiac involvement with severe conduction block and no rigid spine. The common muscle biopsy findings in these patients were only mild myopathic changes which did not suggest dystrophinopathies (1, 2), glycogen (12, 13) or lipid storage disease (14). The mode of inheritance and the findings of emerin immunostaining were not consistent with those of X-linked Emery-Dreifuss muscular dystrophy (6). The clinical, pathological and genetic findings in this family did not suggest other inherited muscular diseases such as autosomal dominant Emery-Dreifuss syndrome (7), mitochondrial myopathy (8), myotonic dystrophy (5), facioscapulohumeral muscular dystrophy (15), distal myopathy with rimmed vacuoles (16), McLeod syndrome (17), Barth syndrome (18), nemaline myopathy (19), multicore myopathy (20) or desmin-related myopathy (9, 10).

Dysrhythmias and AV conduction disturbances are fatal complications in patients with myopathy or muscular dystrophy (Table 1). The disease-related genes or gene loci for some of these disorders have been reported. Goldfarb et al reported two families with desmin-related myopathy and conduction block, and missense mutations in the desmin gene (DES) (10). The mode of inheritance in those families was autosomal dominant (AD) or recessive (AR). Van der Kooi et al reported two families with desmin-related myopathy or LGMD showed some similarities to our patients with regard to skeletal myopathy and cardiac conduction block. For precise comparison, the genetic background of the myopathy and cardiac abnormalities should be clarified in greater detail in these patients.

As for congenital or subclinical myopathy, several patients with cardiac involvement have also been reported. Otsuji et al reported familial cases of childhood-onset autosomal-dominant LGMD in a Chinese family with complete AV conduction block in the adults (22). Muscle biopsies from the proband showed myopathic changes with fatty degeneration, whorled fibers and rimmed vacuoles.

These reported patients with desmin-related myopathy or LGMD showed some similarities to our patients with regard to skeletal myopathy and cardiac conduction block. For precise comparison, the genetic background of the myopathy and cardiac abnormalities should be clarified in greater detail in these patients.

Table 1. Myopathy and Muscular Dystrophy with Dysrhythmias and Atrioventricular Conduction Disturbances

<table>
<thead>
<tr>
<th>Myopathy/Dystrophy</th>
<th>Inheritance</th>
<th>Main cardiac complications</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Desmin-related myopathy</td>
<td>AD</td>
<td>Right bundle-branch block</td>
<td>10</td>
</tr>
<tr>
<td>with desmin gene mutation</td>
<td>AR</td>
<td>Complete AV block</td>
<td>10</td>
</tr>
<tr>
<td>DMRV</td>
<td>AR</td>
<td>AV block</td>
<td>16</td>
</tr>
<tr>
<td>EDMD with STA gene mutations with AD inheritance</td>
<td>XR</td>
<td>Cardiomyopathy, conduction block</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>Cardiomyopathy, conduction block</td>
<td>7</td>
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<tr>
<td>Kearns-Sayre syndrome</td>
<td>Sporadic</td>
<td>AV block</td>
<td>8</td>
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<td>LGMD LGMD1B</td>
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<td>Complete AV block</td>
<td>22</td>
</tr>
<tr>
<td>Myotonic dystrophy and skeletal myopathy</td>
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<td>Cardiac arrhythmia</td>
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</tr>
<tr>
<td></td>
<td>AD</td>
<td>AV block, arrhythmia, hypertrophic cardiomyopathy</td>
<td>5</td>
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<tr>
<td>Restrictive cardiomyopathy and skeletal myopathy</td>
<td>AD</td>
<td>Restrictive cardiomyopathy</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AV block</td>
<td>26</td>
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<td>25, 27</td>
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<td></td>
<td></td>
<td>Dysrhythmia</td>
<td></td>
</tr>
</tbody>
</table>

opathy, and concluded that various types of congenital myopathy were associated with cardiac changes that could result in severe congestive heart failure (23). Dunnigan et al reported 10 patients with subclinical skeletal myopathy who had dysrhythmias as the initial manifestation of cardiomyopathy (24). Gardner et al reported a family with dominantly inherited dilated cardiomyopathy, dysrhythmia and skeletal myopathy producing very mild proximal weakness or proving detectable only upon biopsy (25). Fitzpatrick et al reported an Italian family with an autosomal dominant restrictive cardiomyopathy with AV block and skeletal myopathy (26). Some individuals who survived into the fifth decade developed a progressive, non-wasting skeletal myopathy with nonspecific myopathic changes. Although these patients showed similar clinical findings to our patients, the genetic background should be evaluated in these cases as in the cases of LGMD.

Messina et al performed genetic linkage analysis for an autosomal dominant disorder involving dilated cardiomyopathy, cardiac conduction-system disease, and adult-onset limb-girdle muscular dystrophy (FDL-CDM) and identified a region on chromosome 6q23 (27). Haplotype analysis defined the length containing the genetic defect to a 3-cM interval between D6S1705 and D6S1656. On the other hand, the gene locus for familiar AF has been reported to be localized between D10S1694 and D10S1786, an interval of 11.3 centimorgans (28). We have not performed linkage analysis for the present family, because DNA was available from only four family members including the 3 patients. Cooperative genetic linkage analysis with other groups reporting patients with similar clinical features might allow mapping of a new gene locus responsible for myopathy with conduction block.

In conclusion, this family appears to represent a new type of inherited myopathy with severe AV conductive block and AF which is probably inherited in an autosomal dominant manner. Further studies are needed to clarify the genetic background and the gene locus responsible for the disease.

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