

Primary lateral sclerosis: diagnosis and management

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Abstract

Primary lateral sclerosis (PLS) is a rare neurodegenerative disorder at the upper motor neuron extreme of the spectrum of motor neuron disease. The diagnosis is clinical and based on the characteristic features of slowly progressive spasticity beginning in the lower limbs, or more rarely with spastic dysarthria, typically presenting around 50 years. The absence of lower motor neuron involvement is considered to be a defining feature, but confident distinction of PLS from upper motor neuron-predominant forms of amyotrophic lateral sclerosis (ALS) may be difficult in the first few years. Corticobulbar involvement in PLS is frequently accompanied by emotionality. While there may be dysphagia, gastrostomy is rarely required to maintain nutrition. Cognitive dysfunction is recognised, though dementia is rarely a prominent management issue. PLS is not necessarily life-shortening. Specialised multi-disciplinary care is recommended. Increasing international research cooperation is required if the aspiration of dedicated therapeutic trials for PLS is to be achieved.

Introduction

Primary lateral sclerosis (PLS) is a rare neurodegenerative disorder of the adult central nervous system with the core clinical feature of slowly progressive, pure upper motor neuron (UMN) degeneration. Jean-Martin Charcot (1825-1893) referred to this phenotype as “spasmodic tabes dorsalis” to distinguish it from what he defined as the far more common amyotrophic lateral sclerosis (ALS). German anatomist Wilhelm Erb (1840-1921) also described a distinct degenerative syndrome affecting the adult corticospinal tracts in apparent isolation (1).

PLS is currently considered to lie within the spectrum covered by the umbrella term motor neuron disease (MND), where it represents <3% of the total cases. No large population-based studies of PLS have been reported, but the incidence may be estimated to be less than 0.1/100,000/year. In the relatively few cases studied *post mortem*, PLS appears to share the pathological signature common to nearly all cases of the far more common disorder amyotrophic lateral sclerosis (ALS), namely neuronal cytoplasmic aggregates of the 43kDa transactive response DNA binding protein (TDP-43) (2, 3). In contrast to ALS, there is no clinical or significant electromyographic evidence of lower motor neuron (LMN) involvement in PLS, which occupies the extreme end of the UMN-predominant clinical spectrum (**Figure 1**).

The aetiology of PLS is not known. Aside from a single Canadian pedigree of an apparently pure UMN syndrome (4), no consistent genetic basis for PLS has emerged, nor any clear environmental risk factors. Cases have been described worldwide and without obvious socioeconomic or other environmental influences. A review of the case series of PLS demonstrated varying sex ratios but with a slight-to-moderate male predominance similar to ALS (5). The average age at symptom onset is significantly younger at 50 years, compared to 65 years in ALS (**Table 1**).

PLS is an adult-onset disorder and so distinct from recessive juvenile-onset pure UMN syndromes, such as that associated with the *ALS2* gene coding for a GTPase alsin (6). Defining a precise natural history for PLS has been hampered by its rarity, and variable diagnostic latency, but it is consistently only very slowly progressive. It is not as consistently life-shortening as ALS, though undoubtedly significantly life-limiting as result of disability. Depending on the patient’s age and co-morbidities, the prognosis in PLS is typically at least a decade from symptom onset and often significantly longer.

Making the diagnosis

Stark and Moersch first articulated the diagnostic core of PLS and, nearly three-quarters of a century later, their criteria still capture its essence (7) (**Table 2**). UMN-predominant forms of ALS also show a distinctly slower rate of progression compared to other clinical phenotypes (8) (**Figure 2**), but PLS should be considered a distinct clinical entity and not used as a term to indicate 'benign' or 'slow' cases of ALS.

The principal detractor for a diagnosis PLS is the presence at first assessment, or later development of significant LMN involvement, usually indicating a diagnosis of ALS instead. Gordon and colleagues chose their cut-off for a definite diagnosis of PLS based on the observation that nearly all of those reclassified as ALS were within 4 years of symptom onset (8). With a desire to reduce diagnostic delay, and to allow earlier access to future therapeutic trials, the most recent consensus diagnostic criteria allow a diagnosis of PLS after 2 years of a pure UMN syndrome, covered by a category 'Probable PLS', which becomes 'Definite' at 4 years (9) (**Table 3**).

Symptoms

The symptoms of PLS begin insidiously and may be noted only in retrospect once spasticity has a discernible impact on locomotor function. This makes dating the onset of symptoms more challenging than ALS, which undoubtedly has an impact in reducing diagnostic certainty at first presentation. For 90% of cases of PLS the symptoms begin in the lower limbs. Dysequilibrium, occasionally with actual falls, is commonly noted. There is sense of stiffness to the gait and loss of fluidity that may first become apparent when running. Hyperekplexia may also be noted. Sensory symptoms are absent. A mild degree of urinary frequency is quite a common symptom in PLS, though without significant retention.

In 10% of PLS cases, symptoms emerge within the corticobulbar pathways. Dysarthria is often accompanied by prominent emotional reflex hypersensitivity and pathological yawning, both of which should be specifically asked about in the history.

Examination

Spasticity accompanied by hyperreflexia is the essential sign of PLS. This is usually symmetrical (see Mills' syndrome later) and may involve the upper in addition to the lower limbs at first presentation,

or later with disease progression. In keeping with other causes of corticospinal tract damage, muscle strength on bedside testing may be well-preserved early in the disease, with disability gradually emerging as the facilitatory role of UMN pathways in voluntary movement progressively fails.

There should be no evidence of LMN involvement in PLS. Minor thinning of the small muscles of the hands may be apparent in older patients, and those with more established PLS, but is never generalised and does not conform to the 'split hand' phenomenon (preferential wasting of the lateral hand muscles) noted in ALS (10). Similarly, unless part of an established co-morbidity, there should be no significant sensory symptoms in PLS.

Eye movement abnormalities, typically loss of smooth pursuit, may be noted and saccadometry has demonstrated loss of fixation and particularly prominent anti-saccade errors compared with ALS patients (11). Sustained nystagmus or signs of overt cerebellar dysfunction is not expected in PLS. Although there have been reports of Parkinsonian signs in some cases of PLS, we consider signs such as facial hypomimia in PLS to be a reflection of upper motor neuron dysfunction and thus distinct from similar features of primary extrapyramidal syndromes (see **Differential diagnosis**).

Mirror movements have not been systematically studied in PLS patients but it is our observation that these occur more consistently than in ALS, and may reflect pathological involvement of the corpus callosum, which is a consistent feature of ALS (12), and seen to a greater extent in diffusion tensor imaging studies in PLS (13).

Cognitive dysfunction is recognised in PLS but is unlikely to be detectable in the routine clinic-based examination (see **Management**).

Investigations

PLS is fundamentally a *clinical* diagnosis. The pure UMN nature of this rare condition and current lack of a specific diagnostic biomarker presents a greater opportunity for potential mimic disorders and so leads to a greater reliance on investigations than for more typical forms of ALS (14).

- Magnetic resonance imaging (MRI) is the essential investigation. Brain and whole cord MRI to exclude structural, inflammatory, vascular and metabolic lesions of the white matter is mandatory.
- Focal atrophy of the pre-central gyri is a supportive finding in PLS (15). Electromyography (EMG) is used to exclude occult lower motor neuron (LMN) involvement and muscle denervation suggestive of

emergent ALS, though minor degrees of denervation (especially in the hands) are not incompatible (see discussion in (9)). Although there has been no systematic study in PLS, serum levels of creatine kinase are expected to be within normal range or only mildly elevated in keeping with the absence of LMN involvement, in contrast to the more frequently observed elevated levels in ALS.

A hallmark of ALS is increased cortical excitability in response to short interval paired transcranial magnetic stimulation (TMS) (16), but this has also been demonstrated in cases of PLS (17).

Flumazenil positron emission tomography (PET) demonstrated relative preservation of motor cortex GABA-A receptor binding in both more slowly-progressing forms of ALS (18) and cases of PLS (19), consistent with a role for inhibitory cortical circuits in the pathogenesis of motor neuronal degenerative disorders (20). Focal motor cortical hypometabolism seen using fluorodeoxyglucose PET – the ‘stripe sign’ – has been reported in cases of PLS (21, 22) but the sensitivity as well as specificity of this finding, particularly in discriminating from UMN-predominant forms of ALS, is uncertain.

Blood and CSF neurofilament levels are raised in proportion to the rate of disease progression in ALS (23, 24). In keeping with findings in more slowly-progressive neurological syndromes (25), lower levels are expected in those with PLS but not as a specific feature of diagnostic utility in isolation. Nonetheless, ultimately a combination of biofluid and neuroimaging biomarkers may become part of the routine diagnostic work-up for those with PLS if these can be validated in large cohorts.

Differential diagnosis

The principal diagnostic trap in PLS is the delayed emergence of LMN involvement in UMN-predominant cases of ALS. This provides the basis for the distinction of 'Probable' versus 'Definite' PLS between 2 and 4 years from the onset of symptoms and the reliance on normal EMG findings (9). There are only a small number of disorders that may present with a clinically pure UMN syndrome that need to be considered at the initial presentation to the neurologist. Clinical and basic investigation findings provide the strongest initial steer (**Table 4**).

Hereditary spastic paraparesis

Hereditary spastic paraplegia (HSP) is an umbrella term encompassing a genetically diverse group of disorders characterised by very slowly progressive paraparesis that may mimic PLS to an extent (26). HSP may sometimes involve dorsal column and sphincter dysfunction, but more rarely also the upper limbs, making the distinction from PLS more challenging (27). Additional features in complex genetic subtypes of HSP include ataxia or dementia, but do not include the marked corticobulbar involvement often seen in PLS. As a generalisation, the rate of progression in HSP is slower than in PLS.

The presence of a family history (typically autosomal dominant) is a major clue to HSP over PLS, but is identified in only 60% of cases. Of those with a positive family history, 40% will have mutations in the *SPAST* gene. Establishing a firm genetic diagnosis in the remainder has been improved by panel based screening but a significant proportion of cases remain without a causal gene (28).

Primary progressive multiple sclerosis

Approximately 15% of patients with multiple sclerosis (MS) have a slowly progressive clinical course without remission, termed primary progressive (PPMS). There is a predominance of men and the age at symptom onset is older (into the fifth decade) than more typical relapsing-remitting forms of MS. Within the current diagnostic criteria for the spectrum of MS disorders, the combination of MRI and CSF oligoclonal band testing provide the greatest specificity in distinguishing PLS from PPMS (29).

Metabolic myelopathies

Vitamin B12 or copper deficiency are well recognised causes of slowly progressive myelopathy that may not necessarily have MRI abnormalities, but typically there is associated sensory impairment.

The entity of functional B12 deficiency (associated with a normal serum level but transcobalamin dysfunction) is most commonly seen in those inhaling nitrous oxide recreationally (30), but it remains controversial outside this setting (31).

Adrenomyeloneuropathy is an X-linked peroxisomal disorder involving mutations in the *ABCD1* gene responsible for very long-chain fatty acid transport. Their accumulation in serum is diagnostic (32). There is no effective treatment. Both men and women carriers can develop an adult-onset slowly progressive myelopathy (over 10-20 years), with symptoms typically emerging in the 3rd or 4th decade. Symptoms are confined to the lower limbs (unlike PLS), often with sensory ataxia and bladder symptoms, and often no abnormal MRI findings.

Konzo is a colloquial term used to describe a symmetrical spastic paraparesis sparing sensory and sphincter function observed in children and women of childbearing age in parts of sub-Saharan Africa (33). Epidemics are thought to relate to chronic dietary reliance on insufficiently processed cyanogenic cassava through mixed genetic and environmental mechanisms, with some similarities to lathyrism. The damage is permanent.

Parkinsonian spectrum disorders

Neurodegenerative disorders characterised by Parkinsonism such as corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) can be confused with PLS. Prominent emotional reflex hypersensitivity and early gait instability are common features of both PSP and PLS. The rigidity and bradykinesia seen in the limbs in CBD is typically more asymmetrical. Both conditions have an older mean age of onset (65-70 years) compared to PLS.

Mills' syndrome

The American neurologist Charles Karsner Mills (1845-1931) presented a case of a 53-year-old man with unilateral progressive ascending paralysis without significant sensory loss or muscle atrophy to the Philadelphia Neurological Society in 1899 (34). Gastaut and Bartolomei reviewed Mills' eight and seven other published cases (35). They identified the core features of a slowly ascending hemiparesis over months to years (13/15 cases), often with bilateral pyramidal signs (7/15), a degree of facial weakness (5/15) and occasional minimal hyperaesthesia (3/15).

PET using [11C]-PK11195 demonstrated unilateral microglial activation in the region of the motor cortex contralateral to the ascending hemiparesis as well as in the descending corticospinal tracts (36, 37). With developments in MRI, Mills' syndrome due to solitary sclerosis is now more recognised (38, 39).

Mills' syndrome is a purely clinical description and is likely to be aetiologically heterogeneous but has become synonymous with 'unilateral PLS'. Rare individuals in whom a focal lesion has been fully excluded, are best included under the broader diagnostic umbrella of neurodegenerative disorders of the motor system.

Alexander disease

Alexander disease is a leukodystrophy associated with mutations in the glial fibrillary acidic protein gene, *GFAP*, typically affecting infants and may be lethal. Adult-onset cases are recognised however, with symptoms emerging as old as the seventh decade (40). There is typically progressive bulbar dysfunction with prominent dysphagia, which may be accompanied by a sensory-sparing pyramidal syndrome. The key diagnostic finding is atrophy of the medulla on MRI, which may extend to the upper cervical cord (**Figure 3**).

Autoimmune disorders

The broad spectrum of stiff person syndrome, which is variably associated with anti-glutamic acid decarboxylase (GAD), anti-glycine receptor and anti-amphiphysin antibodies, may include forms with generalised muscle stiffness and hyperekplexia (41). Typically, the emergence of such symptoms will be far less insidious than for PLS, and clearly demarcated by the presence of additional clinical features such as ataxia or encephalopathy.

Management

There is currently no licensed disease-modifying therapy for PLS. The benzothiazole riluzole, licensed in the treatment of ALS, is considered to have a broadly anti-excitatory mechanism of action.

Although there is evidence that PLS has some histopathological features in common with ALS, and similar changes in cortical inhibitory function (17) the very modest survival benefit of riluzole shown in ALS trials is far less certain for PLS. The mainstay of management in PLS is currently symptomatic and optimally delivered through in a multidisciplinary setting, which has been shown to have an independent survival benefit in ALS (42). An annual follow-up is often adequate for those living with PLS, with flexibility to respond to unexpected interim deterioration.

Spasticity

This is typically the most troublesome symptom in PLS, underpinning both the pain and discomfort of the condition, as well as a large part of the associated physical disability. Baclofen is the standard treatment for spasticity but comes with a functional trade-off through its 'unmasking' of limb weakness as a result of losing the splinting effect of increased muscle tone. Unwanted lethargy and broader psychoactive effects may also be problematic. Typical titration is in 10mg increments, beginning once daily to a maximum of 90mg in three divided doses. Tizanidine is an alternative. Focal use of botulinum toxin may sometimes be considered for intractable muscle spasticity that adversely impacts posture.

Emotionality

Reflex emotional hypersensitivity, a more accurate and less opaque term than 'pseudobulbar affect', is a consequence of pathological involvement of the corticobulbar pathways in PLS, and most commonly consists of explosive sobbing, incongruent with any emotional stimulus, and which is difficult to terminate. For a minority there may be a predominantly inappropriate laughing response instead. Both reactions may be severe, with the former occasionally manifesting as a profound 'wailing', and both with potential to cause great social embarrassment. Education of those affected and those around them is important, in particular that it neither indicates underlying depression nor cognitive impairment. Selective serotonin reuptake inhibitors are beneficial to a large proportion of those affected by emotionality even in the absence of depression, though the latter is probably a

relative common co-morbidity due to the chronic nature of PLS. Dextromethorphan in combination with low-dose quinidine is specifically licensed in some countries for the treatment of emotionality in ALS and MS (43).

Dysarthria

Spasticity of the bulbar musculature in PLS results in laboured, 'straining' dysarthria. Progression to complete anarthria is not inevitable and typically takes many years. Nonetheless, communication support e.g. tablet computer voice synthesiser, and picture pointing books are often useful adjuncts. Voice banking referral should be considered in those without established bulbar symptoms.

Dysphagia

Slowed tongue movement and delayed initiation of the pharyngeal phase of the swallowing reflex are common sequelae of corticobulbar involvement in PLS. Unlike ALS, those with PLS are able to adapt their eating habits and maintain adequate nutrition without the need for a softened diet, and only exceptionally require consideration of gastrostomy. Violent coughing reactions may occur where food particles stimulate the epiglottal folds and patients benefit from education from speech and language therapists on mitigating techniques such as chin tucking during swallow. Patient, carers, family and friends need to be reassured that the individual will not choke to death in this setting and that symptoms nearly always pass spontaneously without the need for physical assistance such as the Heimlich manoeuvre.

Oral secretion management

A degree of escape of watery saliva from the mouth (sialorrhoea) may occur as a result of the involuntary reduction in swallowing frequency in those with PLS. If troubling, it may be managed with anti-cholinergic therapy such as a hyoscine patch applied behind the ear, or 1% atropine eye drops (one drop under each side of the tongue up to three times daily). It is unusual to need to progress to other options such as glycopyrrolate or salivary gland botulinum toxin. More tenacious pharyngeal secretions sometimes require mucolytics such as carbocisteine, combined with the provision of a suction machine. The simultaneous use of anti-cholinergics and mucolytics should be avoided.

Cognitive and behavioural change

ALS is accepted to lie on a clinicopathological spectrum with frontotemporal dementia (FTD), with varying degrees of detectable cognitive impairment (typically prominent executive dysfunction, with dementia in up to 15%), and 'frontal' behavioural change e.g. prominent apathy or disinhibition, concrete thinking, loss of food repertoire, reduced social cognition and loss of insight. Until recently there had been few dedicated studies in those with PLS, but these have revealed similar changes (11, 17, 44), though frank dementia is probably rarer than in ALS and so loss of mental capacity is even more exceptional.

The future

Those living with PLS have not been able to share the increasing focus on therapeutic trial design underway in ALS (45). The primary outcome measure of survival commonly used in ALS is less relevant (or indeed practical) for a condition with such a dramatically longer natural history. An adapted functional rating scale has been developed for PLS (46), and the development of therapy more selectively targeting spasticity might be the greatest unmet need in this population.

Understanding those at risk, to eventually allow preventative strategies, may emerge from rapid developments in the understanding of the pathogenesis of ALS. In biomarker development, those with PLS offer a valuable 'extreme' comparator group. Increased awareness of PLS among both primary care physicians and neurologists will help to reduce diagnostic delay.

Key points

- PLS is a rare, sporadic, slowly progressive, 'pure' upper motor neuron syndrome. It is not synonymous with 'benign or slow ALS', but a distinct variant within the spectrum of MND
- The average age of symptom onset in PLS is younger than for ALS (50 versus 65 years)
- The diagnosis of PLS is clinical, with symptoms beginning in the lower limbs for most and symmetrical spasticity the most consistent clinical finding
- Involvement of the bulbar territory is common, wherein emotional reflex hypersensitivity may be severe
- The emergence of significant lower motor neuron involvement within 4 years of symptom onset suggests the more common diagnosis of upper motor neuron-predominant ALS
- PLS is very disabling but may not necessarily be life-shortening

Further reading

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Table 1

Key differences between ALS and PLS

Feature	ALS	PLS
Incidence (per 100,000/year)	1-3	<0.1
Mean age of symptom onset	65	50
Site of first symptoms	Lower limb 30% Bulbar 30% Upper limb 30%	Lower limb 90% Bulbar 10% -
Typical pattern of limb symptoms at onset	Asymmetrical	Symmetrical
Urinary frequency	-	++
Cognitive impairment	++	+/-
Family history	10%	0%
Spasticity	+/-	+++
Pre-central gyrus atrophy	+/-	++
Median survival from symptom onset	3 years	~15 years

Table 2

Summary of Stark & Moersch's 1945 key criteria for PLS, see (7)

<ul style="list-style-type: none">• Insidious onset
<ul style="list-style-type: none">• Slowly progressive without plateau or remission
<ul style="list-style-type: none">• Examination findings limited to the pyramidal tracts (accepting some age-related loss of vibration sense)
<ul style="list-style-type: none">• No evidence of involvement of any part of the nervous system beyond the pyramidal tracts
<ul style="list-style-type: none">• Minimum of 5 years of symptoms

Table 3

Summary of recent consensus criteria for diagnosis of PLS (Table adapted from (9))

<u>1. Core principles</u>	The <u>presence</u> of: <ul style="list-style-type: none">• Age \geq 25 years• Symptoms of progressive UMN dysfunction for at least 2 years• Signs of UMN dysfunction in at least 2 of 3 regions: lower extremity, upper extremity, bulbar
	The <u>absence</u> of: <ul style="list-style-type: none">• Sensory symptoms (unexplained by comorbid condition)• Active LMN degeneration• Alternative diagnosis: UMN pathology demonstrated on neuroimaging, or identified through biofluid testing that provides a plausible alternative explanation for the clinical syndrome
<u>2. Diagnostic certainty</u>	<u>Probable PLS</u> Defined by the absence of significant active LMN degeneration 2-4 years from symptom onset
	<u>Definite PLS</u> Defined by the absence of significant active LMN degeneration 4 or more years from symptom onset

LMN – lower motor neuron
PLS – primary lateral sclerosis
UMN – upper motor neuron

Table 4

Key clinical and investigation-based factors in the diagnosis of PLS versus an alternative disorder
(none are absolute)

Factor	Features favouring PLS	Features favouring alternative diagnosis
Age at symptom onset	<60 years	>60 years
Family history	No family history of progressive spastic paraparesis, ALS, or FTD	First or second-degree relative with progressive spastic paraparesis, ALS, or FTD
Time from symptom onset to first presentation	>2 years	<2 years
Regionality of symptom onset	Lower limb, or bulbar-onset	Upper limb-onset (in isolation)
Extra-pyramidal features	Pure spasticity	Prominent ataxia, rigidity or oculomotor dysfunction
Serum creatine kinase	Normal	>500 IU/L
Electromyography	No denervation or prominent fasciculation	Denervation beyond minor distal hands or prominent fasciculation
MRI	Focal atrophy of the pre-central gyrus or normal brain and cord appearances	Any demyelinating lesion, compressive myelopathy or medullary atrophy

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Figure legends

Figure 1

The spectrum of lower versus upper motor neuron involvement in MND, with PLS as the rare extreme.

Figure 2

Tracheostomy free survival, according to clinically-defined phenotypes within the amyotrophic lateral sclerosis (ALS) spectrum. Cases with a 'pure' upper motor neuron syndrome at presentation (yellow) showed a significantly higher survival compared to all others (from right to left on the graph: red = pure lower motor neuron; turquoise = upper motor neuron-predominant; olive = 'flail arm'; violet = 'classical': limb-onset mixed lower and upper motor neuron; green = 'flail leg'; dark blue = bulbar-onset; grey = respiratory-onset) (Figure from (47)).

Figure 3

Severe atrophy of the medulla and upper cervical cord in a case of Alexander disease (Figure from (48)).