Primary Lateral Sclerosis: Clinical, radiological and molecular features

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General review

Primary Lateral Sclerosis: Clinical, radiological and molecular features

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ABSTRACT

Primary Lateral Sclerosis (PLS) is an uncommon motor neuron disorder. Despite the well-recognisable constellation of clinical manifestations, the initial diagnosis can be challenging and therapeutic options are currently limited. There have been no recent clinical trials of disease-modifying therapies dedicated to this patient cohort and awareness of recent research developments is limited. The recent consensus diagnostic criteria introduced the category 'probable' PLS which is likely to curtail the diagnostic journey of patients. Extra-motor clinical manifestations are increasingly recognised, challenging the view of PLS as a 'pure' upper motor neuron condition. The post mortem literature of PLS has been expanded by seminal TDP-43 reports and recent PLS studies increasingly avail of meticulous genetic profiling. Research in PLS has gained unprecedented momentum in recent years generating novel academic insights, which may have important clinical ramifications.

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Abbreviations: ALS, Amyotrophic lateral sclerosis; AD, Axial diffusivity; C9, orf72hexanucleotide repeat expansion on C9orf72; bvFTD, behavioural variant frontotemporal dementia; CBF, cerebral blood flow; CBT, corticobulbar tract; CC, corpus callosum; Chit1, chito-triosidase; CSF, Cerebrospinal fluid; CST, Corticospinal tract; DCTN1, Dynactin; DTI, Diffusion tensor imaging; DWI, diffusion-weighted imaging; EMG, Electromyography; ERLIN2, ER Lipid Raft Associated 2; fMRI, functional MRI; FTD, Frontotemporal dementia; FUS, fused in sarcoma gene; GM, grey matter; HC, Healthy controls; HSP, Hereditary spastic paraplegia; IR, immunoreactive; JPLS, Juvenile primary lateral sclerosis; LMN, Lower motor neuron; MD, Mean diffusivity; MEG, Magnetoencephalography; MND, Motor Neuron Disease; MRI, Magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MI/Cr, Myo-inositol/Creatine; NAA/Cr, N-acetylaspartate/creatine; NAA/Cho, N-acetylaspartate/choline; OPTN, Optineurin; PBA, Pseudobulbar affect; NCI, neuronal cytoplasmic inclusions; PCL, pathological crying and laughing (PCL); PET, Positron emission tomography; PLS, Primary lateral sclerosis; pNFH, phosphorylated neuro-filament heavy chain; PPA, primary progressive aphasia; RD, Radial diffusivity; SOD1, superoxide dismutase; SPECT, Single-photon emission computed tomography; SSRI, Selective serotonin reuptake inhibitors; TARDBP, transactive response DNA-binding protein gene; TBK1, TANK-binding kinase 1; TCA, Tricyclic antidepressants; TDP-43, TAR DNA-binding protein 43; UBQLN, ubiquitin-like protein gene; UMN, Upper motor neuron; VBM, Voxel-based morphometry.

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1. Introduction

Recent clinical trials in motor neuron disease (MND) invariably restrict recruitment to patients with amyotrophic lateral sclerosis (ALS), and PLS patients are often left out of therapeutic initiatives. The mainstay of therapy in PLS remains supportive and is limited to multidisciplinary interventions to improve mobility, reduce muscle tone and facilitate activities of daily living. There is limited awareness among patients and caregivers of recent advances in PLS research which has generated important novel academic insights in recent years. Research efforts in PLS are very easy to justify on clinical grounds; patients face an unacceptably long diagnostic journey with the fear of converting to ALS, there have been no recent pharmaceutical trials, and the limited awareness of the condition often translates into limited resources and limited research funding. The rationale to review recent advances in PLS is twofold; a number of unresolved academic debates persist and recent research findings may have pragmatic implications for clinical care. Accordingly, our objective is the systematic review of recent advances in PLS research with particular attention to reports that challenge traditional views and may have direct clinical ramifications.

2. Methods

A formal literature review was conducted on PubMed between November 2020 and December 2020 in accordance with the Strobe guidelines. The search terms ''Primary Lateral Sclerosis'' was paired individually with the following keywords

''post mortem'', ''pathology'', ''ubiquitin'', ''TDP-43'', ''neuroimaging'', ''magnetic resonance imaging'', ''diffusion tensor imaging'', ''genetics'', ''frontotemporal lobar degeneration'', ''neuropsychology'', ''functional MRI'', ''single photon emission computed tomography'', ''positron emission tomography'', ''diagnosis'', ''monitoring'', ''outcomes'', ''clinical trials'', ''staging'', ''neurophysiology'', ''electrophysiology'', ''transcranial magnetic stimulation''. Selection criteria included original research articles only; opinion pieces, review articles, case reports, and editorials were not reviewed. Only articles written in English were selected for review. References of original research papers were also reviewed if not captured by the initial search.

3. Results

3.1. *Expanding the clinical profile of PLS*

The core clinical feature of PLS is a slowly progressive upper motor neuron (UMN) dysfunction which is typically adult-onset, often manifests initially in the lower limbs but may also involve the bulbar and respiratory muscles [1,2]. While PLS only represents about 3-5% of MNDs, it carries a markedly better prognosis with longer survival [3]. A distinguishing feature of PLS is the lack of overt lower motor neuron (LMN) dysfunction [4,5] which distinguishes it from other motor neuron disorders. While rare unilateral variants have been described, the majority of patients eventually exhibit bilateral spasticity [6,7]. Mills' syndrome [6] is a low-incidence unilateral form of PLS [8] that has been linked to asymmetric frontal signal alterations on both magnetic resonance imaging (MRI) [9] and positron emission tomography (PET) [7] studies. Unlike in ALS [10], feeding tube insertions are rarely needed in PLS, and full anarthria seldom develops [11]. A common symptom of PLS is pseudobulbar affect (PBA) or pathological crying and laughing (PCL), which refers to context-inappropriate or exaggerated involuntary laughter or crying in response even to minimal stimulus. This symptom has been traditionally linked to corticobulbar tract degeneration, but more recent studies highlight the role of impaired cerebellar gating mechanisms [12–14]. The impact of PBA/PCL is often underestimated; it may lead to gradual withdrawal from social interactions and result in self-imposed isolation. Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) were the mainstay of therapy until the recent approval of dextromethorphan/quinidine for PBA in some countries [15]. Clinical disability in PLS is often evaluated by clinical examination, but composite reflex scores, spasticity scales, PBA questionnaires, combined UMN scores and scales developed for other MNDs are also commonly utilised [16]. These scales include the revised ALS Functional Rating Scale (ALSFRS-r) [17], the Penn Upper Motor Neuron Score (PUMNS) [18], the Modified Ashworth Scale [19], and the emotional lability questionnaire [20]. 2020 has seen the introduction of the first PLS-specific functional rating scale (PLSFRS) [21] which promises to be more accurate in tracking disease-associated functional disability than generic instruments. Contrary to ALS, where non-motor manifestations are universally recognised [22–26], PLS has been traditionally viewed as a 'pure' motor neuron disorder without significant cognitive deficits and the term 'PLS-plus' is sometimes used to label PLS patients with additional extra-motor deficits [27]. While cognitive deficits have been sporadically reported in PLS [1,28,29], these have only been recently corroborated by larger case series and linked to neuroimaging changes [30–33]. The most commonly identified neuropsychological deficits in PLS include deficits in social cognition, apathy, executive dysfunction, and language and verbal fluency deficits [32,33]. Alterations in personality, such as obsessive compulsive behaviour, have also been described in PLS [34]. Some patients may exhibit frank frontotemporal dementia [32], but this is thought to be relatively rare (3.3%) and not associated with GGGGCC hexanucleotide repeat expansions in *C9orf72* [32]. The identification of neuropsychological deficits in PLS are in line with post mortem [35,36] and imaging reports [11,37–44] that have consistently captured cortical and subcortical changes beyond the motor cortex and corticospinal tracts. The characterisation of frontotemporal changes in PLS is clinically relevant, as these may impact on compliance with assistive devices, rehabilitation efforts, fall prevention and participation in clinical trials. Another relatively understudied clinical aspect of PLS is the extra-pyramidal manifestation of the disease, which, coupled with the considerable lower limb spasticity, may increase the risk of falls in this cohort. The clinical evaluation of extra-pyramidal deficits is notoriously challenging in the presence of widespread UMN dysfunction,

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but novel strategies such as computational gait analyses may help to ascertain these deficits [45]. Just like in ALS [45,46], parkinsonism, freezing and postural instability have been previously reported in PLS.

3.2. Successive diagnostic criteria

The diagnosis of PLS is challenging as ALS may initially present as a UMN-predominant syndrome. PLS however carries a considerably better prognosis with a markedly longer survival; therefore the careful distinction between the two syndromes is paramount. Patients with PLS invariably experience a long diagnostic journey and are often apprehensive of conversion to ALS. The attendance of multiple neurologists for diagnostic clarification is not uncommon. The 1945 criteria proposed a minimum symptom duration of five years to establish the diagnosis [47]. In 1992, the Pringle criteria suggested a symptom duration of three years to establish the diagnosis of PLS [4]. The 2006 Gordon criteria put forward a symptom duration threshold of four years to label patients with PLS [27]. Imaging studies have captured MRI alterations in patients with a symptom duration of less than five years [48] and 'suspected' PLS patients have been often included in imaging studies admixed with patients who fulfilled the Gordon criteria [49,50]. In 2020, the new consensus diagnostic criteria [51] recognised the impact of the protracted diagnostic delay, and introduced the category of 'probable PLS' for patients with a symptom duration of two to four years. Few studies have applied the new consensus diagnostic criteria yet, but these have shown that, despite their shorter symptom duration, 'probable PLS' patients already exhibit motor cortex atrophy on imaging, considerable functional disability and widespread UMN dysfunction. [52,53] Therefore emerging data seem to support the introduction of the new 'probable PLS' category, which may curtail the diagnostic journey of patients and facilitate an earlier inclusion into research studies and pharmaceutical trials.

3.3. Post mortem insights

The consensus observation of post mortem PLS studies is primary motor cortex and corticospinal tract degeneration [4,54–56], but the post mortem literature of PLS also includes cases with ante-mortem extra-pyramidal features [57], dementia [58,59], and progressive non-fluent aphasia [60]. Studies predating the availability of immunohistochemistry describe the degeneration of the primary motor cortex and pyramidal tracts with the relative preservation of the LMNs [4,54,61]. Studies availing of immunohistochemistry for ubiquitin describe ubiquitin-immunoreactive neuronal cytoplasmic inclusion bodies in the motor cortex [56,62], but LMN involvement is either mild or absent [56,63]. From a clinical perspective, it is noteworthy that extra-motor ubiquitin-immunoreactive neuronal cytoplasmic inclusion bodies were also detected in hippocampal and prefrontal areas [56,62,64]. Since the identification of TAR DNA-binding protein 43 (TDP-43), extensive frontotemporal and hippocampal burden has been confirmed with limited LMN involvement [56,65]. Widespread cortical TDP-43 burden has been recently reported in association with the *TBK1* mutation, where a clinical constellation of PLS and primary progressive aphasia was ascertained ante mortem [66]. The description of brainstem changes vary in the literature, some studies only highlight descending corticospinal tract (CST) degeneration in the superior brainstem [67] while others also report hypoglossal nucleus degeneration [64]. A recent series of seven PLS cases highlighted the preservation of LMNs; while considerable TDP-43 immunoreactivity was invariably detected in the motor cortex, TDP-43 burden in the LMNs was slight despite the long ante mortem disease duration of the cases [68]. This was one of the very few modern case series in PLS using TDP-43 immunohistochemistry, reporting combined UMN/LMN assessments and providing information on ante mortem extra-motor symptoms. Two out of the seven patients carried the *TBK1* mutation and had comorbid primary progressive aphasia (PPA) [66], and one patient had comorbid behavioural-variant frontotemporal dementia (bvFTD). The primary motor cortex showed neuronal loss, reactive gliosis, and microglial activation, and the CST exhibited reduced myelin staining and microglial activation. There is considerable concordance between neuroimaging studies and post mortem reports [69]. Not only is primary motor cortex [11,70] and CST degeneration [71–73] readily captured by imaging, extra-motor neocortex [11] involvement and brainstem [41,74] and hippocampal degeneration has also been detected in vivo [44,75].

3.4. The genetic profile of PLS

Research studies typically screen their PLS cohorts for ALS-associated, and established hereditary spastic paraplegia (HSP) genes. [11] While previous diagnostic criteria, such as the Pringle criteria required the lack of family history [4], families with multiple members affected with PLS have been described [2,76–78]. Even though ALS-associated genes are often evaluated in PLS, with the exception of GGGGCC hexanucleotide repeat expansions [79], these are rarely identified. In larger series, *C9orf72* mutations were detected in 1/41 and 1/110 of cases [80,81]. In a large PLS series, mutations have also been identified in *PARK2*, *DCTN1* [81], and *SPG7* which is typically linked to HSP [82]. While most PLS case series detect no HSP mutations [44,83], *SPG7* mutation has been linked to PLS-like presentation by several groups [82,84]. Heterozygous *SPG7* mutations have been also described in five siblings with PLS [84] and a kindred of *TBK1* mutation-associated PLS has also been reported [85]. Among ALS-associated mutations, *FIG4* [86], *UBQLN2* [87,88] and *OPTN* mutations [89] have been associated with UMN-predominant MND phenotypes reminiscent of PLS. Juvenile primary lateral sclerosis (JPLS) is linked to *ALS2* [90,91] and *ERLIN2* mutations [92].

3.5. Imaging findings in PLS

The core imaging signature of PLS is associated with motor cortex [11,70], corpus callosum [49] and CST degeneration. [71–73] More recently, brainstem [41,74], subcortical grey matter alterations [44,75], extra-motor cortical changes [11,40,93], and cerebellar degeneration [11] have also been reported. The majority of imaging studies in PLS are either MRI or PET studies

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[94], but a multimodal PET-MRI study can also be identified [95]. Quantitative imaging studies readily capture motor cortex atrophy [70,96–98]? and white matter changes in the CST [99], corona radiata [100–102], brainstem [97], and corpus callosum [100]. Functional studies highlight connectivity alterations in motor networks [39,103] and spectroscopy typically detects reduced N-acetylaspartate/creatine (NAA/Cr) [104–106], myo-inositol/creatine (MI/Cr) [107], or N-acetylaspartate/choline (NAA/Cho) [104] ratios in the motor cortex. While considerable progress has been made in spinal cord imaging in MNDs [108–112], no quantitative spinal studies have been published in PLS to date; only intensity changes have been reported [113]. A number of imaging papers explored correlations between clinical metrics and disability. Tapping rates, ALSFRS-r, and clinical UMN signs have been linked to white matter degeneration [11,98,102], cortical thinning [70,101,114], volume reductions [96,98], metabolic changes [81,104,107], and proton-density alterations [106]. Compared to ALS [115–118], there is a relative scarcity of longitudinal studies in PLS [105,115,119–124]. There are few studies specifically evaluating the imaging differences between PLS and ALS and their conclusions are inconsistent [125]. Some studies identified marked primary motor cortex degeneration in PLS compared to ALS [98,107] but other studies did not confirm this [50]. A recent study highlighted the relative sparing of the post-central gyrus in PLS despite the longer symptom duration of the cohort [11], and PLS-specific subcortical signatures have also been proposed [44]. PET studies typically report comparable patterns of hypometabolism in ALS and PLS [126]. Lower fractional anisotropy values have been detected in PLS than in ALS by some [49,101], but these observations have not been replicated by others [127]. Studies of early or suspected PLS are scarce [52,53,99,106], but some studies include 'suspected' PLS patients with short disease duration who subsequently meet diagnostic criteria on follow-up [50,97]. There are a number of recent studies specifically evaluating 'pre-PLS' [48] or 'probable PLS' [52] demonstrating motor cortex degeneration before meeting diagnostic criteria. Despite advances in machine learning [128–130] and individual scan interpretation [108,131–133], no study to date has evaluated the value of MRI in predicting conversion to ALS versus fulfilling diagnostic criteria for PLS.

3.6. *Wet biomarkers in PLS*

Contrary to ALS, where a number of putative wet biomarkers have been proposed [134–136], progress in the validation of cerebrospinal fluid (CSF) and serum markers in PLS has been relatively slow. The main focus of wet biomarker studies is the identification of serum and CSF indicators that may distinguish PLS from ALS [137,138]. A distinctive CSF 'chitinase' profile has been proposed by some [139], but not fully corroborated by others [137]. The most commonly investigated CSF markers in MNDs are neurofilaments [138]. Some groups detected no neurofilament level differences between PLS and ALS [140], while others suggest that both phosphorylated neuro-filament heavy chain (pNFH) and chitotriosidase (Chit1) may effectively discriminate between PLS and ALS [141].

4. Discussion

Despite its slower clinical progression and markedly longer survival [124], PLS has a number of overlapping clinical features, shared genetic variants, and comparable cerebral imaging signatures with ALS [125]. Aggregation of ALS and PLS cases in the same family is not uncommon and the reliable distinction of PLS from UMN-predominant ALS on clinical grounds can be challenging in patients with short symptom duration. The field of PLS has seen the publication of seminal research papers in the past couple of years, many of which are directly relevant to the clinical care of patients. The recognition of extra-motor pathology, frontotemporal radiological changes and neuropsychological manifestations is a relatively new facet of PLS research. Recent case series confirm sporadic observations of language deficits, executive dysfunction, and, in some cases, overt dementia in patients with PLS. The chronology of motor and extra-motor changes remains to be elucidated by purpose-designed longitudinal studies. Cognitive screening tests developed for ALS may be particularly well suited to screen for frontotemporal dysfunction in PLS as these instruments have been adapted for motor disability. Extra-pyramidal motor and cerebellar dysfunction may exacerbate the motor disability associated with pyramidal degeneration, increase fall risk, and contribute to impaired mobility. Accordingly, extra-pyramidal and cerebellar factors should be carefully considered when planning multidisciplinary interventions, home modifications and rehabilitation strategies. The management of spasticity should rely on the concomitant use of pharmacological and non-pharmacological therapies. Pseudobulbar affect should be specifically screened for and monitored as it may lead to social withdrawal and impact on quality of life. Given the multitude of pharmacological options available for the treatment of PBA, treatment should be escalated and changed depending on response to therapy. Given the multi-system manifestations of PLS, PLS is best managed in a multidisciplinary setting, relying on expert input of physiotherapists, speech and language therapists, social workers, occupational therapists, clinical geneticists, neuropsychologists, and specialist nurses. Clinical electrophysiology has an important role in making sure that there is no evidence of denervation suggestive of alternative diagnoses. Spinal and cerebral imaging is important to rule out potential mimics. In addition to healthcare providers, patients with PLS are often supported by local charities, advocacy groups and national MND associations. Research in PLS is spearheaded by international consortia and disease-specific research meetings are also regularly organised [142]. The publication of the new consensus criteria is an important step to streamline the diagnostic pathway in PLS and is likely to allow the earlier recruitment of patients into research studies. The development of disease-specific clinical instruments such as the PLSFRS will aid the nuanced characterisation of disability trajectories. Advances in neuroimaging and wet biomarkers are likely to provide objective measures to track PLS cohorts longitudinally, and may also serve as prognostic indicators. While recent studies contributed important insights, studies in PLS are often marred by sample size limitations. Given the low incidence of the

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condition, large multicentre studies are urgently needed with carefully harmonised research protocols to meticulously characterise the clinical, genetic and pathological spectrum of PLS.

5. Conclusions

Recent advances in biomarker development, revised diagnostic criteria, disease-specific instruments and increased international interest in the condition may pave the way for the first disease-modifying trials in PLS.

Disclosure of interest

The authors declare that they have no competing interest.

Author contribution

All authors have contributed equally to the drafting of this manuscript

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