Autosomal dominant Late-onset Quadriceps Myopathy: Three Patients of a Taiwanese Kindred

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Abstract

Objective Primary quadriceps weakness/atrophy is a rare disorder with variable etiologies; therefore, this disorder has been regarded as a clinical syndrome rather than a distinct entity. However, three affected patients of a Taiwanese family demonstrate a uniform pattern of quadriceps weakness and atrophy, their clinical manifestations and pattern of inheritance may suggest a new disease entity.

Patients and Methods Three patients in a Taiwanese kindred with selective quadriceps weakness and atrophy, which began after age 40 years, were examined. To disclose the confines of this disorder, muscle CT scans, electromyography, nerve conduction studies and muscle biopsies were performed; and to unravel and better understand the nature of this disorder, histopathological, ultrastructural, immunocytochemical and genetic studies were carried out.

Results In two patients with long-standing disease, muscle imaging showed marked atrophy and fat replacement of the anterior thigh muscles and electromyography showed a mixture of myopathic and neuropathic changes. Muscle histopathology on the mildly affected tibialis anterior showed myopathic changes with myofibrillar degeneration and secondary neurogenic alterations. Immunocytochemical staining was not diagnostic but excluded the dystrophinopathies and other well-known muscular dystrophies.

Conclusion All previously identified diseases resulting in quadriceps weakness and atrophy have been ruled out and the present disorder appears to be a new disease entity of autosomal dominant late onset quadriceps myopathy.

Key words: quadriceps myopathy, autosomal dominant inheritance, late-onset, myofibrillar degeneration

Introduction

Primary selective quadriceps weakness and atrophy is a rare disorder with variable etiologies. In 1922, Bramwell first reported two cases of selective quadriceps weakness (1). Since then, only a few sporadic cases of such a disorder have been reported. Information from cases of such a rare disorder published in the first half of the twentieth century is of limited value since muscle biopsy specimens were not examined by modern histo- and cytochemical techniques. Moreover, the classification of muscle diseases has changed considerably in the past 50 years. Therefore, one can only conjecture as to the possible etiologies even of those cases published after the late 1960s. Even so there have been only about 50 reports of primary bilateral quadriceps weakness/atrophy. A number of disease entities, hereditary and sporadic, neurogenic and myopathic, have been associated with this syndrome. They include myositis (2-4), inclusion body myositis (IBM) (5, 6), Becker muscular dystrophy (BMD) (7-9), Ehlers-Danlos syndrome (10), proximal myotonic myopathy (PROMM) (11), Lewis-Sumner syndrome (12), lamin A/C gene mutation (13, 14), diabetic amyotrophy (15), and neurogenic quadriceps amyotrophy (16-18). Therefore, selective quadriceps weakness/atrophy is considered to be a syndrome rather than a disease entity.

We report three patients from one family, all of whom...
had selective quadriceps weakness. The pattern of inheritance, age of onset, and muscle pathology findings are sufficiently distinct to distinguish them from all other known cases of quadriceps myopathies. We have tentatively labeled this disorder as autosomal dominant late-onset quadriceps myopathy (ADQM).

Patients and Methods

We examined 3 affected patients in the Taiwanese kindred shown in Fig. 1. All had anterior thigh weakness and atrophy. Muscle CT scans, electromyography (EMG) and nerve conduction studies (NCS) were performed in all (patients 1-3). Open muscle biopsies, were obtained from patient 1 (the left tibialis anterior and left biceps brachii), and patient 3 (the right tibialis anterior). Serial frozen sections were stained with H&E, modified Gomori trichrome and a battery of histochemical methods. The specimens for electron microscopy were fixed in 2% glutaraldehyde for 2 hours and then processed for embedding in epon. Ultrathin sections were stained with uranyl acetate and lead citrate.

DNA studies

PCR analyses of the dystrophin gene were carried out on 19 exons (Pm, 3, 4, 6, 8, 12, 13, 19, 43, 44, 45, 46, 47, 48, 50, 51, 52, 60) by 2 sets of multiplex PCR, and on 18 exons (same as above but 46) by 6 sets of semiquantitative-triplex PCR.

PCR analyses combined with restriction fragment length polymorphism were used to look for deletion of exon 7 and exon 8 of survival motor neuron (SMN) gene (19).

The CTG A/C gene was sequenced and analyzed for mutations, such as premature stop codon (20).

CTG repeats in 15th exon of dystrophia myotonica protein kinase (DMPK) gene (21) and CCTG repeats in 1st intron of zinc finger protein 9 (ZNF9) gene were measured (22, 23).

Immunocytochemistry studies

Immunostains and immunolocalizations were performed on 6-μm-thick fresh-frozen sections with the following antibodies: dysferlin with two monoclonal antibodies directed against dysferlin exons 11, 12 and 53, dystrophin with three monoclonal antibodies against mid-rod domain, carboxy terminus and amino terminal domain of human dystrophin, caveolin-3 with monoclonal primary antibodies directed against caveolin-3, emerin with monoclonal antibodies directed against human emerin protein, merosin with monoclonal antibodies directed against laminin alpha 2 chain of merosin in human and rabbit skeletal muscle; α, β, γ, and δ sarcoglycan with monoclonal antibodies against each protein, β-dystroglycan with monoclonal antibodies directed against β-dystroglycan, desmin with mouse monoclonal antibodies against Z-bands of human muscle, titin with mouse monoclonal antibodies against recombinant human titin, myotilin with rabbit polyclonal antibodies against human myotilin, Z-band alternatively spliced PDZ motif-containing protein (ZASP) with rabbit polyclonal antibodies against human ZASP protein, αB-crystallin with rabbit polyclonal antibodies against human αB-crystallin, and major histocompatibility complex class I (MHC-I) antigens with mouse monoclonal antibodies against human MHC-I antigens. The primary antibodies were detected with the Ventana Medical Systems Basic AEC Detection Kit.

Results

All three patients had selective quadriceps muscle weakness and atrophy but sparing the upper limbs. A grandmother of the proband was known to have had the insidious onset of anterior thigh atrophy and weakness around 60 years of age, and she died at age 80. One of her sons, the proband’s father, patient 3, now age 75, had the same problems. One female cousin of the proband, patient 2, was also affected. There were more than 60 offsprings in the proband’s generation, but to date there has been no other definitively affected patient. The disease appears to be inherited through an autosomal dominant trait.

Patient 1 (the proband): The patient was a 47-year-old retired male sergeant, the second of four siblings, who developed thigh muscle weakness and atrophy at age 40. He was a first-class amateur ping-pong player, but could not play beyond age 40 years because of leg weakness. Thereafter his lower limb weakness became evident and he fell frequently, especially when going down stairs. He had difficulty in rising up from the floor and had to use hand railings to climb up stairs.

On physical examination at age 47, all of his muscles were of normal bulk except for the quadriceps muscles, which were atrophic (Fig. 2A). When he stood, he had a lordotic posture and prominent abdomen; and he walked with an unsteady, short-step, foot-slapping gait. He raised the thigh a fraction higher, trod roughly on the ground and made noise. Although he was able to walk on his toes and even to hop, he was unable to walk on his heels. Tendon reflexes in the upper limbs and ankles were symmetrically normal but knee jerks were absent, and the plantar responses...
were flexor.

His cardiac, respiratory, and ophthalmic examinations were normal. His creatine kinase was slightly elevated to 150UI (normal value <130). Muscle CT showed marked muscle atrophy and fat replacement of the quadriceps femoris muscles but sparing of the hamstrings (Fig. 3E). Other than the minimally affected lower leg and paraspinal muscles showing moth-eaten appearance (Fig. 3D & F), the other muscles including hip, pelvic, shoulder and arm muscles were spared.

Motor/sensory NCS and F-wave latencies were normal, but both femoral motor amplitudes were reduced. The EMG changes on vastus medialis and gastrocnemius included markedly increased numbers of long-duration motor unit potentials, a few of them with higher than normal amplitude. Small polyphasic potentials were less frequent; however, the mixture of large and small motor unit potentials were also found in the abductor pollicis brevis, triceps brachii and paraspinal muscles. There was no spontaneous activity in all examined muscles.

He had biopsies of the right quadriceps, left biceps brachii, and left tibialis anterior (TA) at age 47. All of the muscle fibers obtained from the quadriceps femoris were replaced by fat and connective tissue. The left biceps brachii muscle was almost normal with normal fiber type distribution except that about 2% of the fibers had internally located nuclei. In the left TA, there were advanced myopathic changes including marked variation in fiber size and many small fibers (Fig. 4A) which were darkly stained with NADH-TR (Fig. 4B). Some fibers contained sarcoplasmic masses. The larger fibers were mainly type 2 but both type 1 and 2 fibers were atrophic. There was marked peri- and endomysial fibrosis.

On immunohistochemical examination, dysferlin, dystrophin, α-, β-, γ-, δ-sarcoglycans, β-dystroglycan, merosin, caveolin-3, emerin, and MHC-I were normally expressed and there was no abnormal accumulation of desmin, titin, myotilin, ZASP, or αβ-crystallin.

Genetic analysis for dystrophin, SMN, lamin A/C gene showed no mutation. There were 13 CTG repeats in the 15th exon of DMPK gene and no CCTG expansion in the 1st intron of ZNF9 gene.

On electron microscopy, areas of sarcoplasmic masses contained disorganized myofibrillar components, dilated tubular profiles and mitochondrial debris. There were scattered degenerating and regenerating fibers containing irregularly oriented myofibrils, wide Z disks, nemaline bodies, dilated sarcoplasmic reticulum and prominent Golgi networks.

**Patient 2:** This 54-year-old woman, the proband’s cousin, the second of six siblings and mother of six daughters, developed symptoms around 53 years of age when she started to fall frequently. During most of her life she had had no problem keeping up with her peers in activities such as running, hiking, and climbing stairs. One year before our examination she experienced transient lower limb weakness after her usual morning exercise (climbing a long gentle slope). Thereafter lower limb weakness became evident and she fell frequently while climbing up the stairs. Her uncle, patient 3, thought that she had the same problem as his mother.

One year previously, at age 53, she was a well-nourished housewife, and all her muscles were normal except for the quadriceps, which were slightly thin and weak (3-4/5). However, the deep tendon reflexes were all normal.

Creatine kinase was 89 UI. Except for mildly atrophic quadriceps muscles (Fig. 2C), others appeared normal on muscle CT (Fig. 3G-I). EMG showed no significant abnormalities. Muscle biopsy was not performed. Her genetic analyses were unremarkable.

**Patient 3:** This 75-year-old man, the proband’s father, fourth of five siblings, was a martial arts expert when he was young. Muscle weakness appeared at age 60 when he fell frequently.

On examination, he was ambulant but he could not stand up from the floor without help (Fig. 2B). There was marked quadriceps weakness (2-3/5). Tendon reflexes in the upper limbs were normal and symmetric at 2+, but only 1+ in the lower limbs.

Ophthalmic and cardiac examinations were unremarkable. His serum CK level was 67 IU. Muscle CT showed that the quadriceps muscles, predominantly on the right, were almost totally replaced by fat tissue (Fig. 3B). The hamstring muscles were also moderately affected. The paraspinal, abdominal and leg muscles (Fig. 3A & C) showed moth-eaten appearance, though the pelvic, shoulder and upper arms appeared normal. The EMG findings were almost identical to those seen in patient 1.

The right TA muscle biopsy at age 75 showed myopathic
Figure 3. Muscle CT scans of patients 3 (A, B, C), 1 (D, E, F) and 2 (G, H, I) clearly demonstrates selective quadriceps femoris muscle involvement in patients 1 and 3 (B, E) with relative sparing of hamstring, hip, and pelvic muscles (A, D). Lower leg muscles have minimal moth-eaten appearance (C, F). There is no CT evidence to suggest muscle atrophy in patient 2 (G, H, I). Slices at the levels of hypogastrium (A, D, and G), mid-thigh (B, E, and H) and upper third portion of leg (C, F and I).

changes with variation in fiber size, scattered fibers with disorganized intermyofibrillar network (Fig. 4C) and some of them had high acid phosphatase activities (Fig. 4D). There were a few necrotic fibers. Some fascicles contained very atrophic fibers with high NADH activity mimicking group atrophy seen in neuropathic disorders.

Patient 3’s immunohistochemistry studies and genetic analyses were unremarkable.

On electron microscopy, the small round fibers had disorganized intermyofibrillar networks with occasional autophagic vacuoles filled with a variety of membranous and laminated bodies (Fig. 5). Despite active myofibrillar degeneration, satellite cells were not activated indicating poor regenerating process.

Patient 4: The history of this patient, the grandmother of the proband, was obtained from patient 3. She died at age 80; she had complained of difficulty climbing stairs and frequent falls since age 60. She had been examined by several physicians but no definite diagnosis was made. She had no history of stroke or other neurologic disorders.

Discussion

The pedigree described here displays a form of selective quadriceps weakness that appears to be transmitted as an autosomal dominant trait. Its onset late in life, its serum CK normal or minimally elevated, and its muscle pathology myopathic, ADQM is slowly progressive with preferential
cases of quadriceps weakness/atrophy.

First, all ADQM patients have similar clinical features. In short, their initial problem is generally kneeling because of anterior thigh muscle weakness. Although finally spreading to trunk and leg muscles, the weakness is limited to quadriceps for many years. And the inheritance of ADQM is an autosomal dominant pattern despite the fact that its penetrance is low. The reason why its penetrance is low is difficult to determine; however, all three examined ADQM patients have occupations and/or habits connected with high physical activities. Therefore, strenuous exercise may be an environmental codeterminant affecting the penetrance of ADQM. Further, the disease process seems to be myopathic because the muscle biopsies show variation in fiber size and myofibrillar degeneration. In addition, apparent fiber type grouping suggesting denervating and reinnervating processes are lacking despite the longstanding disease process. In fact, features suggestive of neurogenic changes seen in our patients are probably secondarily induced phenomena frequently seen in chronic myopathic processes including chronic muscular dystrophies. Still, muscular dystrophy is unlikely, because necrotic and regenerating fibers are rare and serum CK levels are normal or only very slightly elevated. Also, differing from so-called myofibrillar myopathy,
ADQM has no intracytoplasmic inclusions on light and electron microscopy and no excessive accumulation of related proteins on immunohistochemistry (24-27). Thus, myofibrillar degeneration appears to be the major disease process leading to muscle atrophy as clearly demonstrated in EM photos. For all these reasons, ADQM has its own disease entity.

Second, with some rare exceptions (28, 29), diseases reported to have early selective bilateral quadriceps weakness and atrophy include the following diseases: BMD, limb-girdle muscular dystrophy 1B (LGMD 1B) and 1C, PROMM, IBM, myositis, Ehlers-Danlos syndrome, Lewis-Summer syndrome, diabetic amyotrophy, and neurogenic quadriceps amyotrophy; however the present patients did not appear to have any of these diseases.

It is well known that the quadriceps muscle is occasionally selectively affected in BMD (30); but the present patients had normal dystrophin expression in muscle biopsies and no mutations in the dystrophin gene both rule out the possibility of BMD.

LGMD 1B and 1C can present with autosomal dominant quadriceps weakness; however, their age of onset is much earlier than those of ADQM (31-33). Further, joint contractures, cardiac involvement, and mutation in lamin A/C gene, frequently seen in LGMD 1B, were absent in ADQM patients and serum CK levels tend to be very high in LGMD 1C, but are almost normal in ADQM. PROMM is also transmitted in an autosomal dominant fashion and may present with muscle weakness in the quadriceps, but PROMM can be ruled out because our patients had no myotonia, no cata-ract, no classic muscle pathologic alterations, and no CCTG expansion in the 1st intron of ZNF9 gene (34).

The present patients did not have IBM since their muscle biopsies had no rimmed vacuoles (35, 36), no inflammatory cellular infiltration, and no strong MHC-I expression on membranes of non-necrotic fibers (37). Also, our ADQM patients do not satisfy any of Perelman’s diagnostic criteria for Ehlers-Danlos syndrome (38). Fujiyama et al suggested that Lewis-Summer syndrome must be included in the differential diagnosis of quadriceps amyotrophy (12). Again, none of the present patients had sensory complaints and their NCS were normal. Finally, diabetic amyotrophy (15) was listed in the differential diagnosis of quadriceps myopathy, but our patients were not diabetic.

Alternatively, the question arises as to whether or not ADQM could be a form of adult type spinal muscular atrophy (SMA), or a forme fruste of Kugelberg-Welander disease (16). Although SMA of Finkel type, is transmitted in an autosomal dominant fashion and has late onset proximal muscle involvement of the lower extremities, its clinical manifestations are different from those of ADQM patients’ (39). In addition, the normal fiber type distribution seen in the biceps brachii of patient 1 and the normal EMG recording of patient 2 suggests that our patients did not have SMA. Moreover, none of our ADQM patients showed evidence of SMN gene defect.

In conclusion, the affected patients in this pedigree demonstrate a uniform pattern of quadriceps weakness and atrophy, with autosomal dominant transmission, very late onset and normal or minimally elevated serum CK levels. Since the underlying pathologic process is likely responsible for myofibrillar degeneration, further study is necessary to explore the pathogenetic mechanism which induces such degeneration.

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

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