Benign Calf Amyotrophy

Clinicopathologic Study of 8 Patients

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**Background:** The benign focal amyotrophy disorders have been described since 1959 for the upper limbs and since 1981 for the lower limbs. The clinicopathologic features have pointed to a restricted and self-limiting form of motor neuron disease.

**Objective:** To describe the clinical, electromyographic, and muscle histopathologic features in 8 patients with benign calf amyotrophy.

**Design:** Retrospective review of patient charts, electromyograms, and muscle histopathology.

**Patients and Results:** Eight patients, aged 37 to 88 years, developed insidiously progressive calf muscle weakness and wasting during 1 to 5 years. The gastrocnemius weakness and wasting were bilateral in 4 patients. Initial progression of symptoms was followed by disease stabilization. None had a history of poliomyelitis or family history of neuromuscular disease. Creatine kinase values were mildly elevated in 5 patients. The electromyographic and muscle histopathologic findings were consistent with a chronic neuropathic disorder. Despite the restricted calf muscle involvement clinically, the electromyographic abnormalities suggested more diffuse lower limb involvement. Further studies, including DNA tests and muscle-based protein studies, excluded several types of inherited neuromuscular disorders.

**Conclusions:** Benign calf amyotrophy is a variant of the benign focal amyotrophy disorders. The etiology for these disorders is unknown. Studies to exclude other causes of calf amyotrophy and careful follow-up examinations to document disease stabilization are necessary to diagnose this uncommon disorder.

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The benign focal amyotrophy disorders (BFADs) are a clinically heterogeneous group of disorders causing weakness and atrophy of the upper or lower extremities. These disorders are distinguished from other more common forms of motor neuron disease by the restricted limb involvement, absence of upper motor neuron signs, and slow progression for months to years followed by disease stabilization. Benign focal amyotrophy disorder of the upper extremity is the major variant reported in Western countries, while the lower limb variant is more commonly reported in India. We describe the clinicopathologic findings in 8 unrelated men, including 2 Asian Americans, who presented with benign calf amyotrophy, a variant of the BFADs.

**METHODS**

We reviewed the clinical, laboratory, electromyographic (EMG), and muscle histopathologic data on patients presenting with calf atrophy who were evaluated in the neuromuscular clinics at the University of Connecticut Health Center during the past 10 years. Included in this retrospective analysis were patients who fulfilled the following criteria: (1) insidiously progressive unilateral or bilateral calf muscle atrophy or weakness, (2) no known antecedent injury, (3) no sensory symptoms, (4) no known medical or neurologic disorders that could cause muscle weakness or atrophy, (5) no magnetic resonance imaging evidence of L5 or S1 nerve root disease, (6) comprehensive EMG evaluation, and (7) follow-up information for at least 1 year.

**RESULTS**

Eight patients who fulfilled our criteria are summarized (Table 1). All were men, with a mean age at baseline evaluation of 57 years (range, 37-88 years). All symptoms began insidiously, with a mean age at onset of 53.3 years (range, 36-84 years). Patients reported slow progression of symptoms for 1 to 5 years (mean, 2.4
years). Most presented with calf muscle atrophy, and many also complained of symptoms related to calf muscle weakness (eg, inability to stand on tiptoe or jump). Four patients complained of bilateral symptoms, while the remainder noted symptoms in 1 limb only. Other medical problems included hypertension in 3 patients, coronary artery disease in 1, and mild hypercholesterolemia in 1. None had prior neurologic problems, diabetes mellitus, treatment with lipid-lowering agents, or an attack of severe back pain that led to bed rest. All were born in the United States except patient 1 from the Philippines, patient 4 from Spain, and patient 7 from India. All patients remembered having vaccinations for poliomyelitis, and none reported childhood illnesses resembling this condition. There was no known family history of neuromuscular disease or wasting. On examination, all were found to have bilateral or unilateral calf muscle atrophy (Figure 1). Atrophy of the medial gastrocnemius muscle was a prominent feature in most patients. All had inability or difficulty standing on tiptoe with the involved limb. Patient 3 had noticeable weakness of plantar flexion during the push-off phase of his gait; all other patients had normal stance and gait. None had weakness or prominent atrophy of other muscle groups. Ankle jerks were absent and knee jerks were present in all patients. There were no visible fasciculations. Sensory examination abnormalities and upper motor neuron signs were not observed in these patients. Follow-up clinical evaluations ranging from 1 to 3 years showed no progression or improvement of symptoms.

Creatine kinase values were elevated in 5 patients, with a mean value of 337.8 U/L (range, 134-700 U/L; normal, <269 U/L). The following serum laboratory studies were normal on all patients: complete blood count, erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, fasting glucose, chemistries, calcium, thyroid function studies, parathyroid hormone, lead level, serum protein electrophoresis, immunoelectrophoresis, vitamin B12 level, and Lyme disease serology. Cerebrospinal fluid study results were normal for patients 3 and 4. Of patients who were tested, Kennedy disease DNA tests showed no expanded CAG trinucleotide

<table>
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<th>Patient No.</th>
<th>Age, y</th>
<th>Age at Onset, y</th>
<th>Progression, y</th>
<th>Side</th>
<th>Creatine Kinase, U/L</th>
<th>NCS</th>
<th>LS MRI</th>
<th>Histopathologic Findings</th>
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<td>3</td>
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Abbreviations: DA, degenerative arthritis; LS MRI, lumbosacral magnetic resonance imaging; NC, no change; NCS, nerve conduction study; SNAP, sensory nerve action potential.

*All patients were men and all demonstrated chronic neuropathic findings on concentric needle electromyography.

Figure 1. Photographs of patients 1 (A), 2 (B), and 7 (C) showing bilateral (A), right (B), and left (C) posterior foreleg muscle atrophy. Atrophy of the medial head of the gastrocnemius muscles is especially prominent in patients 1 and 2.
repeat mutation in the androgen receptor gene for patients 1, 2, 3, 4, and 7; spinal muscular atrophy DNA tests showed no deletion mutation in the survival motor neuron gene for patients 2 and 7; and Becker DNA test showed no deletion mutation in the dystrophin gene for patient 3. Antibody titers to the GM1 ganglioside were not elevated for patients 1, 2, 4, and 7.

Magnetic resonance imaging findings of the lower spinal cord and lumbosacral spine were normal or showed only mild to moderate degenerative bony changes (Table 1). There was no evidence of lower spinal cord or L5 or S1 nerve root disease. Patient 1 underwent magnetic resonance imaging of the thigh and foreleg muscles (Figure 2). Positive findings included marked atrophy and increased signal of both medial gastrocnemius muscles (arrows) with relative sparing of thigh and other foreleg muscles.

Nerve conduction study findings were normal in all patients except for a low-amplitude sural sensory nerve action potential in patient 2. There was no evidence of partial motor conduction block, focal or diffuse conduction slowing, or abnormal temporal dispersion of the compound muscle action potentials. Bilateral tibial H-reflex studies showed absent responses for patient 1, prolonged right-sided latency for patient 2, and normal responses for patients 3, 5, and 8. Needle EMG results showed primarily reduced recruitment of large motor unit action potentials in the involved gastrocnemius muscles (Figure 3). Rare low-amplitude fibrillations and complex repetitive discharges were observed in the gastrocnemius muscles of 5 patients. Despite the predominant involvement of posterior foreleg muscles on clinical examination, mild EMG abnormalities extended into other lower extremity but not lumbosacral paraspinal muscles for all patients. We found mild chronic neurogenic EMG changes in the contralateral gastrocnemius muscles for patients presenting with unilateral symptoms. Needle EMG findings of at least 3 upper limb muscles were normal for all patients.

Medial gastrocnemius muscle biopsies were performed on patients 1, 2, and 3. Routine histochemistry showed increased fiber size variability, including hypertrophic and markedly atrophic myofibers (Figure 4). Grouped fiber atrophy was a prominent feature, and many of the atrophic fibers stained dark on the nicotinamide adenine dinucleotide–tetrazolium reductase stain. All showed increased connective tissue deposition. Some of the hypertrophic fibers showed increased numbers of internalized nuclei. Dystrophin and dysferlin immunoperoxidase studies on patients 1 and 2 showed normal membrane expression of these 2 proteins (Figure 5).

**COMMENT**

The differential diagnosis for focal limb amyotrophy is extensive and includes degenerative forms of motor neuron disease (eg, amyotrophic lateral sclerosis and progressive muscular atrophy), late-onset hereditary disorders (eg, Kennedy disease), hereditary motor neuropathies, autoimmune motor neuropathies (eg, multifocal motor neuropathy with conduction block), progressive sensorimotor polyneuropathies (eg, diabetic lumbosacral radiculoplexus neuropathy), focal nerve or root disorders, and focal-onset myopathies (eg, Miyoshi myopathy). The diagnosis of BFAD can only be made when these disorders are excluded.
ders are excluded and when follow-up evaluations document disease stabilization.

A benign focal amyotrophy disorder was first reported in Japan as juvenile muscular atrophy of unilateral upper extremity in 1959. Soon after, descriptions of other patients began to emerge. Since that time, multiple cases and nearly as many terms to describe the various disorders have been reported (Table 2). We prefer to group these idiopathic disorders under the heading of BFADs, as this term reflects the self-limiting nature of these chronic focal motor neuropathies or neuronopathies. Also, this terminology does not necessarily restrict the disorder to a particular limb (eg, wasted leg syndrome) or to a single limb (eg, monomelic amyotrophy), nor does it imply a proposed pathophysiologic condition (eg, Hirayama disease) or suggest a genetic etiopathology (eg, segmental spinal muscular atrophy).

The first important clinical report of BFAD of the lower limb was published in 1981. This clinical study described 40 patients from India, all men, who developed insidiously progressive and self-limiting unilateral leg weakness. Wasting was diffuse in 26, restricted to foreleg muscles in 9, and restricted to the quadriceps muscle in the remainder. Electrophysiologic and muscle histopathologic findings in these patients and others from India were consistent with a chronic neurogenic disorder affecting anterior horn cells or motor axons. Based on their clinicopathologic observations, the authors of this initial article referred to this disorder as the wasted leg syndrome.

Since the initial reports, more than 80 cases of BFAD of the lower limb have been reported, with most cases coming from India. Clinical features of the wasted leg syndrome of India and BFAD of the lower limb of Western countries are similar. There is a preponderance of men. The reports all document sporadic occurrence, without other affected family members. Weakness and wasting are usually restricted to a single limb. Involvement may be diffuse or restricted to certain muscle groups like the gastrocnemius or anterior tibialis muscles. Progression, if noted by patients, occurs during 1 to several years. Thereafter, there is disease stabilization without improvement. Fasciculations are occasionally noted; however, sensory symptoms, back or limb pain, or upper motor neuron signs are universally absent. The creatine kinase value is normal or slightly elevated. Various laboratory study results, including genetic studies for spinal muscular atrophy (SMN gene deletion) and antibodies to gangliosides, have been negative. Despite the unilateral or focal involvement in most cases, EMG studies have documented primarily chronic neuropathic changes in leg muscles remote from and contralateral to the areas of wasting. Upper limb EMG abnormalities are occasionally seen. Muscle histopathologic findings typically show neurogenic atrophy, fiber type grouping, hypertrophic fibers, and secondary myo-

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**Figure 4.** Lateral gastrocnemius muscle histopathologic findings for patients 1 (A and B), 2 (C and D), and 3 (E and F). Gomori trichrome (A) and hematoxylin-eosin (C and E) sections show markedly increased variation in fiber size, with atrophic and hypertrophic fibers, increased connective tissue, pyknotic nuclear clumps, and increased internalized nuclei. Groups of atrophic fibers, many staining dark, are observed on sections stained with nicotinamide adenine dinucleotide–tetrazolium reductase (B, D, and F) (original magnification ×100).
pathic features. Imaging demonstrates atrophy of involved muscles. Magnetic resonance imaging in a recent patient showed muscle atrophy and increased signal on T1-weighted studies consistent with fatty replacement of muscle. Imaging of the lower spinal cord and nerve roots has shown no evidence of a causative lesion. To our knowledge, there are no postmortem studies in BFAD of the lower extremity. Postmortem findings in the upper limb form have revealed spinal cord shrinkage, necrosis, anterior horn cell loss, and mild gliosis involving the anterior gray matter of the cervical spinal cord.

The cause of BFAD of the lower limb is unknown. Compared with progressive muscular atrophy, patients with BFAD have a more restricted and self-limiting disorder. Whether the latter is an arrested form of progressive muscle atrophy is a question that cannot be answered at this time as the etiology for anterior cell loss for both disorders is unknown. The evidence thus far does not favor a genetic cause for BFAD of the lower limb, as none of the described patients have documented a positive family history. Whether there are risk factors for these disorders is unknown as well, although some reports have suggested a correlation between the disorder and strenuous occupation and immobility following injury. The controversy regarding possible chronic spinal cord compression from an aberrant posterior dura, as reported in some cases of upper limb amyotrophy (Hirayama disease), is not an issue in the lower limb variant.

Figure 5. Dystrophin (A and C) and dysferlin (B and D) immunoperoxidase stains for patients 1 (A and B) and 3 (C and D) showing normal membrane expression (original magnification ×100).
Miyoshi myopathy. The study findings in our patients were more consistent with chronic neuropa-thetic rather than myopathic disease. Moreover, the age at onset was older and the creatine kinase values were lower in our patients compared with the typical patient with Miyoshi myopathy. Still, the findings of mixed myopathic and neuropathic histologic features in our patients along with the reports of late-onset calf muscle weakness due to dysferlin and dystrophin deficiency compelled us to exclude these disorders in patients in whom frozen muscle tissue was available.20-22

To our knowledge, this is the largest series of BFAD of the lower limb that has been reported outside India. The prevalence of men and the findings of chronic neurogenic changes on EMG and muscle histopathologic examination are features similar to other reported cases of BFAD of the lower limb in Western countries and the wasted leg syndrome of India. Differences in our patients compared with others include the older age at onset and bilateral symptoms in half of the patients. Despite the restricted clinical involvement of calf muscles, the EMG abnormalities suggest more diffuse lower limb involvement, consistent with other reports. Additional studies in our patients excluded spinal muscular atrophy (SMN gene deletion), Kennedy disease, and late-onset dystrophinopathy or dysferlinopathy as potential genetic causes of the calf amyotrophy. Benign calf amyotrophy appears to be a variant of the BFADs and should be considered in patients, especially men, with static or slowly progressive unilateral or bilateral calf muscle wasting. Studies to exclude other causes of calf amyotrophy and careful follow-up examinations to document disease stabilization are necessary to diagnose this uncommon disorder.

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REFERENCES