Primary Lateral Sclerosis

Subjects: Clinical Neurology

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Primary lateral sclerosis (PLS) is a rare neurodegenerative disorder which causes the selective deterioration of the upper motor neurons (UMNs), sparing the lower motor neuron (LMN) system. The clinical course is defined by a progressive motor disability due to muscle spasticity which typically involves lower extremities and bulbar muscles. Although classically considered a sporadic disease, some familiar cases and possible causative genes have been reported. Despite it having been recognized as a rare but distinct entity, whether it actually represents an extreme end of the motor neuron diseases continuum is still an open issue. The main knowledge gap is the lack of specific biomarkers to improve the clinical diagnostic accuracy. Indeed, the diagnostic imprecision, together with some uncertainty about overlap with UMN-predominant ALS and Hereditary Spastic Paraplegia (HSP), has become an obstacle to the development of specific therapeutic trials.

Keywords: primary lateral sclerosis ; hereditary spastic paraplegia ; ALS

1. Introduction

Primary lateral sclerosis (PLS) is a sporadic neurodegenerative disease characterized by the progressive degeneration of the upper motor neurons (UMNs). It is currently considered as an extreme end of the spectrum of motor neuron diseases (MNDs), of which amyotrophic lateral sclerosis (ALS) is the most represented condition. Although it may share, especially in the early phase, some clinical features overlapping with ALS, PLS is marked by the lack of clinical involvement of the lower motor neurons (LMNs), and by a more protracted clinical course with a better prognosis [1].

The disease was firstly described by Charcot in 1865, but, only ten years later, Erb reported a clinical phenotype characterized by the isolated involvement of the corticospinal tracts named “spastic spinal paralysis” [2].

The prevalence of PLS is estimated to be around 2–3% of total cases of MND [3]. However, this data strongly depended on the population considered, since other studies sustained a higher prevalence (up to 5% of the MND population [4]). The incidence is thought to be less than 0.1/100,000/year, even though the largest population-based study [5] describing the epidemiology of PLS in Catalonia in the period of 2011–2019 and in Valencia in the period of 2013–2019 pointed out an estimated incidence ranging from 0.2 to 0.6 per 100,000 people per year (higher than expected from previous data).

A male predominance has been consistently observed in PLS (range of 2–4:1) [6][7], although other studies suggested a higher prevalence among females [5][8][9]; no difference between races have been reported [8][9][10].

The clinical course is characterized by a progressive motor disability due to muscle spasticity which typically involves lower extremities and bulbar muscles.

Although PLS has been traditionally considered as a “pure” motor neuron disorder, some “extra-motor” features have been systematically recognized in recent years, and supported by post-mortem and imaging reports that have consistently demonstrated cortical and subcortical changes beyond the motor cortex and corticospinal tracts [11]. Extramotor involvement mainly includes some neuropsychological deficits, isolated or widespread, sometimes configuring a frank frontotemporal dementia, and extra-pyramidal features.

There is a general agreement about the fact that PLS is an extremely rare disease, and part of the scientific community still doubts its existence as a unique entity.

In the classical original study from Le Forestier et al. [12] on 20 patients with a diagnosis of PLS, the presence of mild, not-progressing, or even transient LMN signs at EMG, confirmed by muscle biopsy, together with findings from previous post-mortem studies [13][14], led to the consideration of PLS as one end of the continuous spectrum of motor neuron diseases, rather than as a discrete entity. However, the clinical imprecision in the diagnosis, together with some uncertainty about

overlap with UMN-predominant ALS, has become an obstacle to the development of specific therapeutic trials. Furthermore, a further difficulty can be found in the differential diagnosis with hereditary spastic paraplegia (HSP).

2. Neuropathology, Neurobiology, and Genetics of PLS

The main histopathological features of PLS consist of diffuse brain atrophy, the loss of pyramidal neurons in the fifth layer of the precentral gyrus, the degeneration of the white matter associated with cortico-spinal tract, and the relative sparing of lower motor neurons. The degeneration of the primary motor cortex and pyramidal tract is always present, while other findings (such as the involvement of the prefrontal and temporal cortices and ubiquitinated inclusions) are inconstant; damage of the LMNs is quite rare and tend to be slight and isolated [15].

Up to the 1980s, lots of case reports were published reporting standard descriptions of the macro- and microscopic examination of the central nervous system of patients affected by PLS. For instance, Beal et al. [16] illustrated a case with severe atrophy of the precentral gyrus of the cerebral cortex bilaterally, accompanied by a general sparing of the remaining cortices and thinning of the pyramids of the medulla. One of the first and most important reviews about PLS was published by Pringle et al. [17], who described a picture characterized by a complete loss of UMNs in the fifth layer of the motor cortex associated with a chronic degeneration of the cortico-spinal tract; LMNs were found intact and there was no involvement of other cortical areas. In general, the first pathological studies published in literature agreed on the main features of this disease, reporting a condition associated with the loss of Betz cells in the precentral gyrus. Similar data have been confirmed by a subsequent study [18], in which the authors have applied an automated analysis program and confirmed a marked total brain atrophy associated with a focal atrophy of other structures, such as the corpus callosum (especially the mid-anterior, central, and mid-posterior parts, which encompass sensory-motor fibers and projections from the dorsal–prefrontal and superior frontal cortices) and thalami (via a mechanism of Wallerian degeneration), finding a correlation between the atrophy degree and clinical severity [18].

In the late 1990 to early 2000s, several immunohistochemical studies have been published reaching different results. Some of them proved the accumulation of ubiquitin not only in the motor cortex, but also in the prefrontal and temporal cortex, depicting a condition similar to fronto-temporal lobar degeneration and excluding the presence of Bunina bodies, which were thought to be more specific of ALS than other MNDs [19]. Other authors confirmed the presence of ubiquitin-positive inclusions associated with dystrophic neuritis in layer II of the frontal and temporal cortex, accounting also for the presence of isolated Bunina bodies and neuronal inclusions in the posterior part of the putamen and in the lower motor neurons [14][15]. A single case report also described a dendritic ballooning phenomenon, which appeared to be very rare in this condition [20].

The crucial role of the transactive response DNA-binding protein of 43 kDa (TDP-43) in the major part of the MND pathology was first reported by Neumann and colleagues in 2006 [21]. They demonstrated that ubiquitinated cytoplasmic inclusion bodies—already known from the previous descriptions of PLS and FTD pathology—also contained the aggregation of TDP-43. They demonstrated a translocation of TDP-43 from the nuclei to cytoplasm (in association with ubiquitin inclusions) in the cells affected by the disease. This evidence strengthened the already existing idea that MND and fronto-temporal lobar degeneration had been part of a spectrum [22][23]. In line with this evidence, Kosaka et al. [24] reported a new case and re-examined the case originally reported by Tan et al. [15], demonstrating prominent frontotemporal atrophy, and abundant TDP-43 pathology throughout the cerebral neocortex and hippocampus, but only a few inclusions in LMNs, which were substantially preserved. Furthermore, Hirsch-Reinshagen et al. [25] described a family with a TBK1 genetic variant, in which two siblings presented with a combination of PLS and primary progressive aphasia. In both, TDP-43 pathology was present throughout the neocortex, limbic cortex, and many subcortical regions; however, the LMNs were well-preserved and only a single TDP-43 cytoplasmic inclusion was detected in the lumbar spinal cord in one of the two cases.

MacKenzie et al. recently reported the neuropathological findings in seven cases of PLS, revealing the presence of TDP-43 inclusions mainly localized in the primary motor cortex and cortico-spinal tract, but also in the LMNs, although sparse and not associated with substantial pathological changes [26]. The authors confirmed the TDP43 pathology is shared by PLS and ALS, but PLS possess some protective factors against LMN degeneration.

However, the limitations in these studies are the selection of patients mainly classified on the basis of their pathological findings, but with insufficient clinical information to determine if they actually fulfilled the clinical PLS criteria. On the other hand, a number of neuropathological reports demonstrated that PLS can be a rare clinical phenotype of other neurodegenerative diseases, such as Alzheimer’s disease and Lewy body disease [27], progressive supranuclear palsy [28], neuronal intermediate filament inclusion disease [29], globular glial tauopathy [30], and argyrophilic grain disease [31].

The precise molecular and cellular mechanisms of UMN degeneration in PLS remain mostly unknown. Numerous related cellular defects may result in UMN vulnerability, as demonstrated through several mouse models generated based on PLS-linked genetic variants. One of the recognized mechanisms underlying UMN vulnerability is based on intracellular trafficking defects. Indeed, corticospinal motor neurons are selectively vulnerable to the lack of expression of Alsin, a large protein encoded by the *ALS2* gene, implicated in a wide range of cellular functions ranging from endocytosis, membrane trafficking, endolysosomal protein degradation, and apoptotic signaling from mitochondria upon cellular stress [32]. In mouse models, the depletion of Alsin caused the disintegration of corticospinal motor neurons at several levels (cervical spinal cord, pyramidal decussation, and pons) and the disruption of apical dendrites with numerous vacuoles, as well as profound defects in the morphology and function of the mitochondria and the Golgi apparatus [33].

Significant ultra-structural defects in the Golgi apparatus and mitochondria suggest problems with ATP production and energy metabolism, as well as the post-translational modification of proteins and lipid homeostasis [33]. Indeed, PLS-patient-derived fibroblasts have shown elevated ATP demand and consumption, thus needing an enhanced energy metabolism through both oxidative and glycolytic ATP pathways, which, in turn, led to an overproduction of reactive oxygen species [32].

Interestingly, recessive loss-of-function mutations in the *ALS2* gene have been identified in atypical forms of PLS with infantile or juvenile onset [34][35][36], infantile ascending spastic paraparesis [37], and hereditary spastic paresis [35][38], with overlapping phenotypes and no clear genotype–phenotype correlation.

Actually, although the current consensus criteria [7] state that the “screening of panels for pathogenic genetic variants associated with spastic paraparesis should be performed only in cases of progressive UMN syndromes restricted to symmetrical lower limb involvement”, researchers current knowledge of HSP and ALS genetics is widely incomplete. In fact, some families with multiple members affected by PLS have been reported [39][40][41][42], and, for this reason, in the current criteria, there is not mention of “lack of family history”, which was, instead, considered as a clinical criterium in the previous set of criteria (Pringle) [17].

One of the largest studies [43] which analyzed the *C9orf72* gene in a PLS cohort identified the presence of the expansion in 1 patient out of 110. Another relatively large study found that 18% of patients carried a variant in either ALS (*C9orf72*), Parkinson’s disease (*PARK2*), or HSP (*SPG7*) genes [44]. A predicted pathogenic mutation in the *SYNE2* gene was also identified [44].

Among HSP-related genes, *SPG7* variants have been linked to a PLS-like presentation in several studies [45][46], while, among rarer ALS-associated genes, *TBK1* genetic variants [47] have been reported in a family with PLS. Furthermore, *FIG4* [48], *UBQLN2* [49][50], and *OPTN* variants [51] have been associated with UMN-predominant MND phenotypes resembling PLS. Besides *ALS2* [34][35][36], juvenile primary lateral sclerosis (JPLS) has also been linked to *ERLIN2* [52] variants.

In the most recent and largest genetic study on 139 PLS patients [53], likely pathogenic or pathogenic variants in genes related to ALS-FTD (*C9Orf72*; *TBK1*), HSP (*SPAST*; *SPG7*), and the ALS-HSP-Charcot-Marie-Tooth overlap (*NEFL*; *SPG11*) were found in 7% of the cohort, remarking upon the possible significant contribution of genetics in the diagnostic work-up of PLS.

3. Clinical Features

The mean age of clinical onset in PLS is around 50 years, which is about a decade earlier than non-familial ALS, and a decade later than HSP. In the most part of the cases (90%), the onset of symptoms insidiously involves the lower limbs, and patients may complain of a “loss of fluidity” and/or a “loss of stability” in the gait. However, for a significant minority of the patients, a bulbar onset has been described, including dysarthria, nasal speech, and emotional lability configuring a pseudobulbar affect [54]. Dysphagia can be present but usually is not that severe so as to require gastrostomy as in ALS. Similarly, the need for ventilatory support is quite exceptional. In fact, in the prospective NEALS PLS registry [54] of 250 PLS patients, with a three-year median follow-up after enrollment, only 7% required a feeding tube and less than 1% needed permanent assisted ventilation. Usually, PLS slowly generalizes to the upper limbs, while a focal onset involving an upper limb is extremely rare [55]. The rate of progression is much slower than typically encountered in ALS, with an average disease duration ranging from 7.2 to 14.5 years [6].

Depending on the patient’s age and comorbidities, the prognosis of PLS is at least a decade from the onset of symptoms and often significantly longer [54].

Typically, the neurological examination shows only upper motor neuron signs, including spasticity and the spread of reflexes, with the absence of lower motor neuron findings (fasciculations and muscle wasting). Stiffness as a presenting symptom is observed more commonly in PLS than ALS (47% vs. 4%), and limb wasting is rare in PLS (~2%) [56].

An upper motor neuron pattern of weakness may be observed (extensors in upper extremity; flexors in lower extremity), but symptoms referred by the patients are often a combination of increased tone, decreased co-ordination, and mild weakness.

Although the involvement of the lower limbs in PLS is commonly symmetrical, a progressive hemiplegia is a very rare phenotype originally described eponymously by Mills [57]. This latter condition, also known as the “hemiplegic variant”, is characterized by slow progressive ascending weakness, usually starting in a distal lower limb, and then progressing to a proximal ipsilateral lower limb and upper limb, associated with pyramidal signs on the affected side, and sometimes also on the contralateral one [58]. Facial and bulbar weakness may be present, as well as slight sensory disturbances [59]. In most patients, the syndrome remained strictly unilateral after 15 years, although the involvement of the contralateral side has been reported in about 30% [59]. The scarcity of reports on this condition, as well as the paucity of complementary resources necessary to better define its pathophysiological mechanisms, led to doubt about the authenticity of this entity [58]. Sensory disturbances or deficits should not be observed in PLS. Among additional clinical features, the most consistently reported are bladder instability with urinary frequency and retention [60], extrapyramidal features [61][62], and cognitive disorders [62][63][64][65][66][67].

The most common neuropsychological deficits in PLS include problems in social cognition, apathy, executive dysfunction, language, and verbal fluency [62][63][64][65][66][67]. Furthermore, the co-presence of full-blown frontotemporal dementia, which was thought to be relatively rare (2%) [67], was recently found to be more common than expected in PLS patients [62].

Abnormalities in ocular movements, especially the loss of smooth pursuit, and even supranuclear palsy [17], may be present, and saccadometry has shown the loss of fixation and, particularly, prominent antisaccade errors compared to ALS patients [68].

Clinical disability in PLS is evaluated by clinical examination, but combined UMN scores and scales developed for other MNDs are also commonly used. These scales include the revised ALS Functional Rating Scale (ALSFRS-r) [69], the Penn Upper Motor Neuron Score (PUMNS) [70], the Modified Ashworth Scale [71], the emotional lability questionnaire [72], and the more recently validated PLS functional rating scale (PLSFRS) [73].

4. Diagnostic Criteria

Over the years, different sets of criteria were proposed to diagnose PLS.

In 1945, the PLS diagnostic criteria [74] suggested a minimum of a five-year symptom duration for diagnosing PLS, while, in 1992, the Pringle criteria [17] proposed that a minimum symptom duration of three years would have permitted a reliable diagnosis, still describing as core features an adult onset of insidious spastic paresis in the lower limbs (but also in the bulbar or upper extremities), usually symmetric and in the absence of a family history. In 2006, the Gordon criteria [75] recommended a symptom duration of four years to label the diagnosis. Finally, the recent 2020 consensus diagnostic criteria [7], recognizing the implications of diagnostic delay, introduced a category of “probable PLS” for patients with isolated UMN symptoms in at least two of three regions (lower extremity, upper extremity, and bulbar) for 2–4 years. The recognition of a pragmatic category of “probable PLS” reflects the desire to facilitate the earlier inclusion of patients with PLS in future trials of potentially disease-modifying therapy before the disability becomes advanced.

5. Neurophysiological Features

The main diagnostic challenge remains the discrimination of PLS from UMN-predominant ALS patients, especially in the early phase of the disease, when the borderline between these two entities is difficult to delineate. This issue is complicated by the evidence of minimal and not-progressive electromyographic (EMG) denervation signs in some PLS patients [10][17][76][77].

In a study on 29 patients with pure UMN involvement at the initial visit, 13 were later classified as UMN-predominant ALS on average between three and four years from the onset of symptoms, due to the development of denervation, chronic motor unit changes, and fasciculation potentials in one to two muscles at EMG, as well as limited clinical LMN signs. Four of these patients eventually met the WFN El Escorial clinical trial criteria for ALS [75].

In another study on 25 PLS patients, the authors observed a more aggressive and faster disease in patients with evidence of active denervation potentials (increased insertional activity, fibrillations, and/or positive sharp waves) in one or more muscles, even though they did not meet the neurophysiological criteria for ALS [10].

In a large multicentric cohort of 217 patients with pure UMN disease, subjects were categorized into two groups according to the presence or absence of minor denervation signs. The authors found no differences between the two groups in terms of the site of onset, frequency of clinical symptoms, ALSFRS-R scale, vital capacity, or use of non-invasive positive pressure ventilation [77], suggesting that subtle EMG abnormalities can not necessarily be used as a prognostic tool in patients with clinical UMN disease.

A more recent study [78] confirmed these findings of minimal denervation activity in single muscles of PLS patients without a clear progression, even though the authors observed a faster disease progression in patients with a greater amount of EMG abnormalities.

These findings were subsequently corroborated by another cohort study [79] where 21 patients with PLS syndrome associated with definite but limited EMG denervation changes were followed up with for a median of seven years, and around 90% of this cohort maintained the PLS phenotype and diagnosis.

To conclude, although PLS patients lack evident clinical lower motor neuron signs on the neurological examination, several studies report minor and stable changes with needle EMG, including sparse fibrillations, fasciculations, and enlarged motor unit potentials, generally limited to one or two muscles [10][17][76][77]. After four years, the probability of developing new lower motor neuron findings on the EMG becomes low (~20%) [75].

For this reason, EMG findings consistent with mild and not-progressing involvement of lower motor neurons are tolerated in the category of “probable PLS”, coined in the last set of diagnostic criteria [7].

Conversely, if a patient has EMG denervation and, subsequently, developed focal LMN signs and symptoms over the course of four years, but still does not meet the criteria for ALS [80], a diagnosis of UMN-predominant ALS would be more appropriate than PLS [7]. However, the reason for this resistance to LMN degeneration in PLS, at variance from ALS, is widely unknown. The most obvious explanation is that PLS and ALS syndromes present different underlying pathogenic processes.

Besides the LMN assessment, neurophysiological tools can be used to quantify UMN involvement. The most conventional tool is transcranial magnetic stimulation, which have proven abnormalities in the motor-evoked potentials, showing the absence of reproducible cortical responses or longer central motor conduction times in PLS compared to ALS [76]. Furthermore, high threshold measures for cortical stimulation, which suggest cortical inexcitability, are a specific signature of PLS, probably reflecting a greater degree of neurodegeneration within the motor cortex and the corticospinal tracts, as the resting motor threshold reflects the density of corticomotoneuronal projections into spinal motor neurons, as well as the excitability of large motor cortical neurons. These findings also reliably distinguish PLS from HSP [81], where cortical excitability is preserved.

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