Emerging MRI and biofluid biomarkers in the diagnosis and prognosis of multiple sclerosis

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Accurate diagnosis, prognostication of disease course and response to immunotherapy are pivotal in managing multiple sclerosis (MS), for which MRI and biofluid biomarkers are crucial. These biomarkers hold the promise to provide invaluable insights into disease activity, progression, and treatment response, thereby guiding clinical decisions and improving patient outcomes. In this issue of *The Lancet Regional Health - Europe* two articles for the Series on Multiple Sclerosis 2024 by Maria A. Rocca and colleagues on MRI biomarkers in MS[1] and by Massimiliano Di Filippo and colleagues on fluid biomarkers in MS[2] examine their evolving role in diagnostics and prognostics.

The 2017 revision of the McDonald criteria underscores the importance of MRI and biofluid biomarkers in diagnosing MS.[3] As Rocca et al.[1] emphasize, to avoid misdiagnosis, the use of standardized brain and spinal cord MRI protocols[4] across centers and countries is crucial. In addition, MRI interpretation should be performed by qualified radiologists to exclude the presence of potential MS-mimicking CNS pathologies. The appropriate application of the revised criteria efficiently shortens the time to MS diagnosis,[5] indirectly allowing earlier initiation of high-efficacy therapies, thereby potentially limiting the buildup of permanent clinical disability.[6] Nevertheless, one major issue is the lack of reliable biomarkers to monitor and predict disease progression and treatment response, impacting the ability to tailor treatments effectively. While MRI techniques are improving, additional biomarkers are needed to validate and quantify treatment effects. Furthermore, functional and cognitive outcomes, which are essential for evaluating the disease's impact on daily living and overall quality of life, are not adequately incorporated in current criteria and guidelines. These shortcomings in our opinion deserve more attention.

While current McDonald criteria do not prioritize optic nerve lesions due to their limited MS specificity and impact on diagnostic accuracy, evaluating these lesions alongside findings from visual assessments including optical coherence tomography (OCT) and evoked potentials may provide valuable insights into disease dissemination and progression.[7] Alongside cortical lesions (CLs) and paramagnetic rim lesions (PRLs), the central vein sign (CVS) is a promising, distinct feature that enhances diagnostic accuracy by identifying veins within lesions, characteristic of MS pathology.[8]

Beyond diagnosis, MRI biomarkers are crucial for predicting disease outcomes. Conventional measures such as lesion count, volume, location, and gadolinium-enhancement are well-established predictors of disability. Spinal cord lesions are valuable, particularly in progressive MS, for understanding disease severity and predicting disability progression. As stated by Rocca et al.,[1] distinguishing MS-specific neuroimaging features from other demyelinating disorders and MS mimics, however, is challenging. Novel MRI biomarkers such as CLs and PRLs enhance early diagnosis and prognosis. CLs are recognized for their specificity to MS and their correlation with disease progression including cognitive impairment.[9] PRLs, indicative of smouldering inflammation and specific to MS, may serve as predictors of long-term disability.

Additionally, CSF IgG oligoclonal bands have been included as a diagnostic criterium for dissemination in time in the 2017 McDonald criteria for the first time highlighting the importance of biofluid biomarkers in MS diagnostics. Kappa-free light chains (κ-FLC) have been demonstrated to show similar diagnostic value and have the advantage of better accessibility and quantification, rendering them ideal candidates to be added to upcoming revisions of the McDonald criteria.

As outlined in Di Filippo et al.[2] biofluid biomarkers for MS also hold the potential to serve as predictors for disease progression and for monitoring of treatment response. There is cumulating evidence that CSF IgM

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oligoclonal bands, GFAP and CHI3L1 are associated with a more progressive clinical phenotype. Additionally, the blood-based biomarker serum Neurofilament Light Chain (sNfL) can predict clinical relapses in RRMS patients. Combining the different available biomarkers and integrating additional scores as the "Glia-Score" could help to improve specificity and sensitivity in comparison to single biomarker assessments.

Despite these advancements, several challenges persist. There is a need for biomarkers that can reliably identify and distinguish between MS subtypes. In this regard, as nicely outlined by Di Filippo et al.,[2] biofluid biomarkers hold a huge potential because of their ability to directly reflect biological and pathophysiological mechanisms involved in the MS disease course. Specifically, aspects of neuroaxonal damage (sNfL, GFAP), astroglial pathology (CHI3L1, GFAP), microglial involvement (CHIT1, sTREM2) and B-Cell related pathology (CXCL13) have been evaluated in several studies and subtypes of MS disease activity could be classified accordingly. Additionally, protein biomarkers such as CNTN2 and APLP1 potentially reflect synaptic dysfunction during the disease.[10] Through advancements in neuroproteomics and the development of highly sensitive assays, these brain-derived proteins can also be detected in blood enabling easily accessible biomarkers for longitudinal sampling or screening approaches.

Advanced quantitative techniques like magnetization transfer imaging, diffusion tensor imaging, and myelin water imaging provide additional insights into microstructural changes, offering a more nuanced understanding of disease heterogeneity and evolution, regenerative mechanisms, as well as response to therapy. Enhancing the specificity and sensitivity of MRI biomarkers through multi-modal imaging approaches holds promise for overcoming these challenges and further refining diagnostic accuracy. Composite scores, integrating clinical and MRI metrics, represent a significant advancement in MS research (e.g. the MAGNIMS score, or no evidence of disease activity 3 (NEDA-3) and NEDA-4).

Multimodal biomarker profiles combining CSF and blood-based biomarkers with neuroimaging, including OCT, are needed for better MS management. Imaging modalities such as positron emission tomography or 7 T MRI hold promise but are currently not feasible for clinical routine. They may accurately identify patients at high risk of disability progression and guide personalized treatment strategies. Patient-reported outcomes should be included for a more holistic view and improved individual outcomes, together with more proactive and data-driven treatment approaches. Furthermore, artificial intelligence in MRI and biofluid biomarker research holds transformative potential by automating lesion detection, quantifying disease burden, improving the diagnostic accuracy and enhancing clinical decision-making. Additionally, data science-driven approaches can identify composite biomarker scores with predictive or diagnostic values. Rigorous validation and standardization of these emerging tools are needed before their incorporation into clinical practice, imperatively requiring large-scale, interdisciplinary cross-validation studies combining neuroimaging and biofluid biomarkers in MS.

Contributors

L. A. and F.W.: literature search, writing - original draft, review and editing, F.P.: writing - review and editing, supervision.

Declaration of interests

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