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Combined Neurofilament Light and Optical Coherence Tomography Better Predicts Multiple Sclerosis Disease Activity Than Either Measure Alone

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Multiple sclerosis (MS) shows significant interindividual and intraindividual heterogeneity regarding radiologic and histopathologic features, clinical appearance, disease course, and therapy response.[1]

Reliable biomarkers that could (1) predict the individual disease course, (2) identify those patients with MS who would profit of initial high-efficacy disease-modifying therapies, and (3) predict individual treatment response are therefore urgently needed.[2] Besides several other candidates, serum neurofilament light chain (sNfL) protein and optical coherence tomography (OCT) measurements have been proposed as potential surrogate markers to aid in the assessment of disease activity, treatment response, or prognostication in MS.[3-9]

In this issue, Lin et al.[10] investigated the potentially additive value of a combination of sNfL protein together with OCT measurements as a "compound biomarker" for subsequent disease activity in patients with clinically isolated syndrome (CIS) and early relapsing-remitting MS (RRMS). Seventy-eight patients (16 with CIS and 62 with RRMS) were examined with OCT, and their sNfL protein values were determined early in the course of disease. Patients were clinically examined for up to 2 years and categorized into patients with abnormal or normal sNfL protein level (≥/< 80th age-specific percentile), thin or thick ganglion cell and inner plexiform (GCIP) layer thickness (median divider, ≤/> 70.4 μm), thin or thick peripapillary retinal nerve fiber layer (pRNFL) thickness (median divider, ≤/> 100 μm), and thick or thin inner nuclear layer (INL) thickness (median divider, ≥/< 36.4 μm) at baseline. No evidence of disease activity (NEDA-3) criteria violation and its components in the next 2 years was the primary outcomes. Five major observations were made as follows: (1) increased sNfL protein level at baseline was correlated with GCIP layer but not pRNFL or INL thickness; (2) increased sNfL protein level but not pRNFL, GCIP layer, or INL thickness was associated with future NEDA-3 violation and development of new lesions; (3) thinner GCIP layer was associated with future relapses but not new lesions; (4) neither abnormal sNfL protein level, abnormal OCT parameters nor their combination was correlated with future disability accrual; and (5) combinations of increased sNfL protein levels with thinner GCIP layer, thinner pRNFL, or thicker INL were associated with higher risk of NEDA-3 violation than each parameter alone.

Although patients with abnormal sNfL protein level and thin GCIP layer at baseline had approximately 40% and 30% higher risk of not meeting NEDA-3 after 1-year follow-up, respectively, the combination of abnormal sNfL protein level and thin GCIP layer was associated with an approximately 60% increased risk compared with normal sNfL protein level and thick GCIP layer.

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Previous studies demonstrated a correlation between thin pRNFL, GCIP layer, and low total macular volume with increased risk of future disability worsening[4,5,7] and thin pRNFL and GCIP layer with future NEDA-3 violation.[6]

The value of this study[10] is that it provides a "proof of concept" that the combination of biomarkers is more precise than each marker alone. Because OCT parameters are structural markers of previous neuroaxonal damage and sNfL protein is a body fluid biomarker reflecting ongoing, most likely acute or subacute, neuronal damage and thus disease activity, the combination of both measures provides complementary information. Although the authors used the median values of their cohort as dividers for each OCT parameter, it will be important to verify whether these cutoffs are also applicable to other cohorts. The sample size of 78 patients was small, the dropout rate of 50%–70% was high, and the follow-up with 720 days was rather short, warranting confirmation in independent studies. Baseline serum sampling and OCT examinations were performed between 12 and 24 months after disease onset. Shifting the time point to the time of diagnosis when patients are treatment naïve may further increase the predictive value.

It would be interesting to investigate how the predictive value of OCT and sNfL protein for NEDA-3 compares with other established biomarkers such as MRI measures (lesion load or global or regional brain volumes) and CSF markers such as oligoclonal bands and if future brain atrophy or cognitive decline can be predicted. Furthermore, it would be important to evaluate whether these measurements can be combined to an even more sophisticated composite multimodal biomarker and they can also be used in patients with progressive MS.

OCT measurements were analyzed using the Heidelberg Engineering device, and levels of sNfL protein were quantified using the single molecule array by QUANTERIX. Future research is required to validate these assessments across different platforms.

In summary, the combination of sNfL protein and OCT parameters seems to be a very promising composite biomarker that can easily be obtained to predict future disease activity. It is important to note that the findings have to be confirmed in larger prospective and multicenter studies involving earlier time points and longer follow-up and to evaluate whether the predictive potential of sNfL protein and OCT measurements demonstrated on a *group level* can be confirmed for the *individual patient level*. In case of a positive result, the combination of abnormal sNfL protein level and OCT parameters could already serve as the "tip on the scale" in uncertain treatment decisions.

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