ABSTRACT

Primary lateral sclerosis (PLS) is a neurodegenerative disorder of the adult motor system. Characterised by a slowly progressive upper motor neuron syndrome, the diagnosis is clinical, after exclusion of structural, neurodegenerative and metabolic mimics. Differentiation of PLS from upper motor neuron-predominant forms of amyotrophic lateral sclerosis remains a significant challenge in the early symptomatic phase of both disorders, with ongoing debate as to whether they form a clinical and histopathological continuum. Current diagnostic criteria for PLS may be a barrier to therapeutic development, requiring long delays between symptom onset and formal diagnosis. While new technologies sensitive to both upper and lower motor neuron involvement may ultimately resolve controversies in the diagnosis of PLS, we present updated consensus diagnostic criteria with the aim of reducing diagnostic delay, optimising therapeutic trial design and catalysing the development of disease-modifying therapy.

INTRODUCTION

Primary lateral sclerosis (PLS) is a characteristically slowly progressive and selective neurodegenerative disorder primarily affecting the adult central motor system. Progressive muscle stiffness leads to an insidious loss of mobility typically with the development of corticobulbar dysfunction, which may be the initial symptom for a minority. Diagnostic criteria for PLS proposed 75 years ago recognised the potential for clinical overlap in the early symptomatic phase with the more common disorder amyotrophic lateral sclerosis (ALS).1 Like PLS, upper motor neuron (UMN)-predominant ALS has a significantly slower rate of progression compared with classical forms of ALS, with survival frequently extending into a second decade from onset of symptoms.2 The development of clinically obvious and functionally significant, progressive lower motor neuron (LMN) involvement is inevitable in ALS, in contrast to PLS, but may not emerge for several years from the initial clinical UMN syndrome.3 As a result, criteria for the definite diagnosis of PLS have enshrined a minimum duration of symptoms, varying from 3 to 5 years.4,5,6

Among the earliest reported cases, many of those that were said to have a hereditary component4 would now be recognised within the spectrum of hereditary spastic paraplegia (HSP). The development of non-invasive neuroimaging has brought further structural, inflammatory and metabolic mimic disorders into consideration (see later). A ‘gold standard’ postmortem histopathological signature for PLS has proved elusive. While neuronal and glial cytoplasmic inclusions of the 43 kDa transactive response DNA-binding protein, TDP-43, are common to 97% of cases of ALS (across disparate monogenetic and apparently sporadic cases), there have been very few postmortem studies of PLS in the modern era of immunohistochemistry.7 Debate as to whether PLS represents an extreme end of a continuum with ALS, or a distinct disorder is ongoing.

The clinical imprecision in the diagnosis, along with some uncertainty about overlap with UMN-predominant ALS has become an obstacle to therapeutic development for PLS. As the result of a meeting of international PLS experts (3 May 2019, Philadelphia, Pennsylvania, USA), a working group set forth to create more permissive diagnostic criteria, in an effort to spur therapeutic development and to accelerate research into the basic histopathology of PLS.

The core clinical syndrome

There have been consistent clinical observations reported across multiple case series in PLS.8 Mean age at symptom onset is around 50 years which is at least a decade earlier than non-familial ALS, and a decade later than HSP. While there have been cases reported with symptoms beginning in childhood, many of those might now be linked to developmental or monogenetically mediated disorders. A male predominance has been consistently noted in PLS (range 2–4:1). An insidious onset is the rule in PLS, so that individuals are unlikely to reach specialised neurological services soon after the very earliest symptoms. For the majority of patients, symptoms emerge in the lower limbs first, but for a significant minority in the corticobulbar pathways with dysarthria and often prominent emotionality (pseudobulbar affect). Although dysphagia may become marked, the value of gastrostomy is far less clear than in ALS, and the need for non-invasive ventilation in PLS more exceptional. Lower limb involvement in the early symptomatic phase may be articulated as a sense of dysequilibrium or loss of fluidity in gait. Prominent sensory involvement should not be evident. Spasticity with pathological hyperreflexia are invariable examination findings. Although PLS
Electromyographic considerations
The late development of LMN involvement in some cases of UMN-predominant ALS has the potential to lead to misclassification of PLS. This issue is complicated by the presence of ‘low-grade’, non-progressive electromyographic (EMG) signs of limited muscle denervation in some cases of PLS.3-8

Pringle et al allowed ‘at most, occasional fibrillation and increased insertional activity in a few muscles (late and minor)’.4 Gordon et al divided patients into pure PLS and UMN-dominant ALS, with 13 of 29 patients with pure UMN developing EMG denervation and LMN signs on average between 3 and 4 years from symptom onset, four of who met criteria for ALS.5 Other series have not shown such a definitive transition to UMN-predominant ALS, nor the development of LMN signs on examination, though some have reported a latency exceeding 4 years.6 Singer et al divided patients into two categories, with and without EMG findings.20 Neither group went on to develop ALS. They found the group with ‘evidence of active denervation potentials (increased insertional activity, fibrillations and/or positive sharp waves) in one or more muscles’ were older and progressed more rapidly. None of the other series reported any significance to minor EMG findings. Mitutomo et al included patients with normal EMG but allowed minimal changes in one muscle.21 Fournier et al identified 217 patients with pure UMN disease at 20 clinic sites and divided the groups into normal EMG, and minor denervation, and found no differences between groups.22

In general, most patients with minor denervation in a rare extremity muscle remain a pure UMN syndrome, so that these minimal findings on EMG have been permitted. The inverse, someone with minor EMG findings in a rare muscle initially who at 4 years have a completely normal EMG, would also support a PLS diagnosis. Notwithstanding the limitations of using EMG as a biomarker for LMN involvement, the recognition of a pragmatic category of ‘probable PLS’ for those with a progressive, idiopathic upper motor syndrome of between 2 and 4 years from symptom onset, reflects a desire to facilitate earlier inclusion of patients with PLS in future trials of potentially disease-modifying therapy before disability becomes advanced.

Differential diagnosis
HSP has the most clinical overlap with the early symptomatic phase of lower limb-onset PLS.24 HSP and PLS are both fundamentally clinical syndromes. A significant proportion of individuals confidently labelled as HSP on clinical grounds will not carry a recognised pathological genetic variant. Analysis of 90 patients with apparently sporadic UMN syndrome with phenotypes of HSP (involvement of legs only), HSP-PLS overlap (involvement of arms and legs) and PLS (bulbar involvement) showed significant overlap in the age of symptom onset and no differences between the groups in features classically used to distinguish the two, such as mild dorsal column dysfunction or urinary urgency.25

Mimic disorders for PLS are rare and high-resolution clinical MRI of the brain and spinal cord will eliminate the majority of these. With the exception of the neurodegenerative category, the plausibility of many alternative diagnoses greatly diminishes with the duration of a progressive pure UMN syndrome at the time of clinical assessment (table 1).

The role of genetic testing
The classical syndrome of PLS appears to be sporadic and the diagnosis based on clinical features. Screening of panels for
pathogenic genetic variants associated with spastic paraparesis (e.g., SPAST) is warranted in cases of progressive UMN syndromes restricted to symmetrical lower limb involvement. It is reasonable to routinely exclude the most common hereditary cause of ALS in Caucasian populations, namely an expansion in C9orf72 which may present with an UMN-predominant phenotype. However, the plethora of very rare genetic variants reported in association with pedigrees containing ALS-like syndromes, including some with apparently pure UMN phenotypes, should not be considered routine tests in the diagnosis of PLS (box 2).

### Emerging technology

A range of neuroimaging and neurophysiological tools have clear potential to quantify the UMN lesion and may help to refine the diagnostic pathway for PLS. Conversely, tools aimed at demonstrating subclinical LMN involvement, such as muscle ultrasound for the detection of fasciculation, may ultimately offer additional value for the earlier distinction from UMN-predominant ALS.

Transcranial magnetic stimulation studies have noted greater central motor conduction times in PLS compared with ALS, in addition to high threshold measures for cortical stimulation, leading to the development of relative cortical inexcitability, a feature that reliably distinguishes PLS from HSP. Focus on beta-band EMG has considered intramuscular coherence as a potential distinguisher of PLS from ALS, and magnetoencephalography offers a broader analysis of differences in corticomuscular coherence.

Neurofilaments are an emerging biofluid biomarker reflecting the intensity of neuronal loss in a range of neurological disorders. Levels tend to be much lower in PLS compared with ALS, reflecting its much slower progression. Cerebrospinal fluid chitinas, thought to be macrophage-derived, may show a differential pattern of involvement in PLS compared with ALS, but further studies are needed to explore the key distinction of PLS from UMN-predominant ALS.

One of the features noted in some established cases of PLS is a focal ‘knife edge’ atrophy of the precentral gyrus, which is strikingly absent in even advanced cases of ALS. With the refinement of more automated volumetric MRI analysis, coupled to large normative databases, it may be possible to quantify the degree of focal motor cortical atrophy at the individual patient level and integrate this within the diagnostic certainty algorithm. Similarly, the presence of focal fluorodeoxyglucose hypometabolism in the same region—the ‘stripe sign’—has been associated with PLS, but has not been validated against the core diagnostic differentiation of UMN-predominant ALS. Diffusion tensor imaging is a development of standard MRI permitting assessment of the integrity of large white matter tracts through the surrogate marker of the directionality of water diffusion. This suggests greater white matter damage in the region of the central corpus callosum in patients with PLS, but this currently lacks the sensitivity and specificity for the diagnosis of individual patients (figure 1). Cerebellar involvement, corticospinal tract fluid attenuated inversion recovery (FLAIR) hyperintensity, and quantitative susceptibility mapping of iron deposition in the motor cortex have all been noted as increased in PLS. The continued development of volumetric spinal cord imaging and its integration with cerebral structural measures may offer greater potential for distinguishing PLS cases.

All of these tools require further prospective studies to define their precise value in the diagnostic algorithm for PLS.

### CONCLUSIONS

Developments in neuroimaging, neurophysiology and molecular biology have not diminished the long-standing recognition of PLS as a distinct, clinically-defined syndrome. Its rarity and prolonged survival trajectory have resulted in a degree of neglect in terms of therapeutic trials compared with ALS. Traditional reliance on EMG with overinterpretation of minimal markers of LMN involvement may contribute to significant diagnostic

### Table 1  Differential diagnosis of primary lateral sclerosis

<table>
<thead>
<tr>
<th>Neurodegenerative</th>
<th>Key distinguishing features</th>
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<tbody>
<tr>
<td>Upper motor neuron-predominant amyotrophic lateral sclerosis</td>
<td>Development of clinically progressive lower motor neuron involvement.</td>
</tr>
<tr>
<td>Hereditary spastic paraparesis</td>
<td>Family history or relevant genetic variant; symmetrical weakness limited to lower limbs.</td>
</tr>
<tr>
<td>Alexander disease</td>
<td>Focal atrophy and MRI signal change in the medulla, or pathogenic variant in GFAP.</td>
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<tr>
<th>Neuroinflammatory</th>
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<tr>
<td>Primary progressive multiple sclerosis</td>
<td>Inflammatory lesions on MRI of the brain and cord.</td>
</tr>
<tr>
<td>Anti-amphiphysin paraneoplastic syndrome</td>
<td>Positive antibody in context of coincident malignancy.</td>
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<th>Metabolic</th>
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<tr>
<td>Adrenomyeloneuropathy</td>
<td>Cerebral MRI white matter abnormalities; raised serum very long chain fatty acids; pathogenic variant in ABCD1.</td>
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<tr>
<th>Infectious</th>
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<tr>
<td>Tropical spastic paraparesis (Human T-cell lymphotropic virus, HTLV-1 &amp; 2)</td>
<td>Positive IgM serology.</td>
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<tr>
<td>Syphilis</td>
<td>Positive serology.</td>
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<tr>
<th>Structural</th>
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<tr>
<td>Foramen magnum region lesions</td>
<td>MRI appearances.</td>
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<tr>
<td>Parafalcine meningioma</td>
<td>MRI appearances.</td>
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<th>Vascular</th>
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<tr>
<td>Spinal arteriovenous malformation</td>
<td>MRI appearances.</td>
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</table>

It is not a requirement that all are formally excluded, rather investigations are guided by clinical plausibility.

### Box 2  Genetic variants reported in a small percentage of upper motor neuron-predominant syndromes

- SPG7*
- ALS2*
- D4S2963*
- C9orf72
- DCTN1
- PARK2
- ERLIN2
- FIG4
- SYNE2
- VEGFA
- CLN6
- BTD
- LRKK2
- SQSTM1*
- KIF5a*
- KIF1a

Primary lateral sclerosis appears to be a sporadic disorder essentially, with diagnosis based primarily on clinical features rather than genotype. *Familial cases.
delay. The development of an international registry that includes all those with ‘probable PLS’ will allow a more precise delineation of the pathogenesis from ALS, and accelerate therapeutic developments.

Beyond primary disease-modifying therapy, the most pressing unmet need for patients with PLS may well be the treatment of core symptoms rather than extension of survival. The development of more effective relief of spasticity that does not sacrifice muscle strength would have a great impact for those living with PLS, notwithstanding the long-term desire for neuroprotective or regenerative therapy. Recognising that advances in molecular phenotyping may well supersede purely clinical diagnostics, it is hoped that these pragmatic criteria will provide greater confidence to reduce diagnostic delay, thus allowing access to potentially disease-modifying therapies at lower levels of disability.

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content and revisions to the overall manuscript. JS co-drafted the EMG section and provided intellectual content and revisions to the overall manuscript. HM conceived the article and provided intellectual content and revisions to the overall manuscript.

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**Competing interests** MRT is on the Scientific Advisory Board for Orphazyme, has been a paid consultant for Genentech Inc. (2017) and anonymous clients separately through GLG Consulting on the topic of ALS diagnosis, management and biomarker development. He received neurofilament assay kits in-kind from Euroimmun UK (2018). PC has received honoraria from Biogen & Cytokinetics. ZS has received honoraria from Wiley, Cytokinetics & Biohaven. HM is on the Advisory Board of Mitsubishi-Tanabe & Biohaven.

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**REFERENCES**

Correction: Primary lateral sclerosis: consensus diagnostic criteria


In this paper, Georg Haase should have been included in the collaborators list.