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Leg Amyotrophic Diplegia: Prevalence and Pattern of Weakness at US Neuromuscular Centers

Mazen M. Dimachkie[1,2], **Iryna M. Muzyka**[1], **Jonathan S. Katz**[4], **Carlayne Jackson**[5], **Yunxia Wang**[1], **April L. McVey**[1], **Arthur Dick**[1], **Mamatha Pasnoor**[1], **M. Tahseen Mozaffar**[6], **Z. Xiao-Song**[7], **John T. Kissel**[7], **E. Ensrud**[8], **Jeffrey Rosenfeld**[9], and **Richard J. Barohn**[1,3]

[1]Department of Neurology, University of Kansas Medical Center

[2]Department of Neurology, University of Texas-Houston

[3]Department of Neurology, University of Texas-Southwestern

[4]Department of Neurology, California Pacific Medical Center

[5]Department of Neurology, University of Texas-San Antonio

[6]Department of Neurology, University of California-Irvine

[7]Department of Neurology, Ohio State University Medical Center

[8]Department of Neurology, Boston VA Medical Center and Brigham and Women's Hospital

[9]Department of Neurology, University of California San Francisco-Fresno

Abstract

Objective—To identify the frequency of leg amyotrophic diplegia (LAD) at a US academic center, describe the pattern of weakness, and provide comparative data from 8 additional major US academic institutions.

Background—LAD is a leg onset variant of progressive muscular atrophy (PMA). LAD weakness is confined to the legs for at least 2 years and there are no upper motor neuron signs.

Design/Methods—We present a retrospective chart review of 24 patients with the LAD presentation from the University of Kansas Medical Center (KUMC, n=8 cases) and from eight US academic institutions (n=16 cases).

Results—Of 318 subjects identified in the KUMC Neuromuscular Research Database, 82% (260) had amyotrophic lateral sclerosis (ALS), 1.9% (6) had familial ALS, 6.6% (21) had primary lateral sclerosis, and 29 had LMN disease. Of these 29 cases, 16 had PMA, 5 had brachial amyotrophic diplegia, while 8 had LAD. The mean LAD age of onset was 58 years with a male/female ratio of 3/1. Onset was asymmetric in 7/8. We identified a pelviperoneal pattern of weakness (sparing of knee extension and/or ankle plantar flexion) in 4 cases and distal predominant weakness in 3. All patients had electrodiagnostic findings consistent with motor neuron disease confined to the lower extremities. We present LAD disease duration and survival

Please address correspondence to: Mazen M. Dimachkie, MD, 3599 Rainbow Blvd, MS 2012, Kansas City, KS 66160, Phone: 913-588-6970, Fax: 913-588-0609, mdimachkie@kumc.edu.

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data from eight major academic neuromuscular centers. At last follow up, weakness progressed to involve the arms in 6/24 LAD cases and of those two died from progression to typical ALS. From onset of symptoms, mean survival in LAD is 87 months, with 92% of cases being alive.

Conclusions/Relevance—The natural history of LAD differs from typical forms of ALS and PMA. LAD is a slowly progressive disorder that accounts for a fourth of LMN disease cases. An asymmetric pelviperoneal pattern of weakness should heighten the suspicion for LAD.

Introduction

Progressive muscular atrophy (PMA) comprises approximately 10% of patients with motor neuron disease (MND). Some of the patients presenting initially as PMA will develop when followed over time upper motor neuron findings leading to the diagnosis of ALS. True PMA cases represent a pure lower motor neuron presentation of sporadic motor neuron disease and are in a spectrum with ALS and PLS. While PMA typically affects both the arms and legs, some patients have predominantly upper extremity involvement and others may have selective leg weakness referred to respectively as brachial amyotrophic diplegia (BAD) [1,2] and leg amyotrophic diplegia (LAD).[3] These disorders of focal motor neuron disease have a more indolent course. A LMN syndrome confined to legs LAD was first described by Pierre Marie and his student Patrikios in 1918 and was known as the pseudopolyneuritic variant of ALS, the Marie-Patrikios form, or the peroneal form of ALS.[4]

We previously presented our observations on LAD.[3] Wijesekera and colleagues have described patients with the Flail Leg Syndrome which is probably a similar entity though their case definition is different from ours.[5] In this report, we further describe the clinical features of LAD and its pattern of weakness from the motor neuron disease clinic at KUMC and eight other medical centers. We discuss the better prognosis of LAD cases as compared to those with ALS.

Patients and Methods

This is a retrospective chart review of patients with LAD performed with Institutional Board Review approval. Inclusion criteria were presence of progressive leg motor dysfunction, a clinical examination demonstrating a pattern of weakness limited to the lower extremities bilaterally at least 2 years after onset, absence of upper motor neuron signs at 2 years or at first evaluation if conducted later than 2 years from onset and similarly an electrodiagnostic study consistent with disorder of lower motor neurons confined to the legs. None could fulfill the El Escorial criteria for definite, probable, possible or suspected ALS at first presentation. We excluded patients from our analysis if there was any evidence of weakness in neck, bulbar, arm or respiratory muscles before 2 years. Patients were also excluded if there was bladder or bowel dysfunction. We did not include those with unexplained sensory signs or symptoms, abnormal nerve conduction studies (NCS) or any abnormality outside the lumbar myotome on electromyography (EMG) performed at least 2 years after onset. None were included if they had radicular pain, weakness in the distribution of individual motor nerves, or any abnormality on lumbar MRI suggestive of an alternate diagnosis such as spinal stenosis or a mass lesion.

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We identified the frequency of LAD at the University of Kansas Medical Center (KUMC) based on review of all cases of MND from 2004 to 2010. All patients meeting the above criteria continue to be actively followed in our clinics. We provide a detailed description of patients who presented with LAD based on clinical and laboratory data abstracted from the medical records including creatine kinase (CK), NCS, EMG, and lumbar magnetic resonance imaging (MRI). In addition, we provide abbreviated descriptive data on LAD cases from 8 US academic centers with emphasis on disease duration, spread to the arms and survival.

Results

KUMC

Of 316 subjects identified in the KUMC Neuromuscular Research Database, 82% (260) had sporadic amyotrophic lateral sclerosis (ALS), 1.9% (6) had familial ALS, 6.6% (21) had primary lateral sclerosis, and 9.2% (29) had LMN disease. Of these 29 cases, 16 had PMA, 5 had BAD, while 8 had LAD (Table 1).

Case report

Case 1 is a 74 year-old woman presented with a progressive 9 to 10-year history of bilateral leg weakness. Patient noticed initially left leg weakness in early 1996 with catching of the toes on rugs. Over the next 2 years she progressed to involve both legs. She also developed difficulty with using stairs. There were no sensory symptoms, swallowing, breathing or ocular difficulties.

Examination on initial presentation in late 2005 showed on the MRC scale weak hip flexion being right and left respectively 4+/4, hip abduction 4+/4, ankle dorsiflexion (ADF) 4/4- and ankle inversion and eversion 5/4, with normal upper extremity and bilateral ankle plantar flexion (APF) and knee flexion and extension strength. Sensory examination was normal to pinprick, vibration and proprioception. Reflexes were 2 at the upper extremities and absent at the legs with absent Babinski sign, jaw jerk and Hoffmann reflexes. She was unable to walk on her heels or toes.

Laboratory testing demonstrated a normal chemistry profile, sedimentation rate, ANA, rheumatoid factor, GM1 antibody level, B12 and thyroid function, SPEP, SIFE, negative FTA-ABS. Creatine kinase level was mildly elevated at 364 IU/L (normal upper limit 200 IU/L).

On NCS, median and ulnar sensory and motor responses were normal. The compound muscle action potential (CMAP) amplitudes were asymmetrically reduced in the fibular (peroneal) nerve recording from the EDB. The bilateral tibial CMAPs and sural sensory nerve action potentials (SNAP) were normal. Needle electrode EMG showed fibrillation potentials and long-duration polyphasic motor unit action potentials (MUAPs) with decreased recruitment in the bilateral distal and proximal leg muscles. There were fibrillations in the lumbar paraspinal muscles.

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Follow up examination over the next 4 years showed persistent normal strength in the upper extremities. Lower extremities weakness progressed to hip flexion 4/4, knee flexion 4/4-, knee extension 5-/5-, ADF 3/2, APF 5/4, ankle inversion and eversion 4/3, right and left respectively. Muscle stretch reflexes remained absent at the legs. The patient was prescribed bilateral ankle foot orthoses.

Summary of KUMC cases

We identified 8 cases of LAD at the KUMC (Table 1). The mean LAD age of onset was 58 years (29–85) with a male/female ratio of 3/1. None of the patients had family history of the neuromuscular disease. Mean time from first symptom onset to evaluation at KUMC was 7.6 years: 3 years in 2, 4–5 years in 2 & 10–14 years in 4 cases. Onset symptoms were asymmetric in 4 patients and unilateral in 3 cases, with left leg predilection being noticed in 5. First symptoms were indicative of distal weakness in 3 (2 of whom were bilateral asymmetric and 1 affecting the left leg), proximal leg weakness in another 3 cases (2 being bilateral asymmetric and 1 affecting the right leg proximally then distally) and in 2 cases one or both legs were weak proximally and distally.

Mean overall follow up period from disease onset was 10.6 years (4–15). Mean follow up duration from first visit at the KUMC was 3 years (1–5). All cases slowly progressed with weakness remaining confined to the legs. In all 3 cases with unilateral onset, examination on first presentation 5, 10 and 14 years later revealed involvement of the contralateral leg, with 2 remaining asymmetric. Examination demonstrated persistently asymmetric leg weakness in seven cases.

We identified at first evaluation a pelvi-peroneal pattern (PPP) of weakness (relative sparing of knee extension and/or ankle plantar flexion) in 4 cases (cases number 1, 4, 5 and 7), found bilaterally in 3 and symmetrically in only 1 instance. In three other cases (# 2, 3 and 8) weakness pattern was asymmetric and distal while case 6 had an asymmetric proximal motor distribution.

Muscle stretch reflexes were hypoactive or absent in the lower extremities and normal in the upper extremities without Babinski sign, jaw jerk or Hoffman reflexes. No patient lost the ability to ambulate, developed bulbar symptoms or signs, arm spread, or respiratory difficulties. Seven patients required an ankle foot orthotics assistive devices and one needed a walker for longer distances after using a cane previously.

Diagnostic studies

Serum creatine kinase levels were normal in 1 patient and elevated in 7 cases (range 260 to 521 IU/L). Most recent MRI studies of the lumbar spine region were normal except for nonspecific degenerative disc changes without any nerve root or spinal canal impingement. Anti-GM1 antibodies were tested in all cases and were negative.

On NCS, median and ulnar sensory and motor responses were normal in all patients but 2 with median neuropathy at the wrist. Otherwise, sensory responses were normal in the arm and leg. All patients had reduced CMAP amplitudes in the peroneal and/or tibial nerves. F-

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waves latencies were within normal limits. There was no conduction block or abnormal temporal dispersion in any nerve tested.

The KUMC LAD cases had electrodiagnostic findings consistent with motor neuron disease confined to the lower extremities. Seven cases had distal leg fibrillation potentials and long-duration polyphasic MUAPs with decreased recruitment, 5 of whom also demonstrated these findings in the proximal muscles. The remaining case had leg proximal fibrillation potentials whereas long-duration polyphasic MUAPs were identified both proximally and distally. There were no bulbar, thoracic or cervical myotome abnormalities.

U.S. Academic Centers data

We also present summary data comparing the KUMC LAD cases to those from other major academic neuromuscular centers (Table 2). Data from the 8 US academic center show confirmed significant male predominance with only one female patient out of a total of 16 cases. The mean age at onset of symptoms was 57 years with an age range of 38 to 86 years. Out of these 16 cases, six LAD patients developed arm weakness, and of these six cases, two died from progression to ALS.

Combining data from all 9 academic centers, the mean age of onset cases is 57.5 years. The male to female ratio is 7/1. At last follow up, the weakness progressed to involve the arms after 2 to 8 years from onset in 6/24 total LAD cases. Of those, two cases died from progression to typical ALS suggesting 8% mortality. During a mean follow up of 8 years from symptom onset, the mean survival of all LAD cases is 87 months, with 92% being alive at last follow up.

Discussion

We describe 8 LAD patients from the KUMC and 16 cases from large US academic centers with slowly progressive sporadic adult-onset motor neuron disease affecting the lower extremities with variable pattern of involvement. Of the 8 KUMC cases, weakness on first presentation followed in 50% a pelvi-peroneal pattern with relative sparing of knee extension and/or ankle plantar flexion and was distal in 38% or diffuse in 12% of cases. We only included patients when the characteristic lower motor neuron phenotype was confined to the legs at first evaluation performed 2 or more years after symptom onset. During follow up of these 24 patients meeting strict criteria, the majority (n=18) had a purely lower motor neuron syndrome with clinical and electrodiagnostic abnormalities fully restricted to the legs. Six cases (25%) had clinical spread to the upper extremities supported by electrophysiologic findings after 2 years from onset and of those, 2 died from progression to typical ALS. None underwent an autopsy. It is uncertain whether these presentations represent variable manifestations of a single disorder or different clinically overlapping conditions.

Bilateral leg weakness is a presenting symptom in about a third of ALS cases. Therefore, it is impossible to predict if there will be a slow clinical course during the early stages. However, LAD should be a consideration when weakness remains restricted to the legs for two or more years in the absence of upper motor neuron signs thereby failing to fulfill El

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Escorial criteria for ALS. For example, had we set our inclusion criteria at 1.5 year instead of 2 years, we would have included at the KUMC an additional patient who developed upper motor neuron signs and progressed to ALS by the end of the second year. Other features that are relatively atypical of ALS may point toward LAD at an even earlier stage. ALS usually presents with weakness that is more prominent in distal muscles as in 3/8 KUMC LAD cases whereas onset of weakness in the hip girdle is rare. This can be contrasted with the five KUMC patients who first noticed proximal weakness (3) or diffuse leg weakness (2).

Marie and Patrikios described a syndrome of distal onset weakness and wasting of the lower limbs which was asymmetric in onset, absent lower limb tendon reflexes, slow progression and subtle or late upper motor neuron signs.[4] We provided a modern description of this syndrome in 2002 and coined the term LAD.[3] A focal lower motor neuron variant of PMA, LAD is characterized by a variable degree of leg weakness without upper extremities or bulbar muscle involvement for at least 2 years after symptom onset. In 2009, Wijesekera et al described the flail leg syndrome (FLS) which is characterized by progressive distal leg weakness and atrophy.[5] While in FLS weakness is leg restricted for 1 year and pathologic tendon reflexes were allowed, LAD definition does not allow for spread to other myotomes or upper motor neuron signs for at least the first 2 years. Our study findings are consistent with those of Wijesekera et al 2009 in terms of the rarity of LAD and gender predilection. In our cases series, LAD represented 2.5% of all motor neuron disease cases as compared to 3 to 6.3%.[5] While there was no gender difference in the London cohort, LAD affects predominantly males in the US (7/1) and Melbourne (5/1) Cohorts. Despite the mean survival of the US Cohort (87 months) being comparable to the London (76 months) and Melbourne Cohorts (91 months), the mortality rate was much lower in the US (8%) as compared to London (69%). This marked survival difference may be due to the FLS case definition which allowed upon presentation for 67% of the London patients to fulfill El Escorial probable (40%) or possible (27%) ALS while none of our LAD cases did so at first evaluation.

In a prospective Italian study of ALS phenotypes in two regions collected between 1995 and 2004, Chio and colleagues[6] identified the flail leg phenotype in 13% of cases. This was the third most common presentation after classic ALS and bulbar-onset ALS and certainly more common than the flail arm syndrome (5.5%). This phenotype had a male to female rate ratio of 1.03:1 and mean age at onset of 65 years. Unlike our findings, the median survival time of 3 years was surprisingly similar to that of classic ALS and the 10 year survival rate was quite low at 12.8%. There are two potential explanations for these divergent findings. The classification criteria of Chio and colleagues included patients with pathological deep tendon reflexes or Babinski sign in the lower limbs at some point during the disease. We excluded cases with upper motor neuron signs in the first 2 years. Another potential explanation is that weakness in the Italian cases remained restricted for only a mean of 16 months after onset whereas we required our cases to remain confined to the legs for at least 2 years.

Our patients do not conform to previous reports of adult-onset hereditary motor neuropathies[7], where weakness is distal in the lower legs and at times the hands. The age of onset from the second to the fifth decade is earlier than that of LAD. Multifocal motor neuropathy may rarely present with lower-extremity weakness.[8] However, the widespread

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leg muscle involvement, absence of antibodies directed against GM1, and lack of demyelinating features weigh against this diagnosis.

It is important to recognize LAD since the natural history differs from that of typical ALS. In our series, LAD is a slowly progressive disorder that accounts for a 28% of LMN disease cases. We found LAD to be more common than BAD. LAD has a 92% survival rate over mean disease duration of 8 years. An asymmetric pelvi-peroneal pattern of weakness should heighten the suspicion of LAD. As long as it remains confined to the legs for 2 or more years, the prognosis of LAD is more favorable than that of typical ALS. The explanation for a more indolent course of BAD or LAD phenotype as compared to PMA and ALS is unknown.

References

1. Katz JS, Wolfe GI, Andersson PB, et al. Brachial amyotrophic diplegia: a slowly progressive motor neuron disorder. Neurology. 1999; 53:1071–1076. [PubMed: 10496268]
2. Gamez J, Cervera C. Brachial amyotrophic diplegia: a slowly progressive motor neuron disorder. Neurology. 2000; 54:2355. [PubMed: 10970203]
3. Rosenfeld J, Chang SW, Jackson CE, et al. Lower extremity amyotrophic diplegia (LAD): a new clinical entity in the spectrum of motor neuron disease. Neurology. 2002; 58(suppl 3):411–412. [PubMed: 11839840]
4. Patrikios, JS. Contribution à l'Étude des Formes Cliniques et de l'Anatomiepathologique de la Sclérose Latérale Amyotrophique. Paris: Paris University; 1918.
5. Wijesekera LC, Mathers S, Talman P, et al. Natural history and clinical features of the flail arm and flail leg ALS variants. Neurology. 2009; 72(12):1087–1094. [PubMed: 19307543]
6. Chiò A, Calvo A, Moglia C, et al. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. J Neurol Neurosurg Psychiatry. 2011; 82(7):740–6. [PubMed: 21402743]
7. Jokela M, Penttilä S, Huovinen S, et al. Late-onset lower motor neuronopathy: a new autosomal dominant disorder. Neurology. 2011; 77(4):334–40. [PubMed: 21715705]
8. Katz JS, Wolfe GI, Bryan WW, et al. Electrophysiologic findings in multifocal motor neuropathy. Neurology. 1997; 48(3):700–7. [PubMed: 9065551]

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Table 1

Clinical and diagnostic data of 8 KUMC LAD cases

Case	Age at Onset (years)	Sex	Illness◆Duration(years)	Follow up (years)	First symptom	Asymmetry at first symptom	Weakness Pattern at 1st evaluation	Asymmetry at 1st evaluation	CK†
1	64	F	14	4	L distal	Yes	Bilateral PPP	Yes	364
2*	72	M	5	2	L > R distal	Yes	Bilateraldistal	Yes	173
3*	53	M	10	5	R diffuse	Yes	R > L distal**	Yes	521
4	85	M	9	5	Bilateral diffuse	No	Bilateral PPP	No	260
5	29	F	15	1	R proximal → R distal	Yes	R diffuse, L PPP	Yes	346
6	50	M	12	2	L > R proximal	Yes	Bilateral proximal	Yes	334
7	44	M	16	4	L > R proximal	Yes	Bilateral PPP	Yes	500
8	70	M	4	1	L > R distal	Yes	Bilateral distal	Yes	464

PPP: pelviperoneal pattern; R right; L left; M male; F female

*Progression despite adequate lumbar surgery for radiographic spinal canal stenosis

◆Illness duration includes follow up interval

**Chronic denervation atrophy on muscle biopsy

†Upper limit of normal 200 IU/L

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Table 2

Data from 8 other US academic institutions

Patient	Age at onset	Gender	Spread to the arms	Duration of f/u from onset
1	50	M	−	2
2	56	M	−	4–5
3	73	M	+ 3–4 years	10
4	38	M	−	-
5	45	M	−	1.5
6	39	M	+ 2 years	3
7	56	M	+	2
8	60	M	+2 years	9
9	50	F	+7 years	11
10	54	M	−	8
11	47	M	−	6
12	69	M	+8 years	8
13	76	M	−	4
14	86	M	−	10
15	62	M	−	5
16	46	M	−	3