

## **Commentary**

### The reunification of amyotrophic lateral sclerosis

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## Strapline

ALS should be the unifying term for this syndrome and time to question the dogma forged at El Escorial.

## Main text

Traditionally characterised as a neuromuscular disease involving progressive loss of both central and peripheral motor neurones, amyotrophic lateral sclerosis (ALS) is now understood as a neurodegenerative syndrome involving clinical, pathological and genetic overlap with frontotemporal dementia (FTD). Descriptions of progressive lower motor neurone degeneration and associated muscle wasting, termed progressive muscular atrophy (PMA), were published by anatomists such as Charles Bell as early as 1836. Jean-Martin Charcot's later contribution was the unique clinicopathological linking of upper and lower motor neurone degeneration, which he termed ALS, since when PMA has become associated with a lower motor neurone-only variant. Wilhelm Erb and Pierre Marie are associated with identifying the upper motor neurone-only syndrome of progressive weakness, termed primary lateral sclerosis (PLS). In this issue, de Vries and colleagues demonstrate that so-called PMA and PLS cases show cognitive and behavioural impairment within the spectrum now recognised as inherent to more typical ALS (1). In doing this so definitively, with large well-characterised groups, they add to a body of evidence that should call time on the confusing lexicon of phenotypic terms that frequents the penumbra of ALS.

“What type of ALS do I have?” This common question in the clinic reflects public awareness of variation in the clinical presentation and speed of progression of the neurodegenerative disorder most famously diagnosed in Lou Gehrig and Stephen Hawking, with starkly different natural histories. Neither the site of first symptom nor the spread of regional involvement is random in ALS, and progression of weakness is axiomatic. What varies most obviously is the rate of decline in function, though strikingly constant for the individual patient. ALS, despite all its phenotype variation and molecular complexity, has a final common pathway that is typically unmistakable to the experienced clinician (2). ALS might be increasingly considered the genus for a series of cell pathway-defined species, within a family of neurodegenerative disorders.

The clinical essence of ALS is as a variable combination of upper and lower motor neurone signs. It has been recognised in clinic- and population-based studies, that the rate of progression is significantly slower at the two extremes of clinical upper and lower motor neurone-only involvement (3, 4), with a clinical continuum spanning what may be termed upper and lower motor neurone-predominant forms either side of the equal mixture of ‘classical’ ALS. Cognitive impairment in ALS is also associated with a worse prognosis, yet the natural history of ‘pure’ FTD is typically three or four times the median survival of ALS. The broader ALS-FTD syndrome can therefore be envisaged as three variably overlapping pathological ‘networks’ (lower motor neurone, corticospinal tract, cerebral extra-motor) with more slowly-progressing symptoms associated with the more isolated forms of each.

A smaller neuropsychological study previously identified mild cognitive impairment in cases of so-called PMA (5). Histopathological studies identified central nervous system pathology in similar lower motor neurone cases (6, 7), and neuroimaging has permitted *in vivo* demonstration of a similar signature of cerebral white matter involvement common to classical ALS (8). The authors in the present study used the strict Gordon criteria for their cases of PLS, in which the requirement to be four years from symptom onset helps to distinguish it from upper motor neurone-predominant ALS. In this setting PLS represents <2% of the wider syndrome of ALS but the boundary of PLS with upper motor neurone-predominant ALS is strikingly more distinct in contrast to where PMA becomes lower motor neurone-predominant ALS. PLS patients have a consistently younger mean age of onset and the condition is typically not life-shortening in contrast to ALS. The presence or absence in PLS of the ALS histopathological signature of neuronal cytoplasmic aggregates of TDP-43 is uncertain, but neuropsychological studies have reported FTD-spectrum cognitive impairment in PLS (9).

The diagnostic taxonomy of ALS defined at El Escorial in Spain, and subsequently revised at Airlie USA and Awaji-shima Japan, relies in simple terms on the number of body regions where clinical upper motor neurone signs are found in combination with electromyographic evidence of lower motor neurone-related muscle denervation. It is only 60% sensitive however (10), with PMA and PLS regarded as outliers. The categories of 'possible' ALS (1 region with combined involvement) and 'probable' ALS (2 regions) are all-too-easily interpreted by patients as reflecting diagnostic uncertainty on the part of the clinician, whereas in reality they reflect the insensitivity of both the clinical examination (11) and electromyography. Those labelled 'possible'

ALS, as well as PMA and PLS cases, typically find themselves outside the inclusion criteria for therapeutic trials. 'Possible' ALS cases may never move out of this category despite succumbing to the same pattern of functional decline as those with 'definite' ALS (12).

Archaic terms such as PMA and others (e.g. progressive bulbar palsy), for which have lacked consistent definitions, are unhelpful distractors within a syndrome that can be comfortably unified by the single term ALS. Even the synonymous term motor neurone disease has limited recognition outside the UK and is increasingly anachronistic for a condition that consistently involves extra-motor pathology and is not a single disease in genetic aetiological terms. The case for PLS being subsumed is less certain given its highly eccentric natural history and pending additional histopathological insights.

There is undoubtedly a need for improved prognostic stratification at therapeutic trial enrollment to maximize the chance of detecting benefit. Upper versus lower motor neurone burden, along with extent of cognitive and behavioural impairment have a role in this alongside site of symptom onset. Stratification might however be far more meaningfully based on the rate of symptom progression and is increasingly likely to involve genotyping. A diagnostic biomarker based on the cytoplasmic signature of TDP-43 dysregulation common to 98% of all ALS cases is highly desirable but elusive (13). Nonetheless, this study also makes it timely to reflect hard on whether the diagnostic rubric forged at El Escorial, and its derivatives, is fit for the future.

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