Another Dementia Biomarker? (Editorial)

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The growing anticipation of effective early interventions for dementia has intensified efforts to identify early diagnostic and mechanistic biomarkers, particularly for Alzheimer's disease. Many proposed biomarkers, however, require considerable logistical resources and patient participation, often accompanied by discomfort or risk. These range from invasive procedures such as brain biopsy and cerebrospinal fluid analysis to radionuclide imaging (e.g. PET), blood sampling, and neuropsychological testing. New markers derived from established non-invasive and brain-centred investigations are therefore welcome.

In this issue of Neurology, Hall et al. publish a study in which they evaluate multi-shell diffusion-weighted MRI, specifically Neurite Orientation Dispersion and Density Imaging (NODDI), as a marker of brain tissue integrity. The authors examine its role within the current diagnostic framework, alongside amyloid and tau PET, structural MRI, plasma phosphorylated tau-217, and, as the gold standard, clinical diagnosis supported by the Montreal Cognitive Assessment (MoCA) as a severity measure of cognitive impairment.[1] This study is among the first to integrate NODDI-derived metrics with multi-modal biomarkers and cognitive assessment, providing insight into grey matter microstructural measures over the cognitive spectrum.

In Hall et al.'s cross-sectional analysis of data from 303 participants, NODDI-derived free water closely paralleled MoCA performance and demonstrated the strongest association with tau PET, weaker associations with amyloid PET and plasma p-tau217, and a statistically mediated influence of the latter two on free water via brain tau. These findings align with a model in which amyloid accumulation precedes neurofibrillary tangle formation, while plasma p-tau217 reflects a global burden less sensitive to regional microstructural changes

than co-localised tau PET binding. Although cognitively normal participants were included, the associations were primarily driven by individuals with Alzheimer's disease and mild cognitive impairment, emphasising that NODDI's sensitivity within preclinical stages remains to be established.

The study uses biological staging, which also means that nine participants positive for both amyloid and tau PET ($A^+T_2^+$) were clinically classified as cognitively normal, as were 16 participants positive for amyloid PET and plasma tau ($A^+T_1^+$). Such false positives, common in biologically staged samples, highlight the complexities of brain and cognitive reserve (or conversely, the contribution of co-pathologies in false negative cases).[2, 3] Reconciling molecular pathology with individual variability in clinical expression is an enduring challenge with direct implications for diagnostic interpretation of other potential biomarkers.

NODDI, an advancement over conventional Diffusion Tensor Imaging (DTI), employs a three-compartment tissue model comprising intracellular neurites, extracellular space, and isotropic free water to generate maps that more precisely reflect grey matter microstructure and, potentially, the effects of neurofibrillary tangle pathology.[4] Unlike traditional diffusion metrics that summarise microstructure into a single measure, NODDI distinguishes neurite density and orientation, providing biologically interpretable metrics of cellular changes in neurodegeneration. These methodological advantages, however, come at the cost of longer acquisition times and specialised imaging sequences that remain unavailable in many MRI centres. Like other MRI-based techniques, NODDI lacks specificity for tau-related pathology and therefore requires prior confirmation of Alzheimer's pathology using established biomarkers. Confirming this limitation, Hall et al.[1] report significant associations between MoCA scores and medial temporal and hippocampal free water even in participants without amyloid or tau binding (also, cf.[5-7]). These results suggest that free water elevations may

reflect non-specific processes such as neuroinflammation, gliosis or vascular change.[8] Expanding the application of NODDI to grey matter in other dementia subtypes and validating findings against fluid or molecular biomarkers will be essential to clarify its diagnostic specificity.[9]

Despite current constraints, NODDI shows promise as a biomarker for tracking longitudinal changes in tissue integrity, particularly those that precede detectable atrophy. Because NODDI-derived metrics are sensitive to a wide range of biological processes they may capture disease progression or treatment-related effects not detectable with conventional volumetric or diffusion-tensor measures. Longitudinal studies with harmonised acquisition protocols will be critical to determine the sensitivity of NODDI-derived free water measures to such changes.[10] As advanced diffusion sequences become more accessible and acquisition times shorten through optimised protocols, the feasibility of incorporating NODDI into standard protocols will be increasing.

In summary, Hall et al.'s findings are consistent with, but do not yet confirm, the hypothesis that NODDI-derived free water in grey matter represents an outcome measure synchronous with neurofibrillary tangle pathology in limbic structures and with cognitive impairment. As such, it may offer an ecologically valid marker of disease severity and a potential indicator of treatment response. Unlike plasma biomarkers, NODDI provides anatomically resolved information. With further validation requiring longitudinal and multi-modal studies, and after being integrated into standard MRI protocols, NODDI could become a valuable adjunct in the longitudinal evaluation of patients and their therapeutic outcomes.

References:

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