Primary Lateral Sclerosis

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KEYWORDS

• Motor neuron disease • Upper motor neuron disease • Primary lateral sclerosis
• Spastic quadriparesis • Pseudobulbar affect • Neuroimaging

KEY POINTS

- Primary lateral sclerosis (PLS) is a progressive upper motor neuron disease in the absence of clinical signs of lower motor neuron involvement.
- PLS is a diagnosis of exclusion supported by a characteristic clinical history, examination findings, and diagnostic testing ruling out other causes.
- Key examination findings can include spasticity, upper motor neuron pattern weakness, and pseudobulbar findings.
- The pathophysiologic hallmark is dysfunction of corticospinal tracts leading to upper motor neuron signs and symptoms.
- Patients with absence of lower motor neuron signs on electromyogram after 4 years are unlikely to progress to amyotrophic lateral sclerosis.

INTRODUCTION

Primary lateral sclerosis (PLS) is a disorder of progressive upper motor neuron dysfunction, in the absence of clinical signs of lower motor neuron involvement or family history suggestive of hereditary spastic paraplegia. PLS is a diagnosis of exclusion. PLS exists on a spectrum of sporadic motor neuron disorders, including progressive muscular atrophy (lower motor neuron only), and amyotrophic lateral sclerosis (mixed upper and lower motor neuron involvement). PLS is a rare disorder, representing approximately 1% to 4% of all patients with motor neuron disease.[1–3] Although controversy exists as to whether PLS is a distinct pathologic disease from

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amyotrophic lateral sclerosis (ALS), it is clinically distinct, and portends a more benign clinical prognosis, making this a useful clinical category.

- PLS is a progressive upper motor neuron disorder
- From 1% to 3% of patients presenting with motor neuron disease
- Diagnosis of exclusion
- More benign prognosis than ALS

CLINICAL FINDINGS

Although considerable heterogeneity exists between patients, symptoms usually begin in the fifth to sixth decade, unlike hereditary forms of spastic paresis, which usually present earlier and are associated with foot deformities, which are not present in PLS.[4] Most patients present at more than 20 years of age. As is seen in ALS, there may be a slight male predominance. The most common clinical presentation matches Erb's[5] original description of patients with spastic spinal paralysis from the early twentieth century, which included spasticity, hyperreflexia, and mild weakness. Patients may report stiffness, clumsiness, and poor coordination. Most patients report balance difficulties, and, as the disease progresses, increasing falls. Bulbar symptoms can include dysarthria, dysphagia, and emotional lability (fits of laughing or crying, termed pseudobulbar affect). Typically the examination shows only upper motor neuron signs, spasticity, spread of reflexes, and absence of lower motor neuron findings (fasciculations and muscle wasting). Stiffness as a presenting symptom is seen more commonly in PLS than in ALS (47% vs 4%), and limb wasting is rare in PLS (~2%).[6] An upper motor neuron pattern of weakness may be seen (extensors in upper extremity, flexors in lower extremity), but what the patient describes as weakness is often a combination of increased tone, decreased coordination, and mild weakness.

Although visual symptoms are not reported, some abnormalities of eye movements have been described, including saccadic breakdown of smooth pursuits, or supranuclear paralysis.[1,3] Urinary frequency or urgency can be seen in around one-third to one-half of patients.[2,3,7] In general, cognition is reported as being unaffected in PLS; however, some frontal lobe dysfunction can be seen in 10% to 20% of patients. Case reports have described cognitive changes in cases termed PLS plus, or overlap with parkinsonian syndromes.[8,9]

PLS is typically slowly progressive. Patterns of progression most commonly show spread from side to side, and from region to region, with many patients ultimately developing spastic quadriparesis with bulbar involvement. In one series an ascending progression was noted in patients with limb onset, with progression from one side to the other occurring first, followed by ascending progression (average 3.5 years from onset to arm involvement, 5 years from onset to bulbar involvement).[10,11] Other series have described bulbar onset then skipping the arms to appear in the legs.[3] However, overall the rate of progression is much slower than is typically encountered in ALS. The average symptom duration from various case series ranged from 7.2 to 14.5 years.[4] In many patients, progression seems to halt after several years, with varied levels of disability.

Clinical hallmarks of PLS include:

- Insidious onset of stiffness, clumsiness, or mild weakness; or dysarthria, dysphagia, and emotional lability
- Symptoms begin most commonly in the legs, but can begin in the bulbar region or multiple areas of the body
- Signs include spasticity, hyperreflexia, and upper motor neuron pattern weakness

- The absence of diffuse fasciculations or muscle wasting, or sensory symptoms or signs
- PLS is progressive, spreading from side to side and from region to region
- Urinary urgency or frequency may be reported

CASE HISTORY

At age 46 years, a healthy right-handed woman developed a mild left foot drop that caused occasional tripping. An orthopedic examination, electromyogram (EMG), and rheumatologic evaluation at that time were unrevealing. Stiffness and mild weakness of her left leg progressed, and by age 49 years she noted stiffness in her right leg. Increasing difficulty with balance occasionally resulted in a fall. Neurologic examination at that time revealed mild hip and ankle flexor weakness, with bilateral leg spasticity, but no sensory loss or ataxia. An extensive work-up was done, as described later, and she was given a working diagnosis of progressive multiple sclerosis.

When first seen in our PLS clinic at age 51 years (year 5 of her disease), her examination was notable for spastic gait and spasticity of the left arm. Her right upper extremity was normal, as were speech and swallowing. She had symptoms of bladder urgency and an increased startle response. Over the next 5 years, spasticity gradually progressed to involve both upper extremities, as seen in the decline in annual measures of finger tapping, timed gait, and ALS functional rating scale (**Table 1**). Handwriting first became slower in year 7 of her disease, pseudobulbar affect and occasional choking when eating in year 8, and dysarthria in year 9. As her gait and balance worsened, she experienced more frequent falls with injuries: a scalp laceration requiring stitches, a concussion, a broken nose. She progressed from using a cane outside the home in year 6, to dependence on a wheeled walker in year 8, to occasional use of a power scooter outside the home in year 9. However, throughout her course, she has had no respiratory difficulties, no weight loss, and no muscle atrophy. She has reported occasional fasciculations, although none were observed during clinical or EMG examinations.

Her evaluations included multiple brain and spine MRI scans; aortic arch magnetic resonance angiography; abdominal computed tomography scan; cerebrospinal fluid (CSF) examination; and visual, auditory, and somatosensory evoked potentials, all unrevealing. Blood was negative for paraneoplastic autoantibodies, various metabolic and enzymatic measures associated with rare causes of spasticity, and genes known to cause hereditary spastic paraplegia. EMGs done in years 3 and 5 showed no denervation, only incomplete recruitment of motor units in leg muscles.

She began oral baclofen at increasing doses, eventually reaching 60 mg/d. A baclofen pump was placed, with improvement in spasticity and leg cramps.

Table 1
Case history measures of function at annual visits

Disease Year	Age (y)	ALSFRS-R	Finger Taps/s		Timed 6-m (20′) Gait (s)	FVC % Predicted
			Right	Left		
5	51	44	5.1	3.2	10	—
6	52	44	3.8	3.5	12	88
7	53	42	3.1	1.9	19	87
8	54	36	2.3	1.7	18	85
9	55	36	2.1	1.5	17	—

Abbreviation: ALSFRS-R, Revised ALS Functional Rating Scale.

This case features several points that are common in PLS:

- Very slow progression of spasticity and motor slowing, often beginning in the legs
- Balance problems leading to falls
- Mild pyramidal weakness
- Often with sparing of respiratory function
- Possible benefit from intrathecal baclofen and treatment of pseudobulbar affect

DIAGNOSIS

The diagnosis of PLS includes the presence of upper motor neuron dysfunction, in the absence of other neurologic findings, or alternative explanations on diagnostic testing. Ultimately PLS is a diagnosis of exclusion. Although structural, infectious, and demyelinating diseases can cause an upper motor neuron syndrome. After a thorough clinical history and examination the 2 most common differential considerations for PLS are an upper motor neuron presentation of ALS, and the hereditary spastic paraplegias. Additional differential considerations include structural lesions, infection, and demyelinating disease (**Box 1**). Several diagnostic criteria have been proposed.[3,4] In the Pringle criteria, symptoms had to be present for greater than or equal to 3 years; in the Singer criteria greater than or equal to 4 years; and in our ongoing cohort study of multicenter oxidative stress (COSMOS) study in PLS, patients had to have symptoms for greater than or equal to 5 years.[2,3,12] However, common features include the clinical presence of:

- Upper motor dysfunction on examination: spasticity, pathologic reflexes, and upper motor neuron pattern of weakness
- Presentation most commonly in the legs, but can be in the bulbar region, or mixed limb and bulbar
- Slow progression of symptoms ($\geq$4 years) with an age of onset greater than or equal to 20 years

Absence of:

- Marked fasciculations or muscle atrophy
- Sensory signs on examination
- Family history of similar disorder

In addition, laboratory or diagnostic studies must be negative for an alternative explanation for the symptoms. Additional normal studies supportive of PLS include:

- B_{12}, copper, HTLV1/HTLV2, human immunodeficiency virus (HIV) testing, paraneoplastic work-up
- MRI of brain and spine
- CSF evaluation
- EMG (normal, or minimal denervation that does not fulfill El Escorial criteria)

Basic laboratory studies, including serum chemistries, serum B_{12}, and complete blood count, should be normal. Additional studies recommended in patients based on clinical suspicion could include testing for Lyme disease, human T-cell lymphocytotropic virus-1, paraneoplastic panel, HIV testing, polyglucosan body disease, and CSF evaluation. Serum long-chain fatty acids can be evaluated to exclude adrenomyeloneuropathy. Serum creatine kinase level is not particularly useful in the

Box 1
Differential diagnosis for PLS ALS Functional Rating Scale

Structural

Tumor

Cervical spondylomyelopathy

Spinal arteriovenous fistula

Arnold-Chiari malformation

Demyelinating

Multiple sclerosis/primary progressive multiple sclerosis

Vitamin E deficiency

Hereditary

Hereditary spastic paraplegia

Leukodystrophy (metachromatic, adrenoleukodystrophy)

Polyglucosan body disease

Infectious/inflammatory

Tropical spastic paraparesis (HTLV1/HTLV2)

Human immunodeficiency virus

Syphilis

Sarcoidosis

Metabolic/toxic

Subacute combined degeneration (B_{12} deficiency)

Vitamin E deficiency

Lathyrism

Neurodegenerative

ALS

Abbreviation: HTLV, human T-lymphotropic virus.

work-up of PLS, although case series suggest that it may be increased in fewer patients than in ALS.[4]

Electromyogram

Although patients with PLS lack lower motor neuron signs on clinical examination, several studies report minor or transient changes with needle EMG in some patients with PLS. These changes include sparse fibrillations, generally limited to 1 or 2 muscles; fasciculations; and enlarged motor unit potentials.[1,2,7,13] After 4 years the probability of developing new lower motor neuron findings on EMG is low (~20%).[14]

Imaging

The criteria proposed for a clinical diagnosis of PLS include brain imaging without structural abnormalities, although atrophy of the precentral gyrus is allowed.[3,4] Occasionally, clinical MRI scans show T2 hyperintensity within the corticospinal tracts, although this is a variable and nonspecific finding thought to result from wallerian

degeneration, and T2 shortening within the gray matter of the precentral gyrus, which is likely caused by iron uptake by activated microglia.[15,16]

A common theme that has emerged from quantitative MRI studies is that imaging changes in PLS are less diffuse than in patients with ALS, being more restricted to motor regions. Within motor structures, the severity of changes is often greater in patients with PLS than in patients with ALS, possibly reflecting the longer duration of disease. Quantitative MRI has shown that brain atrophy affects gray and white matter in patients with PLS.[17] The precentral cortex and underlying white matter are particularly affected.[18] The precentral gray matter becomes thinner and thinning continues to progress for many years.[18,19] Metabolic markers show dysfunction of the motor cortex. With fluorodeoxyglucose-PET, a stripe of hypometabolism may be seen in the precentral gyrus.[20] *N*-Acetyl aspartate, a neuronal marker measured in magnetic resonance spectroscopy studies, was reduced in the precentral cortex.[10,21,22] Flumazenil-PET, which binds to receptors for gamma-aminobutyric acid on cortical neurons, was decreased in patients with PLS, particularly in motor regions, whereas patients with ALS also had decreased binding in frontal regions.[23]

White matter integrity in PLS has been compared with groups of healthy controls, patients with ALS, and patients with hereditary spastic paraparesis in several studies using diffusion tensor imaging (DTI). All agree that fractional anisotropy is reduced and mean diffusivity is increased within the corticospinal tracts and midbody of the corpus callosum in PLS.[24–29] Patients with PLS had a more restricted distribution of affected white matter tracts compared with the widespread pattern seen in patients with ALS, and the magnitudes of diffusion changes were greater. Some studies also note greater diffusion changes in subcortical white matter and proximal portions of the corticospinal tract in patients with PLS.[24,25,28] Longitudinal studies showed that the same tracts were affected 6 months and 2 years later, but progressive thinning of the corticospinal tract occurred.[18,28] Most DTI studies have not found significant group-level differences outside motor tracts in DTI; however, in patients who have mild cognitive impairment, small and scattered diffusion changes may be seen in extramotor association tracts.[30,31] MRI sequences specific for myelin also show a broader distribution of white matter changes than are seen with DTI.[32]

Imaging findings in PLS include the following:

- Diagnostically, MRI in PLS should be without structural abnormalities, with the exception of atrophy of the precentral gyrus
- MRI T2 imaging hyperintensity can be seen in the corticospinal tracts, which corresponds with decreased fractional anisotropy and increased mean diffusivity on DTI
- Metabolic imaging shows decreased function in the precentral gyrus (magnetic resonance spectroscopy, PET)

Summary

The diagnosis of PLS requires a characteristic clinical history and neurologic examination suggesting insidious onset of slowly progressive upper motor neuron dysfunction in the absence of family history, diagnostic testing, or signs suggesting another disorder.

PATHOPHYSIOLOGY

- The fundamental defect in PLS is dysfunction of descending corticospinal tracts.

Motor unit estimation studies showed either normal or mild reduction in motor unit numbers in hand muscles.[22,33] During voluntary movement, recruitment is incomplete. The motor neurons tend to have slower and less variable firing rates than in patients with ALS or controls, which may reflect expression of channels that promote stable membrane states.[34,35]

Transcranial magnetic stimulation (TMS) has been used to assess the excitability of the motor cortex in patients with PLS. TMS most commonly finds that motor evoked potentials from muscles of affected limbs are unobtainable or have slightly delayed central motor conduction times.[10,12,36,37] When surface evoked potentials can be elicited by TMS, thresholds for excitation are increased, although intracortical inhibition is reduced.[10,36] The relative inexcitability of the cortex particularly affects the fastest conducting corticospinal axons that synapse directly on lower motor neurons. TMS evoked cortical peaks were delayed and prolonged in peristimulus time histograms of motor unit firing, produced by desynchronized impulses of dying corticomotoneuronal axons.[37]

Loss of functional motor cortical neurons has also been revealed by other physiologic measures. In a longitudinal study of one patient with PLS, beta-band intramuscular coherence during precision grip disappeared concurrently with cortical inexcitability measured with TMS.[38] Intramuscular coherence between hand and forearm muscles is thought to arise from common corticospinal inputs. Movement-related cortical potentials, measured from back-averaged electroencephalograms, were reduced in 10 patients with PLS.[39] The reduction affected components of the potentials generated by the motor cortex and components generated by premotor and supplementary cortical motor areas. The loss of fast-conducting corticospinal axons results in slow and effortful voluntary movements in PLS that are likely to use slower conducting or indirect descending cortical projections or to be relayed through more primitive motor pathways. For example, startle produced by descending brainstem pathways is enhanced in PLS.[10]

The long duration of disease in PLS may allow adaptive changes in brain function. Two studies have examined functional connectivity in patients with PLS using resting state functional MRI. This method measures correlated signals associated with blood deoxygenation as a surrogate for neuronal activity in brain regions. Both studies found functional connectivity was increased in PLS compared with controls. Sensorimotor regions of the 2 sides had increased connectivity that was correlated with disability; functional connectivity was also increased in frontal networks and was associated with executive function.[40] The other study, which searched for new patterns of function connectivity, found increased functional connectivity between the cerebellum and several cortical regions that were not structurally connected.[41] It is not clear whether the increased functional connectivity reflects loss of selective activation or develops as a form of compensation for the loss of motor cortical circuits.

Autopsy

Autopsy findings in PLS are rare, and only a few have been performed after the discovery of Bunina bodies and ubiquitinated neuronal inclusions as being key pathologic features in ALS. In autopsy reports since 1997 common features include degeneration of the corticospinal tracts, absence of Betz cells, or decreased pyramidal cells in the precentral gyrus. However, most cases were described as complicated PLS, including dementia, and some reports had Bunina bodies, or ubiquitinated inclusions, which, because of the overlap in symptoms between ALS and PLS, make it possible that these were cases of upper motor neuron presentation of ALS, or other neurodegenerative disorders.[4]

Genetics

PLS is a sporadic disease. The main differential consideration is hereditary spastic paraplegia (HSP). HSP can show autosomal dominant, recessive, or X-linked inheritance, and to date more than 50 different genes have been described. The most common autosomal dominant form is caused by mutations in SPG4 (spastin), accounting for 30% to 40% of families, and the most common recessive mutation in SPG11 (spatacsin) accounts for up to 50% of recessive cases.[42] In general, in pure HSP the legs are most commonly affected, with variable bladder spasticity, and some vibratory loss in the feet. HSP generally presents younger than PLS, in the 20-year to 30-year range, but considerable variability exists. There is also potentially overlap between juvenile ALS, early onset HSP, and what is termed juvenile PLS (all caused by mutations in the alsin gene, ALS2).[43]

A couple of large case series have looked for genetic mutations in patients with PLS. One study looking for *C9orf72* repeat expansions found mutations in 0.9% of 110 patients with PLS.[44] A more recent study by the PLS CSOMOS study group found *C9orf72* mutation in 2.9% of 34 patients with PLS.[12] Only 1 patient had a mutation associated with HSP in *SPG7*. Additional pathologic mutations were identified in *DCTN1* and *PARK2*. Ultimately, as it becomes possible to more specifically define the phenotype in PLS, the ability to identify pathogenic mutations may increase. However, most patients meeting clinical criteria for PLS are sporadic.

Summary

Although there is no pathognomonic pathologic change in PLS, several changes are consistent with the diagnosis:

- TMS reveals unobtainable or slightly delayed central motor conduction times, with increased thresholds for activation
- Loss of fast-conducting corticospinal axons may shift to slower conducting or indirect descending corticospinal projections
- Although autopsy data are limited, loss of descending corticospinal pathways is common
- Only a minority of patients with PLS meeting clinically definite criteria have pathologic mutations

PROGNOSIS

A question of great concern to patients with PLS is whether their condition will convert to ALS. A small fraction of patients with ALS initially present with pure upper motor neuron findings, but most develop lower motor neuron signs and EMG findings within 4 years.[6,14,45] Patients who do not have lower motor neuron findings after 4 years typically remain with clinically pure upper motor neuron dysfunction with a normal lifespan.[2,6,11] However, there are a few reported cases of patients with PLS developing late slowly progressive lower motor neurons and EMG findings, even several decades later.[46]

THERAPEUTIC STRATEGIES

There is no cure for PLS. Most treatment strategies are intended to alleviate symptoms and improve functioning. Nonmedication approaches to PLS include physical and occupational therapy for range of motion exercises, gait and balance training, and evaluation for assistive devices. Riluzole, the only US Food and Drug Administration approved drug for ALS, which provides a modest increase in survival (about 3 months),

has not shown any clear benefit in patients with PLS. For spasticity, first-line oral agents include baclofen, tizanidine, or valium. For patients who achieve some benefit with antispasticity drugs but are limited by sedating side effects of oral agents, a trial of intrathecal baclofen may be useful, with subsequent baclofen pump placement. Management of excess oral secretions or drooling is similar to that used for ALS. Most patients are first tried on oral anticholinergic medications: amitriptyline, scopolamine, glycopyrrolate, or atropine drops. For drooling unresponsive to oral therapies, botulism toxin injections into submandibular glands may be beneficial.[47] For pseudobulbar affect (bouts of uncontrollable laughter and crying) the combination of dextromethorphan and quinidine (Nuedexta) may prove beneficial. Tricyclic antidepressants may prove beneficial for patients in whom Nuedexta does not work. For further discussion of symptom management, the reader is referred elsewhere in this issue.[48]

Recommendation:

- Periodic evaluation with physical and occupational therapy
- Oral antispasticity drugs
- Consider baclofen pump
- Oral anticholinergic agents for drooling, or botulism toxin injections
- Combination dextromethorphan and quinidine, or tricyclic antidepressants for pseudobulbar affect

SUMMARY AND FUTURE DIRECTIONS

PLS is a sporadic and progressive disorder of upper motor neuron dysfunction. Despite being functionally debilitating, lack of lower motor neuron findings after 4 years portends a more benign prognosis than ALS. There are several characteristic patterns of progression in PLS, suggesting the possibility for an underlying, as-yet undefined genetic contribution to the disease. However, the largest case series to date identified mutations in only a minority of patients. Treatment of PLS remains supportive, including physical therapy and drugs for spasticity, drooling, and pseudobulbar affect. A better understanding of the pathophysiology of PLS may help guide development of future disease-directed therapies. A large multicenter study is ongoing to gain a better understanding of the natural history, genetics, and pathophysiology of PLS.[12]

DISCLOSURE

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