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ALS Regional Variants (Brachial Amyotrophic Diplegia, Leg Amyotrophic Diplegia, and Isolated Bulbar ALS)

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Synopsis

Amyotrophic lateral sclerosis is a rapidly progressive, invariably fatal disease, comprised of mixed upper and lower motor neuron involvement in different spinal cord regions. Characteristic initial presentations have implications for prognosis. Bulbar onset patients progress more rapidly than limb-onset patients, or patients with a pure lower motor neuron presentation. Other regional variants have been described where disease is restricted to one spinal region at presentation, including a flail arm or flail leg, and restricted respiratory or bulbar disease. More recent descriptions of regional variants suggest some ALS patients have disease isolated to a single spinal region for many years, including: brachial amyotrophic diplegia; leg amyotrophic diplegia; and isolated bulbar palsy. More clearly defining regional variants will have implications for prognosis, but also for understanding the pathophysiology of ALS, for identifying genetic factors related to slower disease progression, and for future clinical trial planning.

Keywords

Motor neuron disease; Amyotrophic lateral sclerosis; Flail arm; Flail leg; Leg Amyotrophic Diplegia; Brachial Amyotrophic Diplegia; Isolated Bulbar ALS

Introduction

ALS is a rapidly progressive disease characterized by degeneration of motor nerves in the brain and spinal cord that is invariably fatal, with overall median survival between 3–4 years.[1, 2] Three classic clinical presentations have been described which have clear prognostic correlates in survival: bulbar onset disease is more rapidly progressive than limb-

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onset disease; and both progress more rapidly than pure lower motor neuron disease (progressive muscular atrophy).[1–3] The average US prevalence for ALS is 3.9/100,000.[4] Approximately 2/3 will present with limb-onset, and 1/3 with bulbar onset.[2] A much smaller frequency of motor neuron disease patients present with progressive muscular atrophy (~5%).[2, 5] In addition to the classic presentations of ALS, many other variants have been described at lower frequency, including: flail arm or flail leg, respiratory or bulbar only, and pure upper motor neuron presentations. Clinical experience has shown that some patients have disease isolated to single spinal region for many years. While only limited case series to date have tried to better delineate these slow progressors, what is clear is a group of patients do not progress as rapidly as classic ALS, and these patients appear to have extended survival (Table 1).[5–9] Brachial amyotrophic diplegia (BAD) and leg amyotrophic diplegia (LAD) are variants of progressive muscular atrophy with disease confined to one spinal region. Isolated bulbar ALS (IBALS) have symptoms confined to speech and swallowing, and can be comprised of both upper and lower motor neuron involvement, but as in BAD and LAD, symptoms remain confined to the bulbar region for extended periods. Here we describe the clinical presentations, diagnostic considerations and prognosis for these regional ALS variants, and conclude with pathological considerations, and future directions.

- Classic clinical presentations for sporadic ALS include limb-onset (about 2/3), bulbar onset (about 1/3), and pure lower motor neuron (~5%)
- These patterns have implications for prognosis, with bulbar faster than limb-onset, and both faster than progressive muscular atrophy
- Some patients have disease isolated to single spinal regions for years
- These potentially slower progressing regional variants include:
 - brachial amyotrophic diplegia (BAD)
 - leg amyotrophic diplegia (LAD)
 - Isolated bulbar ALS (IBALS)

[Tags: overview of ALS clinical patterns and epidemiology; regional ALS variants]

Case Vignette #1 (BAD)

A 55 year-old man presented with a 6 month history of progressive painless proximal arm weakness. There are no associated sensory complaints. Weakness started in the right arm and progressed to involve the left arm after 3 months. Within a year his weakness spread over the proximal arms and shoulder girdles in a symmetric fashion. There is no bladder involvement.

On examination, there are significant atrophy and weakness of the shoulder girdles causing the arms to hang on the sides, man in the barrel picture. Muscle strength testing demonstrated symmetric 2/5 (Medical Research Council, MRC) strength on shoulder abduction, shoulder flexion and extension and elbow flexion, 4/5 wrist and finger flexion and 3/5 wrist and finger extension and finger abduction. Facial strength, neck flexion and

extension, and strength in the lower extremities were normal. Fasciculations were noted over the upper extremities. Sensation was normal. Muscle stretch reflexes were absent in the upper extremities and normal at the lower extremities. This case illustrates NP 5 without upper motor neuron signs restricted to the arms. But BAD, as in this case, starts with proximal rather than distal asymmetric weakness. For full pattern description, please refer to the chapter in this issue titled “Patterns of Weakness, Classification of Motor Neuron Disease & Clinical Diagnosis of Sporadic ALS”.

Nerve conduction studies showed low amplitude median and ulnar compound muscle action potentials (CMAP). There was no electrodiagnostic evidence of conduction block or demyelination. Median, ulnar and radial sensory nerve action potentials (SNAP) were normal. Needle electromyography showed active and chronic denervation changes with reduced recruitment throughout the upper extremities and cervical paraspinal muscles, with leg sparing. Creatine kinase (CK) level was mildly elevated at 250 IU/L. Magnetic resonance imaging (MRI) scans of the brain and cervical spine were unremarkable. GM1 Ab titers were normal.

Over the following 3 years, weakness in the arms progressed to 0/5 MRC in the deltoid, biceps, elbow and wrist extension and hand intrinsic muscles with 3/5 strength at rest and finger flexion.

His physical examination remained restricted for total 6 years when he developed 4/5 neck flexion weakness and diffuse 4/5 lower extremity weakness.

Respiratory and bulbar function remained normal.

This case of NP 5 without upper motor neuron signs eventually evolved from arm restricted to leg involvement.

Brachial Amyotrophic Diplegia

Clinical Features—Patients with brachial amyotrophic diplegia (BAD) have motor neuron disease confined to the cervical spinal cord region. This regional variant has also been described as flail arm or man-in-the-barrel syndrome. The differential diagnosis for BAD includes bilateral cortical watershed infarcts, spinal cord infarction, and infectious etiologies. The majority can be distinguished based on clinical history, and basic diagnostic testing. The main differential for BAD in the absence of other clinical or diagnostic abnormalities is regional presentation of classic ALS. BAD accounts for between 2–11.4% of patients presenting with motor neuron disease, and the mean age of onset is similar to ALS at 53.3–57.3 years.[8–11] Patients are more likely to be male than the general ALS population, with a male to female ratio ranging from 1.5–5 to 1. Symptoms can begin asymmetrically, but usually progress to include both arms (70%) Figure [1, 2]. Unlike arm-onset ALS which usually presents with distal weakness, the majority of BAD patients have proximal weakness at presentation (70%).[8, 10, 11] In most series patients with BAD have only lower motor neuron involvement at presentation, with decreased or absent reflexes (47–90%), and some series define this group as a variant of progressive muscular atrophy. Progression of symptoms after 12 months has been variable from case series to case series.

In one of the largest series (UK and Melbourne study) the time until second spinal region involvement was 34.3 months.[9] Figure 3 In another case series (US study) limiting BAD patients to 18 months without signs of progression for inclusion, only 20% developed subclinical denervating changes in the lower extremity over 3–11 years of follow up.

- BAD patients present with proximal arm weakness
- Reflexes are reduced or absent
- May be more common in male patients

Diagnosis—The definitions for BAD differ by case series, but common features include:

- Insidious onset of weakness in the proximal arm muscles
- Decreased or absent reflexes
- Symptoms confined to one spinal region for 12–18 months

In the absence of:

- Sensory symptoms or signs

Diagnostic testing should include:

- Normal MRI of the cervical spinal cord
- Negative GM1 antibody testing
- Consideration for genetic testing for spinal muscular atrophy and/or spinobulbar muscular atrophy

Electrodiagnostic testing reveals normal sensory studies. Motor conduction studies may show axonal changes, but should have normal conduction velocities and no conduction block. Multifocal motor neuropathy, which needs to be ruled out with serologic testing, is more commonly asymmetric and distal than BAD. Electromyography should support a denervating process in the cervical region (including fibrillation potentials, positive sharp waves, fasciculations and large polyphasic motor units), without involvement of other spinal cord regions. Patients most frequently do not meet El Escorial criteria for ALS at presentation. Case series, however, have varied on the length of time symptoms need to be isolated, and some patients may meet probable or possible ALS criteria (70% in UK and Melbourne study).

Genetic testing is not required. That said, one must consider a brachial amyotrophic presentation of spinal muscular atrophy or spinobulbar muscular atrophy. These disorders can sometimes be delineated by electro diagnostic testing (sensory changes in SBMA) or family history. A number of case series have described patients with SOD1 mutations described in sporadic ALS in patients with BAD.[12, 13] It is unclear whether this simply represents the natural frequency of SOD1 mutations in motor neuron disease, or is particular for BAD.

Prognosis—Overall the prognosis for BAD is better than classic ALS. Although a large Italian study of ALS suggested patients with flail arm presentation had survival no different

than classic ALS, they included patients with upper motor neuron findings at presentation. [5] Other case series have shown a clear benefit in survival: in the UK and Melbourne study of patients with BAD limited to one region for at least 12 months they found mean survival of 76.8–79.9 months, with 52–52.6% alive at 5 years, and 13–15.8% alive at 10 years; in the US study there were no deaths in 3–11 years of follow up (n=10 patients);[8] and in two additional smaller studies showed no deaths in 2–10 years of follow up.[10, 11]

- There is increased 5 and 10 year survival in patients with BAD compared to classic ALS

[Tags: brachial amyotrophic diplegia; BAD]

Case Vignette #2 (LAD)

A 65 year-old man presented with one year history of falls. His toes would catch when walking. He noticed weakness first in the left foot which progressed to involve the right foot. There was no pain or sensory complaints. Over the following year he developed difficulty getting out of a chair and climbing stairs.

On examination, muscle strength testing showed hip flexion of 4+/5 on the right and 4/5 on the left, hip abduction 4+/5 on the right and 4/5 on the left, ankle dorsiflexion 4/5 on the right and 4+/5 on the left with sparing of knee flexion and extension and of ankle plantar flexion. Upper extremity strength was also normal, as were facial strength and neck flexion and extension. Sensory examination was normal to pinprick and vibration testing. Muscle stretch reflexes were absent in the lower extremities and normal at the upper extremities.

Laboratory testing demonstrated a normal chemistry profile, sedimentation rate, ANA, but CK level was mildly elevated at 340 IU/L. GM1 Ab titers were normal.

Nerve conduction studies showed normal median and ulnar motor studies. Peroneal CMAPs showed asymmetrically reduced amplitude. Tibial CMAPs and sural SNAPs were normal. Needle electromyography showed active and chronic denervation changes with reduced recruitment in the lower extremities with sparing of the arms. There active denervation changes in the lumbar paraspinal muscles.

His weakness remained restricted to the lower extremities throughout 5 year of follow up.

This case illustrates NP 5 without upper motor neuron signs restricted to the legs with distal asymmetric weakness. For full pattern description, please refer to the chapter in this issue titled “Patterns of Weakness, Classification of Motor Neuron Disease & Clinical Diagnosis of Sporadic ALS”.

Leg Amyotrophic Diplegia

Clinical Features—Patients with LAD have weakness confined to the lumbosacral spinal cord region. A lower motor neuron syndrome in the legs was first described by Pierre Marie and his student Patrikios in 1918 known as pseudopolyneuritic variant of ALS, the Marie-Patrikios form, or the peroneal form of ALS.[14] LAD has also been described as flail leg. LAD accounts for between 2.5–6.3% of motor neuron disease, and has a similar mean age of

symptom onset to classic ALS, between 55–57 years of age.[7, 9] Similar to BAD there appears to be a greater male predominance in LAD than classic ALS, with a male to female ratio between 1:7 to 1. Onset is asymmetric in about half of patients, but typically progresses to include both lower extremities, and muscle stretch reflexes are absent or diminished. Two large case series evaluated patients with LAD: the UK and Melbourne study, where symptoms were confined to the lumbar region for 12 months; and a US and major academic center study, where symptoms were confined to the lumbar region for 24 months.[7, 9] In the UK and Melbourne study about 2/3 of patients met El Escorial criteria for probable or possible ALS. In contrast in the US study none of the patients met criteria for probable ALS. About half of patients showed an initial pattern of weakness described as pelviperoneal, with sparing of the quadriceps and ankle plantarflexors.[7] The remaining patients showed either diffuse weakness, or a distal pattern of weakness. Progression of disease was seen more commonly than in BAD. In the UK and Melbourne study the mean time for progression to a second spinal cord region was 37.9 months.[9] In the US and major academic centers study 25% of patients progressed to include a second spinal cord region at 2 years of follow up.

- LAD patients present with a pelviperoneal pattern of weakness, or diffuse or distal weakness
- Reflexes are reduced or absent
- May be more common in male patients
- About 25% progress to include a second spinal cord region at 2 years of follow up

Diagnosis—The definitions for LAD differ by case series but common features include:

- Insidious onset of weakness isolated to the legs
- Decreased or absent reflexes at presentation
- Symptoms confined to one spinal region for 12–24 months

In the absence of:

- Sensory symptoms or signs

Diagnostic testing should include:

- MRI of the spine
- Negative GM1 antibody testing

Nerve conduction studies demonstrate only age appropriate sensory changes, and motor conduction studies reveal reduced CMAP amplitude, without evidence for demyelination or conduction block. Electromyography shows denervating changes, including fibrillation potentials, positive sharp waves, and long duration polyphasic motor units.

Like classic ALS serum CK may be elevated, with patient values in prior studies ranging from 100–500 IU/L.

Prognosis—Like BAD patients with LAD have a better overall prognosis than classic ALS. Mean survival was reported between 75.9–87 months.[7, 9] The UK and Melbourne

study reported a 5 year survival rate of 63.9–76.9% and 10 year survival of 5.3–23.1%.[9] The US and major academic centers study showed an 8 year survival of 92% - the increased survival likely due to limiting the inclusion of subjects to patients with isolated lumbosacral symptoms for 24 months.[7]

- Survival in LAD is longer than in classic ALS

[Tags: leg amyotrophic diplegia; LAD]

Clinical Vignette #3 (IBALS)

A 48 year-old man presented with 6 month history of dysphagia. He has been having speech difficulty for the past 4 months. He has been using a handkerchief for the past couple of months because of drooling. There is no associated shortness of breath, arm weakness or leg weakness. He has no sensory complaints. There is no double vision or droopy eyelids. Within the first year, he needed to use a communication device and a PEG tube was placed to support his nutritional needs.

On examination, there is atrophy and fasciculations of the tongue. Palatal elevation is minimal. He has marked spastic dysarthria. His muscle strength testing showed orbicularis oculi is 5/5, orbicularis oris is 3/5, and tongue is 2/5 as he is unable to protrude his tongue through his cheek. Neck flexion and extension are 5/5 and the rest of his motor examination is full. Sensation was normal large and small fiber modalities. Jaw jerk is 3+ but otherwise muscle stretch reflexes were 2/4 all over.

Nerve conduction studies of the right arm and leg were normal. Needle electrode examination showed active and chronic denervation changes at the genioglossus muscle. Electromyographic examination of the cervical, thoracic and lumbar regions was normal.

CK level was mildly elevated at 240 IU/L. MRI of the brain was unremarkable.

His exam remained restricted for 7 years before he developed shortness of breath.

This case illustrates NP 8 with upper and lower motor neuron focal midline symmetric bulbar dysfunction. For full pattern discussion, please refer to the chapter in this issue titled “Patterns of Weakness, Classification of Motor Neuron Disease & Clinical Diagnosis of Sporadic ALS”.

Isolated Bulbar ALS

Patients with bulbar onset ALS often have a less favorable prognosis with short survival time of about 24 months.[3, 5] However, clinical experience has shown there is a minority of patients who appear to have symptoms restricted to the bulbar region, often for many years. A large California study, although not identifying this group of patients for their study, mentions their anecdotal experience with at least two patients in this clinic.[3] Although limited literature exists at this time, there appear to be a group of patients with bulbar presentation who appear to have isolated symptoms for extended periods of time, (isolated bulbar ALS, or IBALS). Two series have been published or presented at national meetings: an Australian study of 12 patients; and a study at the University of Kansas of 7

patients (KU study).[6, 15, 16] Patients with IBALS represent about 4% of patients presenting with motor neuron disease.[6, 15, 16] Age of onset is slightly older than classic ALS, with one study reporting a mean age of 61 years. [6] Unlike BAD and LAD, the Australian study reported a female predominance, with a female to male ratio of 3 to 1.[6] Patients with IBALS may have upper motor neuron and/or lower motor neuron signs in the bulbar region. Patients may demonstrate a flaccid or mixed dysarthria, or spastic dysarthria, and may have diffuse hyper-reflexia. About half show emotional lability, while only 1/3 demonstrate tongue wasting. The KU study only included patients if initial EMG did not show denervating changes in any region outside the bulbar region.[15] Respiratory function is usually preserved initially. PEG tube placement may be required early in the course of the disease due to difficulty swallowing and risk of aspiration.

- IBALS have weakness confined to the bulbar region
- Patients may have difficulty with speech or swallowing but respiration is usually preserved
- Patients may show flaccid or spastic dysarthria
- Possibly more common in female patients

Diagnosis—The diagnosis of IBALS is suggested by the presence of:

- Insidious onset of symptoms isolated to the bulbar region for at least 6 months
- Spastic or flaccid dysarthria, or mixed dysarthria
- Preserved respiration at presentation

In the absence of:

- Sensory symptoms or signs

Diagnostic testing should include:

- MRI of the brain
- Consider autoantibody screening (acetylcholine receptor antibodies, LEMS antibody possibly)

Exam may show pathologically brisk reflexes, including positive jaw jerk or Hoffman's sign. Electromyography should show denervating changes isolated to the bulbar region (fibrillation potentials, positive sharp waves, large polyphasic motor units). Despite the denervating changes in the bulbar region, CMAP amplitudes in the limb should be preserved. The Australian study found a number of differences between IBALS patients and bulbar ALS patients: including larger CMAP amplitudes at the abductor pollicis brevis; and smaller motor evoked potentials on transcranial magnetic stimulation.[6]

Prognosis—Although there is more limited data on survival than for BAD or LAD, IBALS also appears to have a more benign prognosis compared to classic ALS, and to bulbar ALS in particular. Survival in IBALS was prolonged in the Australian study compared to bulbar ALS, with 75% alive at 54 months, compared to 45% for bulbar ALS. The KU study was less restrictive in inclusion, including all patients who presented with

isolated bulbar symptoms, and no evidence for involvement of other regions on EMG. But they still saw benefits in survival: with 75% still living with between 2–8 years of follow up, with 40% still having symptoms isolated to the bulbar region.[15]

- IBALS patients may have increased survival compared to bulbar ALS

[Tags: isolated bulbar ALS, IBALS]

Summary and Future Directions

BAD, LAD and IBALS are unique regional variants of motor neuron disease. Understanding the natural history of these phenotypes may help provide guidance regarding prognosis for patients with an otherwise bleak prognosis. These regional variants do not meet clinical trial diagnostic criteria for definite ALS; and identifying them may be important for clinical trials which include patient with El Escorial probable or possible criteria. Including patients with regional variants in ALS clinical trials may obscure the effectiveness of a therapy due to their slower progression, or increase the variability in response. And future trials including these patients should consider stratifying their inclusion between groups. There are currently no predictive features that suggest the diagnosis of BAD, LAD or IBALS early in the process – so all three are really diagnosis based on time: the longer symptoms remained confined to one spinal cord region the better the prognosis. Understanding the genetic and environmental factors that predispose patients to these regional variants may yield important information about the pathogenesis of ALS, and may reveal potential protective modifying genes.

- A better understanding of the natural history of regional variants is essential for ALS management and for understanding genetic and environmental modifiers of ALS

[Tags: regional variants ALS; genetics; pathophysiology; clinical trials]

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Key Points

- Regional variants of ALS include brachial amyotrophic diplegia, leg amyotrophic diplegia, and isolated bulbar ALS, and can overlap with classic ALS presentations
- Regional ALS variants have symptoms isolated to a single spinal cord region for periods of time > 1 year
- Brachial and Leg amyotrophic diplegia are regional variants of progressive muscular atrophy
- Regional ALS variants may have slower disease progression so are important clinical distinctions

Figure 1. A 59-year-old man with brachial amyotrophic diplegia 7 years after his initial symptom

(A) BAD phenotype causing the arms to hang flaccidly at his sides. (B) Note the severe neurogenic atrophy throughout the arm and shoulder girdle with normal bulk in the sternocleidomastoid.

Please get permission from:

Katz JS, Wolfe GI, Andersson PB, et al. Brachial amyotrophic diplegia: a slowly progressive motor neuron disorder. *Neurology* 1999;53(5):1071–1076.

Figure 2.

Flail arm syndrome from Gower's original description in 1888.

Please get permission from

Gowers WR, A manual of diseases of the nervous system: spinal cord and nerves. London: Churchill, 1888;1:356–81

Figure 3.

(A) Kaplan-Meier survival curves for each phenotype category in the London population.

(B) Survival curves for each phenotype after adjusting for age at onset, gender, riluzole use, El Escorial category at presentation, and diagnostic delay at the covariate means using Cox regression model. PMA _ progressive muscular atrophy.

Please get permission from:

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.

Table 1

	BAD	LAD	IBALS
Isolated symptoms for	12–18 months	12–24 months	6–24 months
LMN/UMN	LMN	LMN	LMN/UMN
Symmetry	Can start assymmetric; most progress to Symmetric	Asymmetric	-
Pattern	Proximal	Pelvi-perineal; or distal	Bulbar restricted
Months until second region involved	34.3	37.9	NR
5 year Survival	52–52.6%	63.9–76.9%	75% *

* only 1 study – 75% at 54 months

NR = not reported