**BRIEF COMMUNICATIONS**

**BETHLEM MYOPATHY IN A TAIWANESE FAMILY**

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*Abstract:* We report three cases of Bethlem myopathy from three consecutive generations of a Taiwanese family, including one woman aged 70, one man aged 40, and a boy aged 8. The clinical features of the patients included autosomal dominant inheritance, childhood or adolescent onset, mainly proximal and extensor involvement, early diffuse joint contractures, and absence of cardiac involvement. These features fulfilled the diagnostic criteria for Bethlem myopathy. Though the clinical course of the disease was once thought to be benign, our female patient became wheelchair-bound at the age of 53. This suggests that the disease process in Bethlem myopathy is slow but ongoing.

Bethlem myopathy is a rare autosomal dominant myopathy. It was first reported in 1976 by Bethlem and van Wijngaarden in three unrelated Dutch families [1]. The clinical features include childhood onset limb-girdle weakness, slow progression, widespread joint contractures, and absence of cardiac involvement [2]. Mohire et al described a large French-Canadian family and proposed the name Bethlem myopathy [3]. Subsequently, patients in other parts of the world have been described [4–7]. The features of autosomal dominant inheritance, juvenile onset, limb-girdle muscular dystrophy with diffuse joint contractures, and non-specific findings of muscle histopathology separate Bethlem myopathy from other myopathies, such as Emery-Dreifuss muscular dystrophy [8–12], rigid spine syndrome [13, 14], and congenital myopathy [1, 2], and constitute a new disease entity. Recently, it has been shown that Bethlem myopathy is due to a type VI collagen disorder with mutations of the alpha 1 to 3 subunits [15, 16]. This rare type of hereditary myopathy has not been previously reported in Taiwan; we describe three cases of Bethlem myopathy from three generations of a Taiwanese family.

**Case Reports**

A 40-year-old male patient presented with muscle wasting and contractures in the wrists and ankles. On inquiry regarding the family history, he stated that his mother and his elder son had similar clinical features. His mother had two brothers and six sisters and he had one sister and one brother, none of whom were affected. He had two sons, the elder, aged 8, also suffered from gait difficulty and contractures of the distal limbs, while the younger, aged 2, was normal in developmental milestones and free of neuromuscular symptoms. The authors examined the index case, his mother, and his two sons. Other family members refused examination. The detailed history of these three patients is described below.

**Case 1**

This 40-year-old male, a native Taiwanese, was the index case. He was not floppy at birth and had normal early developmental milestones. He began to stumble easily at the age of 4 and had poor athletic performance throughout the school years. He gradually developed pes equinovarus and toe walking at the age of 10. Rapid progression of joint contractures, including interphalangeal joints, knees and elbows, were noted during the adolescent period. His Achilles tendon was lengthened due to a tight heel cord at the age of 18 and no further shortening was noted thereafter. Diabetes mellitus was diagnosed when he was 30 years old. Physical examination at the age of 40 showed flexion contractures at the ankles, elbows, wrists, and all interphalangeal joints. Other abnormalities found on physical examination included pes equinovarus, tightness of both heel cords, and dark brown patches on the skin of the lower limbs (Fig. 1A). He had muscle wasting of all four limbs. There was no
evidence of facial weakness, scapular winging, muscle hypertrophy, or percussion myotonia. Manual muscle power testing using Medical Research Council (MRC) grading showed grade 4 proximally and 5 distally, with extensors weaker than flexors (except in the hip joint). Neck flexors also exhibited mild weakness. Tendon reflexes showed a generalized decrease. The creatine kinase (CK) concentration was 133 U/L (normal, 37–289 U/L). Concentric needle electromyography (EMG) demonstrated abundant short and small amplitude polyphasic potentials with an early recruitment pattern. Some large polyphasic potentials were also seen. No spontaneous discharges were recorded. Motor and sensory nerve conduction velocities were normal. Echocardiogram and electrocardiogram were both normal. Fasting glucose concentration was 20.7 mmol/L (376 mg/dL). HbA1C was 9.3% (normal, 4.1–6.2%). Urine analysis showed glucosuria (3+). Muscle biopsy from the left quadriceps showed increased variation in fiber size and fiber splitting, and markedly increased central nuclei. No cellular infiltrates were found. There was no evidence of muscle type grouping or angulated fibers (Fig. 2).

Case 2
This boy was the elder son of Case 1; he was 8 years old at first examination. He had frequent falling at 2 years of age, and toe walking was noted at the age of 4. He used Gower’s maneuver to stand up at the age of 5. Gait difficulty and joint contractures deteriorated rapidly thereafter. Examination revealed normal cranial musculature, mild distal weakness and moderate proximal weakness with extensors more seriously involved than flexors. Tendon reflexes were normal. Flexion contractures were seen at the elbows, interphalangeal joints, knees, and ankles. A waddling gait and toe walking were observed. He had normal intelligence. The CK concentration was 588 U/L. Concentric needle EMG demonstrated normal motor units with early recruitment. Motor and sensory

Fig. 1. Contractures of elbows and fingers are evident in (A) Case 1 and (B) Case 3. Dark brown patches on the skin of both cases over the lower limbs are postinflammatory pigmentation secondary to herb drug application. Case 3 also presented with contractures of the knees and ankles.

Fig. 2. Muscle biopsy from Case 1 shows marked variation in fiber size, an increased number of central nuclei, and round and atrophic muscle fibers of both type I and type II (ATPase pH 9.4, original magnification x 200).
conduction velocities were within normal limits. Electrocardiogram was normal. He underwent Achilles tendon lengthening surgery at the age of 9, however, contractures of ankle joints developed 1 year later.

Case 3
This 70-year-old female was the mother of Case 1. She also had normal early developmental milestones. Toe-walking was evident at age 12. Elbow and heel cord contractures developed gradually. She became a tailor and was married at the age of 26. Disease progression was slow enough that she could handle most of her daily activities without difficulty through most of her adult life. It was not until the age of 53 that, after casting for left Tibial fracture, she could not walk because of contracture of the left knee. Weakness of the upper limbs was severe enough to prevent her from using crutches, and she became wheelchair-bound thereafter. Diabetes mellitus was diagnosed at the age of 63. Examination at the age of 63 also revealed atrophy in the shoulder girdle and lower limbs. Facial musculature was spared. Muscle power testing revealed MRC grade 3 proximally and 4 distally. Flexion contractures were observed at the interphalangeal joints, knees, elbows, and ankles, and there were dark brown patches on the skin over the lower limbs (Fig. 1B). Generalized hyporeflexia was also noted. The CK concentration was 20 U/L. Concentric needle EMG demonstrated abundant polyphasic potentials with mixed short and long duration, small to large in amplitude with an early recruitment pattern. Electrocardiogram was normal.

Discussion

Our three patients had the following clinical features: early onset (childhood or adolescence); general weakness, more severe at the proximal muscles and extensors; early joint contractures, especially at the elbows and ankles but not in the spine; very slowly progressive course; absence of cardiac involvement; autosomal dominant inheritance, involving both sexes in three consecutive generations; normal to mildly elevated CK concentrations; normal mentality; and myopathic changes on muscle biopsy. The early-onset autosomal-dominant myopathy with contractures in our patients were identical to the previously reported features of Bethlem myopathy. Our literature review found 10 pedigrees of such myopathy. Most patients were European and two were from Japan [1–7, 15–17].

There are several other types of myopathy with early joint contractures including Emery-Dreifuss muscular dystrophy, rigid spine syndrome, and congenital myopathy. Emery-Dreifuss muscular dystrophy is characterized by early contracture of the Achilles tendons, elbows, and posterior cervical muscles and cardiac conduction defects, and is usually inherited as an X-linked recessive trait [8–12]. Our patients did not have cardiac abnormality and the inheritance pattern was autosomal dominant, thus the presence of Emery-Dreifuss muscular dystrophy was unlikely. Rigid spine syndrome occurs sporadically and mostly in males and is characterized by severe contractures of the spine [13, 14], which was not found in our patients. The muscle histopathology in the present three cases revealed a morphologically non-specific myopathy, which indicates an absence of congenital myopathy [1, 2]. Incomplete expression of the dominant gene of myotonic dystrophy must be differentiated from Bethlem myopathy [3]; however, neither facial weakness nor myotonia was found in our patients.

Contracture of the joints in Bethlem myopathy is actually due to contracture of the flexor muscle rather than the joint itself. The angle of finger flexion is more prominent when the wrist is extended than when it is flexed. The number of joints with contracture increased with age in our patients. The son of the index case in this report developed recontraction of the ankle joint quickly 1 year after Achilles tendon lengthening surgery at the age of 9 years. Corrective surgery for contracture in childhood should be delayed as early recompression might occur and also because of the dynamic nature of contracture in childhood [17]. Prolonged casting should be avoided in patients with Bethlem myopathy because of the possibility of inducing irreversible joint contracture. The natural course of Bethlem myopathy in adults is not always as benign as was originally reported [1]. The oldest of our three patients was confined to a wheelchair from the age of 53, Jobsis et al found that more than two-thirds of patients over 50 years of age used a wheelchair for some ambulation and suggested that the disease process was slow but ongoing [17].

References