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Imaging denervation in motor neuron disease for future clinical trials: a longitudinal cohort study

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Background: A key area-of-need in motor neuron disease/amyotrophic lateral sclerosis (MND/ALS) translational research is a tool to objectively track disease progression over short timescales, to reduce duration and cost of clinical trials. Previous studies have focused on the central nervous system.

Objective: To assess the utility of whole-body MRI to quantify muscle denervation longitudinally in patients with MND, as a novel biomarker, and to probe pathophysiological mechanisms in vivo.

Patients and Methods / Material and Methods: In a prospective longitudinal observational cohort study, 29 MND patients and 22 age and sex-matched controls were assessed with clinical measures, electrophysiological motor unit number index (MUNIX) and T2-weighted whole-body muscle MRI, at first presentation to our clinic and four months later. Between-group differences and associations were assessed using multivariable regression models, adjusted for age and gender. Within-subject longitudinal changes were assessed using paired t-tests. Patterns of disease spread were modeled using mixed effects multivariable regression, assessing associations between muscle relative T2 signal and anatomical adjacency to site of clinical onset.

Results: MND patients had higher relative T2 muscle signal than healthy volunteers at baseline (all-regions mean + 30%(95%CI 15-45) $p < 0.001$), that was associated with greater disability on patient-reported scales (-0.009(-0.001,-0.02),$p = 0.023$), and greater weakness and lower MUNIX in multiple individual muscles. Relative T2 signal in bilateral tibialis anterior increased over four months in patients (Figure) (right:+10.2%(2.0-18.4),$p = 0.017$; left:+14.1%(3.4-24.9),$p = 0.013$). Anatomically contiguous disease spread on MRI was not demonstrated.

Conclusion: Whole-body muscle MRI offers a new approach to the objective assessment of denervation and spread in MND in vivo. Muscles inaccessible to conventional clinical and neurophysiological assessment may be investigated.