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Decoding Disability Worsening in MS: The Case for Combining CSF and Serum Biomarkers

Mr. Quigley:

You're listening to *NeuroFrontiers* on ReachMD, and this is an *AudioAbstract.* I'm Ryan Quigley, and today, we're exploring a new multicenter study in the *International Journal of Molecular Sciences* that sheds light on how combining cerebrospinal fluid and serum biomarkers can help sharpen prognostic accuracy in multiple sclerosis, or MS.

MS is characterized by variability, including multiple pathways to disease progression. While some patients worsen because of incomplete recovery after relapses, others experience progression that's independent of relapses, which may or may not appear as active lesions on MRI.

Two main processes—inflammation and neurodegeneration—contribute to worsening disability in patients. We currently don't have a reliable way to identify or stratify patients early, so it's difficult to predict which path their disease will take. That's why there's interest in the potential for biomarkers in serum and CSF to help fill this gap. If validated, biomarkers collected early in the diagnosis could help risk-stratify patients based on their disease progression pathway and, in turn, inform a tailored treatment strategy much sooner.

This study looked at three key biomarkers collected at disease onset in 535 patients with relapsing-remitting MS: serum neurofilament light chain, or sNfL; serum glial fibrillary acidic protein, or sGFAP; and lipid-specific IgM oligoclonal bands, or LS-OCMB.

Let's dive into the findings. First, high sNfL and LS-OCMB positivity were independent predictors of inflammatory-associated worsening, with the greatest risk in patients carrying both markers. In contrast, elevated sGFAP specifically predicted *non-inflammatory* progression, emphasizing its role in the chronic neurodegeneration seen in patients with non-active progression independent of relapses.

And finally, the immune signatures offered further understanding of the underlying mechanisms of disease. Regulatory T cell enrichment correlated with lower sNfL among LS-OCMB-positive patients, suggesting a protective effect. Meanwhile, in LS-OCMB–negative patients, sNfL levels instead tracked with CSF complement C3, pointing to innate immunity as a key driver of damage.

So, how might these findings translate into clinical practice? They suggest that patients negative for all three markers may do well on moderate disease-modifying therapies, while those positive for both sNfL and LS-OCMB may benefit from early escalation to high-efficacy options. Additionally, elevated sGFAP identifies patients at risk for progression unresponsive to relapse-suppressing therapies, underscoring the need for new treatments targeting chronic inflammation and neurodegeneration.

Now, there were some limitations of the study. Only a subset of participants underwent flow cytometry, which reduced statistical power and limits the strength of subgroup analyses. The reported association between regulatory T-cell frequencies and serum NfL levels therefore requires confirmation in larger cohorts. In addition, classification of disease activity relied solely on brain MRI, since spinal cord imaging near clinical events was rarely available. This dependence on brain imaging may have underestimated certain forms of disease progression, though the overall conclusions appear robust.

What emerges from these findings is a potential direction toward biologically-informed MS management where clinicians tailor therapies not just to disease activity but also to the mechanism of injury. The integration of serum and CSF biomarker profiles into early MS care may allow earlier, more personalized—and most importantly—more effective interventions.

This has been an *AudioAbstract* for *NeuroFrontiers,* and I'm Ryan Quigley. To access this and other episodes in our series, visit ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!

Reference:
Monreal E, Fernández-Velasco JI, Sainz de la Maza S, et al. Combining CSF and serum biomarkers to differentiate mechanisms of disability worsening in multiple sclerosis. *Int J Mol Sci.* 2025;26(14):6898. doi:10.3390/ijms26146898