

Commentary

Non-invasive *in vivo* neuropathology of the *C9orf72*-related ALS-FTD syndrome

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Diffusion tensor imaging is a uniquely valuable tool for stratifying a clinically heterogeneous multi-system cerebral neurodegenerative syndrome.

The unmistakable neurodegenerative disease amyotrophic lateral sclerosis (ALS) is a common clinical endpoint for an expanding range of upstream cellular pathway derangements (1). Clinical, genetic and molecular signatures shared with frontotemporal dementia (FTD) have rendered the brain axiomatic to ALS pathology (2); a core feature of what is a motor and para-motor multi-system degeneration, rather than a secondary after-thought over-shadowed by the more visible consequences of peripheral lower motor neuron loss. For the emerging era of therapy for neurodegenerative disorders to flourish, tools that can assess pathology at the system as well as cellular level are essential. In this issue, Floeter and colleagues demonstrate the potential of advanced structural MRI of the brain in this respect, exploring the relationship of white matter tract integrity using diffusion tensor imaging (DTI) to clinical parameters in a genetically homogeneous but clinically heterogeneous group of individuals carrying the *C9orf72* repeat expansion (REF HERE).

Underlying nearly one in every ten cases of ALS and FTD is a hexanucleotide GGGGCC repeat expansion in *C9orf72*. This genetic variant may be associated with cases of both 'pure' ALS and FTD as well as the overlapping forms, and within the same pedigree. The absence of a family history of ALS or FTD appears increasingly insecure as a barrier to offering routine genetic testing to all newly diagnosed individuals (3). The *C9orf72* expansion genotype shares the TDP-43-positive cellular pathology common of nearly every case of ALS and 50% of FTD (the latter

dominated by the behavioural variant). Widespread extra-motor cortical MRI changes have been noted among symptomatic carriers, even in ALS-predominant cases (4), reflected in the frequent finding of significant cognitive and behavioural change in such individuals.

The current gold standard for assessing motor decline is decline in the Revised ALS Functional Rating Score (ALSFRS-R). Questions across each of the core domains (bulbar, upper limb, lower limb and respiratory) undoubtedly capture the consequences of muscle wasting i.e. lower motor neuron degeneration, but may not necessarily be tuned equally to markers of upper motor neuron or wider cortical involvement (5). As well as exploring both cognitive and behavioural changes in relation to MRI metrics, Floeter and colleagues also usefully considered changes in relation to the emerging concept of clinical stage. This is attractive for defining disability milestones that are maximally meaningful to patients, and which might serve as a simpler trial outcome as well as health economic measure. The authors used the first of these staging systems published by the UK King's College London group (6), though alternatives exist (7). They found that both reducing ALSFRS-R and advancing clinical stage (albeit related measures) were reflected by DTI changes in both corticospinal tract and interhemispheric motor callosal pathways. Clinical stage was additionally, though weakly, linked to more anterior callosal MRI changes that were expected and found in relation to cognitive and behavioural scores. The latter are not part of the staging system, and natural history studies in non-*C9orf72* ALS cohorts do not suggest a consistent evolution of these non-motor symptoms over time. The link to staging may therefore reflect the greater anterior brain involvement associated with this genotype, even in apparently motor-predominant cases. Separately, the corpus callosum emerged once again as something of a regional

compass to the wide burden of cortical pathology inherent to the ALS-FTD syndrome (8).

Longitudinal study is very challenging in ALS where typically rapidly-accruing disability, especially orthopnoea due to diaphragm involvement, may eventually preclude MRI. Such studies are however essential for testing biomarkers for potential as therapeutic trial outcome measures. Longitudinal white matter DTI changes were disappointingly modest in a previous more heterogeneous (and likely more benign) ALS-only cohort, though in which spreading grey matter pathology was prominent (9). A high proportion of Floeter and colleagues' study participants returned for at least one follow-up evaluation, and over an interval would be feasible as a therapeutic trial outcome measure. However, the authors importantly acknowledge that ALS-predominant cases were under-represented in the follow-up cohort, so that the whole-brain DTI changes reflect the FTD end of the pathological spectrum. They comment too that longitudinally-acquired pathology involved more superficial white matter than that detected at baseline, and with a posterior direction of travel in keeping with the model proposed in FTD based on *post mortem* patterns of TDP-43 pathology (10). Floeter and colleagues infer Wallerian degeneration, but there is no parallel grey matter analysis with which to explore these concepts more fully. The increasing feasibility of advanced MRI studies combining data from multiple centres presents future opportunities to study larger groups of more homogeneous phenotypes (11).

A broad range of objective outcome measures will be valuable for testing the near-future genetic therapy strategies anticipated for the *C9orf72* expansion, and neuroimaging is a unique non-invasive candidate that reflects tissue pathology on a

large scale. Seven individuals in this study were asymptomatic carriers of the expansion, but the temporal lobe changes reported in a previous study (12) were not reproduced. Measures sensitive to cerebral function, rather than structure, may be more suited to the longer-term goal of biomarkers suitable for assessing preventative and neuroprotective strategies in ALS and FTD (13).

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