

NEUROPHYSIOLOGICAL FEATURES OF PRIMARY LATERAL SCLEROSIS

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Abstract

Primary lateral sclerosis (PLS) is a motor neuron disease characterized by spinobulbar spasticity, absence of progressive lower motor neuron (LMN) dysfunction and marked by a slow functional decline. Electromyography is essential to exclude significant LMN involvement, particularly in the context of distinguishing PLS from amyotrophic lateral sclerosis (ALS), given that the prognosis is substantially better, and respiratory complications are unusual, in PLS. Nevertheless, minor neurogenic changes and occasional fasciculation potentials can be observed in PLS. The most useful technique for the objective assessment of upper motor neuron (UMN) dysfunction is transcranial magnetic stimulation (TMS), which in PLS is characterized by a high cortical threshold and delayed central conduction times. TMS is sensitive to identify cortical dysfunction in PLS and might have potential for monitoring UMN function in longitudinal studies and in clinical trials. The findings of TMS need to be interpreted in the context of the clinical presentation and phenotype, particularly in the differentiation between PLS and ALS. While other neurophysiological techniques have been investigated, studies to date have tended to involve small patient cohorts and as such, their value in distinguishing PLS from ALS remains unclear.

Introduction

Primary lateral sclerosis (PLS) is an uncommon, slowly progressive neurodegenerative condition characterized by upper motor neuron (UMN) clinical manifestations. A number of mimic disorders should be considered in the differential diagnosis, but the most difficult diagnostic challenge remains distinguishing PLS from the more common amyotrophic lateral sclerosis (ALS).¹⁻³ Clinical and neurophysiological signs of lower motor neuron (LMN) degeneration are present in the latter, but are typically absent or minor in PLS.^{1,3} Despite these general considerations, the distinction between UMN predominant ALS and PLS remains imprecise.² The very different prognosis, and relative preservation of LMN in PLS suggests that PLS is a distinct entity, in spite of some similar neuropathological findings.¹⁻⁴ There is currently no consensus on the best approach to identify the presence of LMN involvement: clinical examination and a variety of ancillary tests have been utilized, most frequently needle electromyography (EMG)⁵ and neuromuscular ultrasound (US),⁶ and most recently magnetic resonance imaging (MRI)⁷ and electrical impedance myography (EIM).⁸ The roles of muscle biopsy and serum creatine kinase (CK) as markers of LMN disease remain uncertain. UMN function in PLS has been investigated by transcranial magnetic stimulation (TMS),⁹ neuroimaging,¹⁰ intermuscular coherence,¹¹ corticomuscular and intercortical coherence.¹² These techniques may be useful for investigating the pathophysiological mechanisms that underlie UMN dysfunction in PLS and for monitoring disease progression in clinical practice and in treatment trials.

The aim of this review is to assess the utility of the potential utility and role of neurophysiological assessments in the diagnosis and monitoring of progression of PLS.

1. Identification of upper motor neuron involvement

1.1 Transcranial Magnetic Stimulation (TMS)

TMS is a non-invasive method that measures functional integrity of the upper motor neuron (UMN), and thus can be used to support a clinical diagnosis of PLS. TMS evokes compound motor potentials through stimulation of the motor cortex to activate UMN pathways, based on the principle that electromagnetic induction can stimulate neural tissue. The brief, intense magnetic fields preferentially stimulate horizontal interneurons in the superficial layers of the cortex which then activate the apical dendrites of pyramidal neurons and induce efferent volleys along the corticospinal pathways to the anterior horn cells, peripheral nerves and muscles.⁹

In terms of conduction pathways, Brown and co-authors performed TMS in 7 PLS patients and determined that central conduction time was very delayed in 3 patients, and motor responses were absent in the others.¹² In contrast, motor responses were recordable in all ALS patients and central conduction times were only moderately delayed.¹² In another small study of 7 PLS patients, the authors described higher thresholds, lower motor amplitudes, longer central conduction times and reduced cortical silent periods compared with ALS patients, although a few PLS patients had normal central conduction times.¹³ Kuipers-Upmeijer and colleagues investigated 10 PLS patients and confirmed that TMS responses were often absent due to very high thresholds (mainly in the lower limbs).¹⁴ When evoked responses were present, this was associated with an increase in central motor conduction time. Moreover, the authors found significant limb asymmetry in the central conduction in some patients, a finding also reported

by others.¹³ Forestier and colleagues investigated 7 PLS patients with TMS and found that motor responses were absent in the lower limbs, and abnormal, sometimes asymmetrical, in the upper limbs.¹⁵ This same group published a further study of 20 patients with PLS,¹⁶ and found that motor responses were absent in both the upper and lower limbs in 12 patients, but absent only in the lower limbs in two patients. In the remaining patients central motor conduction times were increased. Zhai and co-authors¹⁷ studied 24 PLS patients, recording TMS motor responses in hand muscles. They observed that in the typical, ascending clinical presentation, responses were absent, but in the most atypical presentations (multifocal, asymmetric or patchy distribution) responses were often normal, as in the rare paraparetic form.¹⁷ However, only hand motor responses were investigated, so that the relevance of lower limb changes in TMS of the different phenotypes of PLS was not assessed.

In more recent studies, motor cortex inexcitability was observed in 10 out of 14 PLS patients (70%) but in only 25% from 82 ALS patients.¹⁸ This relative inexcitability of the motor cortex occurs when the threshold required to evoke a response is higher than the output of the stimulator, consistent with previous reports that demonstrated high cortical thresholds in PLS patients. In the remaining 4 PLS patients, resting cortical motor threshold was high, short interval intracortical inhibition (SICI) was abnormally reduced and intracortical facilitation (ICF) was increased.¹⁸ The same research group later investigated 21 PLS patients and described similar results for cortical inexcitability (65%), and that resting cortical motor threshold was significantly higher in PLS ($75.5 \pm 6.2\%$) compared to ALS ($62.3 \pm 12.6\%$, $p = 0.046$).¹⁹ They confirmed that SICI and ICF were abnormal in PLS, as may also be observed in ALS.¹⁹ These observations support the notion that cortical dysfunction is a pathophysiological marker across

different motor neuron disease phenotypes, with changes more prominent in PLS.¹⁷

Importantly, investigation of patients diagnosed with hereditary spastic paraplegia (HSP) established that these patterns of abnormality in cortical function as described in PLS were absent in HSP.¹⁸

In an alternative approach to the examination of cortical function, Weber and colleagues investigated 12 PLS patients using peristimulus time histograms.²⁰ In these studies, the cortical thresholds of single motor units were higher in PLS than in ALS, as was the duration of the primary peak, although the onset latency of the primary peak and desynchronization were similar.

Overall, markers of cortical hyperexcitability can be observed early in the disease course of PLS, but with disease progression, the motor cortex becomes progressively inexcitable, corresponding to a severe loss of motor neurons, typically with a greater level of dysfunction involving excitatory pathways compared to inhibitory synapses. In support, neuropathological and imaging studies have identified severe atrophy of the cortical motor strip and selective depletion of Betz cells in layer V, changes which likely contribute to the neurophysiological abnormalities.²¹

Pulman (personal communication) recently reviewed patients clinically diagnosed with motor neuron disease who underwent TMS from 2010 to 2018 at Columbia University Irving Medical Center. There were 97 subjects, comprised of the following groups: PLS (n = 39), ALS (n = 37), PMA (n = 21), and 32 age and sex matched controls. Central motor conduction time of > 2 SD above the established laboratory average values was classified as severely prolonged. The central motor conduction times were abnormal in all PLS patients (sensitivity of 100%), and

significantly slower in PLS than every other group ($p < 0.01$, figure 1). Even more significant was the ratio of UMN-to-LMN conduction latency, which was also higher in PLS than in the other clinical groups ($p < 0.001$, figure 2). Central conduction time was prolonged in 61 of 62 subjects with clinically definite UMN signs when all motor neuron groups were combined; therefore the specificity of TMS for PLS diagnosis was 63% in this study. TMS was normal in 22 of 35 subjects without clinical UMN signs.

1.2 Intermuscular Beta Coherence

Beta-band (15-30 Hz) coupling between muscles (intermuscular coherence) is a physiological phenomenon derived from a common cortical drive transmitted by the corticospinal tract.²² A group of investigators studying intermuscular coherence in upper limb muscles identified severe reduction in 8 PLS patients.¹⁰ Issa et al., comparing ALS patients with a control population, found a significantly reduced intermuscular coherence in the ALS group.²³ While this may represent a promising technique, more studies will be needed to determine its role in the investigation of PLS patients.

1.3 Magnetoencephalography (MEG)

Functional cortical studies using MEG considered the preparation, execution and recovery phases of motor activity in both ALS and PLS patients.²⁴ A delayed hemispheric lateralization of the post-movement beta rebound in the PLS group (figure 3) was consistent with the exaggerated callosal involvement noted in MRI studies compared to ALS.²⁵ Increased resting-state cerebral MRI functional connectivity has been linked to rate of symptom progression in

ALS.²⁶ In keeping with this concept, PLS patients showed a comparative lack of the increase in MEG-based functional connectivity noted in those with ALS.²⁷

2. Lower Motor Neuron Dysfunction

2.1 Nerve Conduction Studies & Electromyography (EMG)

Assessment of the lower motor neuron compartment has tended to require normal findings as consensus for a diagnosis of PLS.^{3,28} The presence of mild changes of denervation as identified by EMG, not sufficient to satisfy the revised-El Escorial²⁹ or Awaji criteria³⁰, may be used to differentiate PLS from ALS. Follow up observations establish that most UMN-predominant ALS patients progress to fulfil diagnostic criteria for ALS, with EMG changes preceding the development of clear clinical signs of ALS by 6 months.²⁸ However, approximately 25% of patients with minor EMG changes do not progress to clear ALS, even with extended clinical follow-up (5 to 11 years),²⁸ suggesting that some PLS patients may exhibit minor but stable EMG changes. In a careful retrospective study the authors reported follow-up EMG investigations of 21 patients diagnosed as PLS.³¹ Three of these patients (14%) developed definite LMN changes consistent with a diagnosis of ALS after the 4-year period typically used to determine PLS, while an additional 5 patients developed EMG abnormalities prior to that period. These findings support the importance of follow-up EMG investigation to evaluate LMN dysfunction in patients with predominant UMN involvement.³¹

Other studies have permitted the presence of minor EMG abnormalities in PLS, and have not noted an impact in terms of diagnostic certainty or disease progression.³² Le Forestier and

colleagues¹⁵ investigated nine patients diagnosed with PLS who had a disease duration of 3.6 to 12 years at the time of recruitment. Follow-up EMG studies for 3 years revealed abnormalities in 6 patients (fibrillation potentials, positive sharp waves or neurogenic motor unit potentials). In two patients, the abnormal spontaneous activity was transient. In another study from the same group,¹⁶ 20 PLS patients underwent follow-up EMG studies 24 to 84 months after the initial study. At entry, 6 patients (mean disease duration 10.6 years) were found to have active denervation that normalized in 3 on follow-up studies. Of the 14 patients in the initial group with completely normal needle EMGs, 5 developed active denervation and 3 others were noted to have transient findings of active denervation.¹⁶ Singer and colleagues (2005)³³ reported EMG abnormalities in 10 of 25 patients with PLS, generally characterized by features of active denervation (fibrillation potentials and positive sharp waves), or fasciculation potentials in a few isolated muscles. Changes were more frequent in distal muscles and in older patients, and were associated with faster disease progression.³³ In previous studies, neurogenic motor units potentials were rarely identified, but in another report these were evident in 4 of 10 PLS patients¹². A recent report retrospectively analyzed 76 PLS patients followed longitudinally in four ALS centers in Germany.³⁴ In this study, 42% of patients had signs of LMN involvement described as “occasional pathologic spontaneous activity or chronic neurogenic alterations”, without detailed information.

It is generally accepted that motor unit recruitment is abnormal in the presence of spasticity, with lower firing rates and reduced firing rate variability during mild contraction.³⁵ Spasticity can be associated with hyperexcitability of the lower motor neuron, thereby facilitating the activation of spinal motor neurons with consequent reduced variability of firing rates, probably

due to activation of inward persistent sodium currents producing a stable plateau potential.³⁵

Decreased firing rate variability in PLS has been observed by a number of authors using an array of different neurophysiological methods.³⁵⁻³⁸

More of a conundrum are the fasciculation potentials that may occasionally be observed in PLS patients.³⁹ In a study that recorded fasciculation potentials in the first dorsal interosseous through surface potentials in 6 PLS patients with a long disease duration, and with a completely normal EMG of the target muscle (except for fasciculation potentials), the authors recorded fasciculation potentials with a frequency of 0.03 Hz (about 10 times less frequent than in a parallel group of ALS patients). This frequency remained stable in successive tests performed in each subject 2 to 4 times, at 6-month intervals.⁴⁰

In terms of other studies of the lower motor neuron compartment, motor amplitude of the phrenic nerve in patients with PLS was similar to matched controls⁴¹ and remained stable on longitudinal assessment.⁴² However, the motor response had a lower variability between end-expiration (diaphragm relaxation) and full-inspiration (diaphragm contraction) than healthy controls and ALS patients, indicating less diaphragm mobility due to spasticity, in spite of normal pulmonary function tests (forced vital capacity and maximal inspiratory pressure).⁴¹

2.2 Other indicators and biomarkers of LMN disease

Increased creatine kinase (CK) has been utilised as a marker of muscle fiber injury, as typically observed in rapidly progressive LMN disorders. CK is raised in about 40% of ALS patients.⁴³ In comparison, CK has been reported as mildly increased in 16%¹⁴ to 40%^{13,33} of PLS patients, although serum CK levels did not correlate with clinical or EMG findings.

Muscle Biopsy is frequently used to differentiate a LMN disease from a primary myopathy, the former indicated by small groups of atrophic angular muscle fibres (denervation) and fiber type-grouping (reinnervation). Neurogenic features were found in 5 of 9 PLS patients on muscle biopsy in one study, correlating with EMG changes.¹⁵ In another study of 20 patients by the same authors, similar histopathological changes were found in the same proportion (60%).¹⁶ These studies are in agreement with another report³³ describing neurogenic changes in all muscle biopsies investigated in a small population of 4 PLS patients.

In terms of neuroimaging approaches, muscle MRI has not been studied in PLS, while CT has revealed muscle atrophy in 2 of 9 patients.¹⁵ Muscle ultrasound and electrical impedance myography are other biomarkers of LMN disease, but have not been so far tested in PLS. Both would be of interest, the former to detect fasciculations and characterize possible modifications in muscle echogenicity, and the latter to assess alterations in muscle structure.

3 – Peripheral and Central Sensory tracts

In PLS, motor and sensory conduction studies usually remain normal. In comparison, approximately 20% of ALS patients exhibit a mild axonal sensory neuropathy,^{44,45} although there are no similar studies about in PLS.

Somatosensory evoked potentials (SEPs) have rarely been studied in PLS patients. An early study included 8 PLS patients and determined that lower limbs SEPs were abnormal in 7.⁴⁶ Forestier et al.,¹⁶ reported abnormal symmetrical or asymmetrical results in 11 of 20 PLS patients; in addition the P100 component of the visual evoked potentials was delayed in 9

patients. Similar findings were found by other authors investigating SEPs in upper and lower limbs in small numbers of subjects with PLS.^{14,47} In another study of patients with adult UMN syndromes, 36 with bulbar involvement were included who likely had PLS. Lower limbs SEPs were abnormal in one-third in these patients.⁴⁸ In contrast, Brown et al.,¹²¹ reported normal SEPs in 4 PLS patients who were studied, although methodological details were not provided.

Conclusions

PLS is a complex phenotype that remains a clinical diagnosis, with key features of dysfunction of UMNs with consequent spasticity, and a long disease course. It is not uncommon to find minor EMG changes. In particular slight neurogenic changes in isolated muscles and rare fasciculation potentials may be observed, and there is no evidence that this makes progression to ALS more likely. Fibrillation potentials and positive sharp waves in patients who appear to have PLS are of uncertain clinical significance. These may be transient, but should be closely followed up as they may herald a predominantly UMN-presentation of ALS. The degree of minor LMN abnormalities that should shift a diagnosis towards UMN-ALS or that could indicate future progression to ALS remains unknown.

With regard to other diagnostic studies, TMS is frequently abnormal in PLS, in particular demonstrating very high cortical thresholds, relative cortical inexcitability and increased central conduction times. As such, a normal TMS study in a patient with suspected PLS should cast strong doubt on the diagnosis. The specificity of TMS for differentiating PLS from ALS is not very high as similar TMS features can also be observed in both. Other techniques such as neuroimaging, electrical impedance myography, MEG and intermuscular coherence require

further study to test their utility. Based on studies to date, TMS may have a role for monitoring UMN function in PLS, but longitudinal studies are needed. At this stage of knowledge neurophysiological features are not enough to define PLS as a consistent diagnostic cluster, but are relevant to monitor progression in this group of patients.

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Figure 1 - Motor conduction times.

Motor conduction findings are presented showing the total motor conduction times on the left, peripheral motor conduction times in the center, and the differences of the two, the central motor conduction time (CMCT) on the right. PLS is represented by solid red squares and (*) denotes significant difference from other subject groups. Note that all CMCT in PLS are significantly different from every other group at $p < 0.01$.

(Including 39 PLS patients, 37 ALS patients, 21 PMA patients and 32 age and sex matched controls)

Figure 2 - UMN-to-LMN conduction latency ratios

UMN-to-LMN conduction latency ratios are represented for the different groups. These ratios are notably higher and significantly different in PLS compared to other clinical groups, $p < 0.001$.

(Including 39 PLS patients, 37 ALS patients, 21 PMA patients and 32 age and sex matched controls)

Figure 3 – MEG recording

Evolution of MEG beta-band power lateralization around a unilateral motor response, with data epoched around movement completion. PLS patients show a diminished degree of lateralization during the post-movement rebound phase (horizontal bar, $p < 0.05$), (see Proudfoot *et al.*, 2017, figure with permission of the author).²¹