Diagnostic shifts in ALS?

From clinical specter to imaging spectra

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Paradigm shifts are occurring across the realm of amyotrophic lateral sclerosis (ALS). In the past, we instructed medical students that ALS was solely a clinical diagnosis; that careful clinical examination raised the specter of this devastating condition, and neurophysiologic testing provided confirmation. We taught that ALS was an isolated clinical syndrome; that neuroimaging was not helpful for the diagnosis, other than to exclude mimic syndromes; that patients did not have significant dementia; and finally, that little could be done to predict or alter an individual patient's course.

All these truisms have now been challenged. The identification of TDP-43 in 2006 and the *C9ORF72* gene in 2011 provided supportive evidence concerning the overlapping nature of ALS and frontotemporal dementia.[1] We now know that a substantial proportion of patients with ALS develop cognitive impairment, dementia, and neuropsychiatric syndromes, especially the patients with *C9ORF72*. And over the last few years, advanced neuroimaging techniques have revealed unique cortical and subcortical abnormalities that may yet prove helpful in both the diagnosis and prognostication of individual patients.

Increasingly, advanced imaging techniques are utilized to interrogate cortical activation patterns in a variety of disease states, including ALS. Diffusion tension imaging (DTI) measures fractional anisotropy (FA) and mean diffusivity to assess white matter integrity, and DTI tractography to visualize white matter tracts, giving marvelous images of the human "connectome." These structural connectivity methods can estimate the relative strength of intra- and interhemispheric connections, whereas functional connectivity can be used to investigate internodal connections. Moving back into the realm of chemistry, MRS can quantify actual brain metabolites. Various neuroimaging signatures are now touted as biomarkers for disease progression, a tantalizing prospect given the many difficulties with clinical prognostication. Indeed, the resurgence in imaging research has already resulted in a dedicated ALS neuroimaging symposium in 2010,[2] producing criteria for DTI, regional volume estimation, functional MRI, and MRS, while emphasizing the importance of robust reproducibility and good patient tolerability when using such a multimodality approach.

With this backdrop, Stagg et al.[3] have made a further unique contribution to the ALS imaging field, described in this issue of *Neurology*®. The authors performed a prospective study using whole-brain MRS imaging (MRSI) and DTI in 13 patients with primary lateral sclerosis and ALS. Mean *N*-acetylaspartate (NAA), FA, and mean diffusivity measurements were extracted from the corticospinal tracts (CSTs), compared between groups, and then correlated with degree of disability. They utilized a novel whole-brain MRS technique, the Metabolite Imaging and Data Analysis System (MIDAS).[4] Some argue that MIDAS, compared with conventional MRS measures, has higher intrasubject reliability and accuracy, both of which have been problematic in prior MRS studies.[5] Indeed, many researchers have ceased their pursuit of MRS in view of the extent of these problems, so the applied method represents quite an advance. The other exciting development is that MIDAS, unlike prior MRS methods, does not calculate NAA levels as a ratio to creatine or choline, but rather uses intensity-normalized metabolite values, thereby enabling comparison of results for individual metabolites between subjects.

Using whole-brain analysis, Stagg et al. identified lower NAA in patients compared with controls throughout the cerebral CSTs. What is particularly relevant to ALS clinicians is that patients with less disability at time of scanning had higher mean corticospinal tract NAA concentration, even when corrected for age. Perhaps surprisingly, no relationship between CST DTI measures and disability was identified. These results led the authors to conclude that whole-brain MRS demonstrated consistent reductions in NAA within the CST, albeit in their small heterogeneous group of ALS patients, some with rather long disease durations. Furthermore, there seemed to be a relationship between CST NAA levels and level of disability, meaning that CST NAA had greater sensitivity than DTI-derived changes. Clearly, these findings require further validation

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in larger, more representative ALS patient cohorts, before the performance of longitudinal whole-brain MIDAS can be critically evaluated as a marker of therapeutic efficacy.

The absence of an association between DTI measures and disability may seem contradictory to previous studies. Specifically, Rose et al.[6] demonstrated a reduction in FA within multiple intra- and interhemispheric motor pathways as a primary feature of patients with mixed upper and lower motor neuron abnormalities. Using fMRI with regional volume estimation, Cosottini et al.[7] identified increased functional activation in frontoparietal circuits despite associated frontoparietal cortical atrophy, suggesting an over-recruitment of extant sensory-motor networks, perhaps rendered hyperexcitable by the loss of inhibitory interneurons. In addition, the findings from Verstraete et al.[8] suggested that patients with ALS had reduced motor network white matter connectivity, with the authors concluding that upper motor neuron degeneration affected both primary and secondary motor connections.

The early identification of such changes may provide further support for the causal primacy of upper over lower motor neuronal degeneration, as indeed originally suggested by Charcot and Joffroy.[9] ALS is now being increasingly viewed primarily as a disorder of the corticomotor neuron, with subsequent anterior horn cell degeneration developing through an anterograde neurodegenerative spreading process.[10] Regardless, when taken in total, these recent neuroimaging findings outline a model of ALS as a "systems degeneration," bringing us one step closer to an understanding of how ALS disease spread may occur. This may provide new insights both into the tracking of disease progression, and eventually into disease causation itself. Perhaps these chemical spectra will provide a novel means of early diagnosis of ALS, a disease that still remains a forbidding clinical specter to patients and their families.

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REFERENCES

1. Renton AE, Majounie E, Waite A, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron 2011;72:257–268.
2. Turner MR, Grosskreutz J, Kassubek J, et al. Towards a neuroimaging biomarker for amyotrophic lateral sclerosis. Lancet Neurol 2011;10:400–403.
3. Stagg CJ, Knight S, Talbot K, Jenkinson M, Maudsley AA, Turner MR. Whole-brain magnetic resonance spectroscopic imaging measures are related to disability in ALS. Neurology 2013;80:610–615.
4. Maudsley AA, Darkazanli A, Alger JR, et al. Comprehensive processing, display and analysis for in vivo MR spectroscopic imaging. NMR Biomed 2006;19:492–503.
5. Maudsley AA, Domenig C, Sheriff S. Reproducibility of serial whole-brain MR spectroscopic imaging. NMR Biomed 2010; 23:251–256.
6. Rose S, Pannek K, Bell C, et al. Direct evidence of intra- and interhemispheric corticomotor network degeneration in amyotrophic lateral sclerosis: an automated MRI structural connectivity study. Neuroimage 2012;59:2661–2669.
7. Cosottini M, Pasaresi I, Piazza S, et al. Structural and functional evaluation of cortical motor areas in amyotrophic lateral sclerosis. Exp Neurol 2012;234:169–180.
8. Verstraete E, Veldink JH, Mandl RC, van den Berg LH, van den Heuvel MP. Impaired structural motor connectome in amyotrophic lateral sclerosis. PLoS One 2011;6:e24239.
9. Charcot J, Joffroy A. Two cases of progressive muscular atrophy with lesions of the gray matter and antero-lateral bundles of the spinal cord [in French]. Arch Physiol Neurol Pathol 1869;2:744–754.
10. Kiernan MC, Vucic S, Cheah BC, et al. Amyotrophic lateral sclerosis. Lancet 2011;377:942–955.