Received: 7 June 2021 | Accepted: 30 July 2021

DOI: 10.1111/ene.15049

european journal of neurology
the official journal of the european academy of neurology

EDITORIAL

The diagnostic challenge of primary lateral sclerosis: the integration of clinical, genetic and radiological cues

Primary lateral sclerosis (PLS) is a low-incidence motor neuron syndrome which has overlapping clinical features with several other neurodegenerative conditions. There are currently no approved disease-modifying therapies for PLS and no forthcoming pharmaceutical trials have been announced. The early diagnosis of PLS is challenging as upper motor neuron predominant amyotrophic lateral sclerosis (ALS) and 'apparently sporadic' hereditary spastic paraplegia (HSP) may present with very similar clinical manifestations. The distinction of PLS from ALS is hugely important because ALS is associated with a considerably shorter survival [1]. The differentiation of PLS from HSP is just as important; it is indispensable for the genetic counselling of family members and, as the two conditions progress, they exhibit divergent disability profiles and different prognoses [2]. Accordingly, subsequent diagnostic criteria for PLS put an emphasis on the absence of a family history of motor neuron disorders and set a minimum symptom duration criterion. The 1945 diagnostic criteria for PLS required a minimum symptom duration of 5 years, the 1992 Pringle criteria put forward a symptom duration of 3 years, and the 2006 Gordon criteria suggested a symptom duration of at least 4 years to diagnose patients with PLS if they exhibited progressive spinobulbar spasticity without evidence of lower motor neuron involvement and had no relevant family history. While setting a long symptom duration criterion reduces the risk of misdiagnosing patients who may later develop lower motor neuron signs consistent with ALS, it leads to prolonged diagnostic uncertainty for patients with suspected PLS. The protracted diagnostic journey, seeking second opinions, and the apprehension of transitioning to ALS are invariably a source of significant anxiety for patients with suspected PLS and their caregivers. Recognizing the implications of diagnostic delay, the 2020 consensus diagnostic criteria for PLS are more permissive and include the category of 'probable PLS' for patients with a symptom duration of 2–4 years [3]. Emerging evidence supports the validity of this new category. Recent research has demonstrated that 'probable PLS' patients with a symptom duration of 2–4 years already exhibit pathognomonic clinical and radiological signs consistent with 'definite PLS' and are unlikely to develop ALS [4].

In the past two decades, there have been several reports of PLS cases in ALS kindreds [5,6] highlighting the heterogeneity of motor neuron disease (MND) phenotypes within single pedigrees and challenging the emphasis on the absence of family history to ascertain the diagnosis of PLS. Accordingly, the recent consensus criteria signal a departure from relying on family history and provide specific genetic screening recommendations instead [3]. In line with the evolution of diagnostic practices in PLS, in this issue of the *European Journal of Neurology*, Corcia et al. highlight the co-occurrence of ALS in families of PLS patients [7]. They describe seven patients with PLS who had a first degree relative with ALS and two patients with PLS who had a second degree relative with ALS.

The authors also highlight that two PLS patients developed comorbid frontotemporal dementia. This is another under-recognized facet of PLS which is not only typically regarded as a strictly 'sporadic' condition but also traditionally viewed a 'pure' upper motor neuron disorder. It is increasingly recognized that PLS may be associated with cognitive and behavioural manifestations, and verbal fluency deficits, language deficits and apathy are not uncommon [8]. In line with clinical observations, recent imaging studies of PLS have captured widespread degeneration outside the motor cortex and corticospinal tracts [9] involving frontotemporal and subcortical brain regions [10].

The study of Corcia et al. [7] not only showcases the aggregation of MND phenotypes with different survival profiles in single pedigrees, but also highlights that multicentre initiatives and international collaboration are indispensable for the characterization of low-incidence motor neuron syndromes. Instead of reporting a case report with potentially limited impact, the authors have recruited illustrative PLS cases from five European MND centres across three countries. While strong international collaboration exists in ALS research and a multitude of consortia acquire carefully harmonized genetic, imaging and epidemiology data, PLS research is less well coordinated. In contrast to well-established ALS registries which are invaluable resources for well-powered analyses, the first large multicentre PLS registry has just recently been set up under the auspices of the Northeast ALS Consortium (NEALS).

After years of lagging behind ALS initiatives, research in PLS has gained considerable momentum in the past couple of years; disease-specific clinical instruments have been developed (PLSFRS), patients with PLS increasingly undergo meticulous genetic evaluation, imaging studies have mapped longitudinal trajectories and the postmortem literature of PLS has been expanded by landmark pTDP-43 studies. The implementation of more permissive diagnostic criteria, the validation of precision clinical instruments and the development of viable radiological markers will hopefully pave the way for the first disease-modifying pharmaceutical trials in PLS.

ACKNOWLEDGEMENTS

The authors are supported by the Spastic Paraplegia Foundation (SPF).

CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Both authors have contributed equally to the drafting of this manuscript.

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How to cite this article: Bede P, Siah WF. The diagnostic challenge of primary lateral sclerosis: the integration of clinical, genetic and radiological cues. *Eur J Neurol.* 2021;00:1–2. https://doi.org/10.1111/ene.15049

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