Emery-Dreifuss Muscular Dystrophy-Related Myopathy with TMEM43 Mutations

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Ethical Publication Statement

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.
Introduction

TMEM43 is a protein found within the inner nuclear membrane that is associated with the linker of the nucleoskeleton and cytoskeleton (LINC) complex [1]. Mutations in the TMEM43 gene reportedly result in the autosomal dominant condition known as Emery-Dreifuss muscular dystrophy (EDMD)-related myopathy [2], but clinical data are limited. We identified a filioparental case of EDMD-related myopathy in which the father and son were carriers of TMEM43 mutations.
Case Reports

Patient 1

A 33-year-old Japanese man presented for evaluation. He was not hypotonic at birth, but he had a delayed onset of walking. He had poor athletic performance throughout his school years and had an unusual tendency toward keloid formation on scars. He began toe-walking at age 10. Given the similarities of his clinical course with that of his father, he was also diagnosed with EDMD. He was not from a consanguineous marriage and had one healthy sister. Progressive joint contractures, including his knees and right elbow, were noted during adolescence. During junior high school, he had difficulty climbing stairs without using a handrail. He was diagnosed with atrial fibrillation at age 28. Physical examination at the time of presentation showed flexion contractures at the ankles and right elbow. He did not have a high arched palate or facial involvement. Muscle atrophy was noted, primarily in the neck, trunk, and proximal limbs, as well as keloid formation (Figure 1A, B). He could not put his palms together or extend his wrist joints when his fingers were extended (Figure 1C-E). Manual muscle testing showed moderate weakness of neck extension (Medical Research Council grade 2) and of hip and knee extension (2), with mild weakness of shoulder abduction and extension (4), elbow flexion and extension (4), hip flexion (4) and extension (2). Creatine kinase (CK) was 287 IU/l (normal 62-287). Computerized tomographic (CT) scanning demonstrated diffuse skeletal muscle atrophy. Fatty infiltration and atrophy were observed in proximal limbs, especially in the gluteus maximus and quadriceps, whereas distal limb muscles remained relatively intact.

Electrocardiogram, echocardiogram, and Holter monitoring showed no abnormalities. Forced vital
Patient 2

This is the father of Patient 1. He had no other family history of this condition. He began toe-walking at the age of 13. At age 17, muscular disease was suspected, and a deltoid muscle biopsy led to a diagnosis of muscular dystrophy. His symptoms were not progressive. He was evaluated by a neurologist at age 48 years. Physical examination showed flexion contractures at the elbows, knees, wrists, and ankles. Neither a high arched palate nor facial involvement were seen. Muscular atrophy was diffuse, yet muscle weakness was milder than that in Patient 1. MRC grading of 3 was noted for the pectoralis major, infraspinatus, and quadriceps muscles, while other muscles were graded primarily as 4 to 5. CK was 220 IU/l. Needle electromyography (EMG) revealed abundant high and low amplitude polyphasic potentials with early recruitment. No abnormal spontaneous activity was observed. Electrocardiogram, echocardiography, and Holter monitor were normal. Forced vital capacity was 97% of predicted. CT demonstrated marked fatty infiltration and atrophy in the deltoid, biceps, triceps, quadriceps, and gastrocnemius muscles, whereas iliopsoas, hamstrings, soleus, and tibialis anterior muscles were relatively intact. Biopsy of the left biceps brachii muscle (Figure 2) revealed fatty infiltration and mild necrotic and scattered regenerating fibers with some ring fibers. Immunohistochemical stains including dystrophin, caveolin, dysferlin, alpha-dystroglycan, beta- and gamma sarcoglycan, collagen VI, emerin, and laminin a2 chain showed no abnormalities. The patient died from cancer at age 59. We could not confirm that keloid formation was part of his clinical
history.

Genetic Analysis

Preparation of genomic DNA from peripheral blood, whole-exome sequencing by Hiseq1000 (Illumina), and sequence data analyses were carried out as previously described [3]. We identified heterozygous missense mutations, c.235G>A (p.Glu85Lys) in *TMEM43* in both patients.
Discussion

Liang et al. reported TMEM43-related myopathy associated with the same mutation in two Japanese patients [2]. Our study added the following clinical features: 1) TMEM43 EDMD-related myopathy showed the typical EDMD skeletal phenotype with joint contracture, pes equinus, and axial-proximal dominant muscle weakness with limitation of finger extension; 2) phenotypes were similar between the father and son carrying the same mutation; and 3) neurological examination and muscle CT revealed truncal and proximal muscle atrophy, with significant quadriceps involvement.

Cardiac involvement with this mutation appears to be patient-dependent. Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) type 5 is also caused by mutations in TMEM43, and is characterized by ventricular tachycardia, heart failure, sudden cardiac death, and fibrofatty replacement of cardiomyocytes [4, 5]. Of the two patients previously reported to have TMEM43 EDMD-related myopathy, one patient had atrial fibrillation with bradycardia, which led to pacemaker implantation [2]. Our patients presented with no cardiomyopathy even in their fifties, although Patient 1 had a history of atrial fibrillation. However, longitudinal observation of the natural history is required.

We could not confirm whether Patient 2 or any other patients with this mutation had keloid formation, and thus cannot conclude that keloid formation is a clinical feature of this disease. No correlation has been noted between skin collagens (which play an important role in keloid formation) and the LINC complex. Further investigation, including clinical data on TMEM43 EDMD-related myopathy, is necessary.
Conclusion

We report the clinical phenotypes of patients with EMDM-related myopathy involving a mutation in

*TMEM43*. Characteristic features are muscle atrophy, primarily in the trunk and proximal muscles, especially the quadriceps. Cardiac involvement appears to be patient-dependent.
Abbreviations

CK: creatine kinase

FVC: forced vital capacity

NCNP: National Center of Neurology and Psychiatry
References


Figure legends

Figure 1.

Clinical images of Patient 1. A, B: Axial and limb muscle atrophy were seen. Ankle joint contractures due to pes equinus were seen, and he could not put his heels down on the floor when standing. Keloid formation was seen (black arrows). C: He could not bring his palms together with his fingers extended. D, E: He could extend his wrists with his fingers flexed, but not with his fingers extended.

Figure 2.

Muscle pathology of Patient 2. A: HE staining showed moderate variation in fiber size with fibers measuring from 20 to 100 microns in diameter. Some fibers with internal nuclei were seen. A few necrotic fibers (inset) and regenerating fibers were seen. Bar = 50 µm B: NADH staining showed a few ring fibers. Bar = 100 µm. C, D: ATPase staining at pH 12.6 (C), and pH 4.6 (D). Some type 2C fibers (asterisks) were seen.