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COMMENTARY

The neuroradiology of upper motor neuron degeneration: PLS, HSP, ALS

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The neuroimaging literature of motor neuron diseases is dominated by studies in ALS (1,2). There is a relative paucity of quantitative MRI studies in other motor neuron diseases despite the considerable disability, lack of disease modifying therapies and diagnostic challenges associated with most MNDs (3). Radiological reports in primarily lateral sclerosis, Kennedy's disease, hereditary spastic paraplegia and spinal muscular atrophy are dominated by case series, and multimodal quantitative protocols have only been recently implemented in non-ALS MNDs (4–6).

In this edition of Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, Navas-Sánchez et al. present an intriguing study of motor cortex and corticospinal tract (CST) degeneration in hereditary spastic paraparesis type 4 (SPG4) (7). The authors used a multiparametric imaging approach to evaluate pyramidal tract degeneration using both fixel-based analyses and probabilistic tractography. The authors identify clinico-radiological correlations and detect inferior-predominant CST degeneration. The study offers multiple learning points which are relevant to other MNDs. While correlations between CST metrics and motor disability are confounded by co-existing lower motor neuron degeneration in ALS (8), these are pertinent to upper motor neuron predominant disorders such as PLS and HSP (9). Fixel-based analysis (FBA) is a relatively novel framework which offers integrity indices for single fiber populations and permits the evaluation of crossing fibers. White matter degeneration in MND is typically evaluated by tract-based methods (10), template-based approaches (11), or tractography (12) which makes the appraisal of crossing fibers challenging. Non-Gaussian diffusion protocols, such as diffusional kurtosis imaging (DKI), q-space imaging (QSI) or neurite orientation dispersion and density imaging (NODDI) have only been recently applied to MND datasets and have already contributed important insights (13–15). Furthermore, CST changes in MND are often preferentially assessed in the posterior limb of the internal capsule, and the segmental profile of the pyramidal tracts are seldom systemically characterized from the superior corona radiata to the spinal cord (16–19).

A number of radiological cues are associated with HSP on standard clinical imaging, such as the thinning of the corpus callosum, spinal cord cross-sectional area reduction, ventricular enlargement and periventricular T2/FLAIR signal hyperintensities. Characteristic bilateral signal change in the forceps minor in SPG11/SPG15 has been referred to as the "ear-of-the-lynx sign" which is best seen on axial views at the frontal horn of the lateral ventricles. The specificity of qualitative cues in HSP however is contentious (20); corpus callosum thinning and forceps minor degeneration are also commonly observed in other motor neuron diseases (21).

Cortical change in SPG4 has been previously investigated by voxel-based morphometry (22) and cortical thickness analyses (23). White matter degeneration in SPG4 has been evaluated by tract-based special statistics (TBSS) (22), voxel-based FA analyses (24), and tractography (23). A consensus finding of these studies is that CST changes are more readily detected than the more elusive primary motor cortex atrophy. In addition to standard grey and white matter techniques, a variety of volumetric approaches (24), thalamus imaging (25), resting-state functional MRI (26), magnetic resonance spectroscopy (27) and spinal cord morphometry (23) have also been applied in SPG4. PET studies often capture metabolic changes beyond the motor cortex including the involvement of frontotemporal regions (28).

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Despite sample size limitations, and the divergent methodologies of existing SPG4 studies, pyramidal tract degeneration, motor cortex thinning, thalamus atrophy, cerebellar involvement and frontotemporal changes are relatively consistent observations.

One of the main drawbacks of single-phenotype studies is that imaging findings are identified based on comparisons to healthy controls and the identified patterns are often interpreted as a "signature" of the cohort. The specificity of these findings however can only be ascertained if multiple phenotypes and disease controls are also included in comparative analyses. This is a common challenge of MND imaging, where low-incidence phenotypes often show similar anatomical patterns of degeneration. Cerebral changes in PLS for example are difficult to distinguish from ALS; both exhibiting CST, corpus callosum, cerebellar and some degree of frontotemporal change (29–31). Only the departure from "single group versus controls" study designs and the inclusion of several relevant cohorts will permit the comparative characterization of imaging traits and enable the definition of phenotype-specific signatures. Distilling phenotype-specific features can then be utilized in classification algorithms to aid the categorization of single subjects (32,33).

Imaging initiatives across the spectrum of MNDs offer invaluable learning opportunities and resourceful imaging protocols can be readily adopted and developed to be utilised in other MND phenotypes. Concepts in study design and data interpretation frameworks are also largely transferrable. Advances in academic imaging in MND are likely to gradually filter down to pragmatic clinical and pharmaceutical trial applications.

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