Editorial Commentary

Serum neurofilament light chain rate of change in Alzheimer's disease: potentials applications and notes of caution

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Recent years have seen an increase of the use of imaging and fluid biomarkers as a key tool to help in the differential diagnosis of Alzheimer's disease (AD), especially in its pre-dementia stages (1).

In AD clinical practice, fluid biomarkers are currently focused on beta-amyloid and tau species assessment in the cerebrospinal fluid (CSF) and the development and standardization of this approach led over the years to an increased understanding of the AD neuropathological cascade, a paradigm shift in clinical trials recruitment strategies and improved diagnostic accuracy in daily clinical practice (2). CSF biomarkers, however, are ill-suited to be used as a screening tool in the general population or to monitor patients over time, leading to multiple approaches to develop blood-based markers for AD (3) albeit with limited success due to the lower concentration of the target proteins in blood compared to CSF, the interference of other plasma proteins and the presence of degrading proteases, which are all variables of difficult analytical management (4).

In such scenario, a promising serum-based biomarker of neural damage currently extensively evaluated in a number of neurological conditions, is represented by neurofilament light chain (NfL) level assessment (5). NfL is a cytoskeleton protein expressed in large caliber myelinated axons, and it is released in the extra-cellular fluid as consequence of axonal damage. Thus, while other fluid markers such as beta-amyloid and tau are aimed to help in the diagnosis of a specific clinical conditions (i.e., AD), NfL is instead a trans-diagnostic marker of neurodegeneration. The broad applicability of serum NfL assessment to a number of different neurological conditions as well as the commercial availability of sensitive assays for its assessment in serum and CSF (6) make NfL an attractive putative serum-based marker of neurodegeneration also in AD.

In an issue of *Nature Medicine*, Preische *et al.* (7) evaluated NfL level over time in pre-symptomatic AD mutation carriers, non-carriers (used as a control group) and symptomatic carriers and evaluated both cross sectional CSF and serum NfL levels as well as longitudinal changes in serum NfL levels over time. In line with previous reports (8,9), NfL levels in serum and CSF were strongly correlated in all patients, but the strength of the observed association increased the confidence in the interpretation of the longitudinal serum NfL data. Taking into account cross sectional serum NfL values, a significant difference between pre-symptomatic mutation carriers and controls was evident at 6.8 years before estimated onset in carriers, while using the yearly rate of change in serum NfL the difference between carriers and non-carriers was evident at least a decade earlier. Serum NfL rate of change, moreover, closely reflected progressive atrophy in a specific AD-associated area (i.e., the precuneus) and changes in cognition.

Interestingly from a pathophysiological perspective,

the rate of change of serum NfL peaked in carriers during the conversion phase to clinically evident cognitive impairment (i.e., those asymptomatic patients who became symptomatic at follow-up visits) and reached a plateau in symptomatic carriers, even if absolute values of NfL tended to slowly increase over time. A similar pattern of longitudinal concentration changes has been also reported for other CSF or blood proteins, such as those reflecting brain neuroinflammation (10,11) and proposed as possible evidence of microglia activation in the earliest phase of AD (12,13). These data suggest that longitudinal serum NfL assessment, associated with the evaluations of other serum and CSF components, could represent a useful tool to study *in vivo* the cascade leading to neurodegeneration.

Indeed, also taking into account that the elevation of serum NfL values in AD—either familiar or sporadic—has already been reported in the literature (2,14,15), the presence of robust longitudinal assessment of NfL levels and of their rate of change over time represents the most novel finding provided by the work of Preische *et al.* (7).

In an ideal and yet-to-come general population screening for neurodegenerative conditions, serum NfL could be the first test to perform given its high negative predictive value (3,16); and if elevated could be followed by other diagnostic biomarkers to confirm the presence of neurodegeneration and to define the underlying process and its prognosis. The data presented by Preische and colleagues, however, suggest that longitudinal rather than cross-sectional serum NfL values could be more informative given its increased sensibility, possibly due to inter-individual differences in baseline serum NfL levels and the possible—but transient-impact on serum NfL levels of non-neurodegenerative brain injuries such as trauma or stroke (5). The application of serum NfL as a tool to screen for neurodegeneration in the general population, however, is still to come, both given the lack of current disease modifying treatments for these conditions and the uncertainties regarding the timing of serum NfL changes in sporadic neurodegeneration.

If the application of serum NfL as a screening test is not yet ready for clinical use, the time is almost ripe to apply this tool in the diagnostic pathway of mild cognitive impairment (MCI) of unknown origin in association with other biomarkers (15), as well as an outcome marker in clinical trials to assess the response to a disease-modifying drug, in line with what is currently proposed in other neurological conditions such as multiple sclerosis (17).

To reach these aims, however, efforts are needed to reach a standardization of pre-analytic and analytical procedures, to longitudinally explore the dynamic changes in sporadic AD as well as in other neurodegenerative conditions and to evaluate the possible additional or alternative diagnostic role of other CNS-derived serum proteins. Despite these considerations, the work of Preische and colleagues represent a key step in the development and validation of a clinically-relevant approach to assess neurodegeneration using easy-to-collect serum samples.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:280-92.
2. Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol 2016;15:673-84.
3. O'Bryant SE, Edwards M, Johnson L, et al. A blood screening test for Alzheimer's disease. Alzheimers Dement (Amst) 2016;3:83-90.
4. Blennow K, Zetterberg H. The Past and the Future of Alzheimer's Disease Fluid Biomarkers. J Alzheimers Dis 2018;62:1125-40.
5. Khalil M, Teunissen CE, Otto M, et al. Neurofilaments as biomarkers in neurological disorders. Nat Rev Neurol 2018;14:577-89.
6. Rissin DM, Kan CW, Campbell TG, et al. Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations. Nat Biotechnol 2010;28:595-9.
7. Preische O, Schultz SA, Apel A, et al. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. Nat Med 2019;25:277-83.
8. Bacioglu M, Maia LF, Preische O, et al. Neurofilament

Light Chain in Blood and CSF as Marker of Disease Progression in Mouse Models and in Neurodegenerative Diseases. Neuron 2016;91:56-66.
9. Mattsson N, Andreasson U, Zetterberg H, et al. Association of Plasma Neurofilament Light With Neurodegeneration in Patients With Alzheimer Disease. JAMA Neurol 2017;74:557-66.
10. Brosseron F, Krauthausen M, Kummer M, et al. Body fluid cytokine levels in mild cognitive impairment and Alzheimer's disease: a comparative overview. Mol Neurobiol 2014;50:534-44.
11. Suárez-Calvet M, Kleinberger G, Araque Caballero MÁ, et al. sTREM2 cerebrospinal fluid levels are a potential biomarker for microglia activity in early-stage Alzheimer's disease and associate with neuronal injury markers. EMBO Mol Med 2016;8:466-76.
12. Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: Current evidence and future directions. Alzheimers Dement 2016;12:719-32.
13. Fan Z, Brooks DJ, Okello A, et al. An early and late peak in microglial activation in Alzheimer's disease trajectory. Brain 2017;140:792-803.
14. Weston PSJ, Poole T, Ryan NS, et al. Serum neurofilament light in familial Alzheimer disease: A marker of early neurodegeneration. Neurology 2017;89:2167-75.
15. Lewczuk P, Ermann N, Andreasson U, et al. Plasma neurofilament light as a potential biomarker of neurodegeneration in Alzheimer's disease. Alzheimers Res Ther 2018;10:71.
16. Henriksen K, O'Bryant SE, Hampel H, et al. The future of blood-based biomarkers for Alzheimer's disease. Alzheimers Dement 2014;10:115-31.
17. Kuhle J, Kropshofer H, Haering DA, et al. Blood neurofilament light chain as a biomarker of MS disease activity and treatment response. Neurology 2019;92:e1007-15.

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