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Serum neurofilament light chain uncovers neurodegeneration early in the course of Alzheimer's disease

This scientific commentary refers to 'Stage-specific links between plasma neurofilament light and imaging biomarkers of Alzheimer's disease', by Benedet *et al.* (doi:10.1093/brain/awaa342).

The symptomatic phase of Alzheimer's disease represents a relatively late stage of a disease process involving the silent accumulation of pathology over decades. Models of Alzheimer's disease progression facilitate academic study and staging of participants in clinical research and may inform enrolment in trials of putative disease-modifying therapies. Models such as the popular 'ATN' criteria (Jack *et al.*, 2018) assert that Alzheimer's disease neuropathological change progresses through measurable and sequential stages, beginning with the accumulation of amyloid-β (A) followed by aggregation and deposition of hyperphosphorylated tau within neurons (T) resulting in neuronal dysfunction and degeneration (N). The sequential nature of these models has motivated the use of anti-amyloid-β drugs with the goal of initiating therapy at the first sign of pathology: the A+T–N– stage (Sperling *et al.*, 2020). Support for this notion relies on the belief that either amyloid-β deposition starts a pathological cascade with great inertia or that neuronal damage and degeneration begin early in the disease process. Regardless of the exact mechanism, this logic has been extended to explain the successive failures of treatment trials targeting cerebral amyloid, and to argue that therapy must be initiated at ever earlier disease stages to slow or arrest disease (Aisen *et al.*, 2020). In this issue of *Brain*, Benedet and co-workers use neurofilament light chain (NfL)—a serum-based marker of neuroaxonal injury—to quantify neuroaxonal degeneration as early as the amyloid-β-only disease stage, well before neuroradiological evidence of neurodegeneration is typically apparent (Benedet *et al.*, 2020).

Biomarkers are objectively measurable surrogates that reflect pathology, predict outcomes or identify response to therapy (Blennow *et al.*, 2015). The Alzheimer's disease literature is awash with candidate biomarkers. The most studied include CSF or PET measures of amyloid-β or tau deposition, and structural neuroimaging markers of cerebral atrophy. These candidate biomarkers provide an unprecedented window into ante-mortem brain changes associated with Alzheimer's disease. This view informs models of Alzheimer's disease progression, improves diagnostic accuracy in clinical (Rabinovici *et al.*, 2019) and research settings (Jack *et al.*, 2018), and facilitates enrolment of presymptomatic patients in clinical trials (Sperling *et al.*, 2020). Despite the clinical and statistical validity of these measures, adoption into clinical practice has been limited by issues related to access, cost and patient/provider perceptions. PET imaging is expensive, resource intensive, and limited to large centres; CSF sampling is perceived to be invasive; and MRI-based neuroimaging requires specialized processing and may be contraindicated in patients with metallic implants or severe claustrophobia, for example. As a result, there is great interest in serum biomarkers that both provide information on Alzheimer's disease pathophysiology and permit the tracking of disease progression.

NfL is a cytoskeletal protein expressed predominantly in large myelinated axons that is released in response to injury (Trojanowski *et al.*, 1986) and that is measurable in CSF and serum. NfL is thus a general marker of neurological injury and not a specific marker of Alzheimer's disease. However, NfL is elevated in Alzheimer's disease, and the fact that it can be reliably assayed in serum makes it an attractive biomarker of neurodegeneration (Forgrave *et al.*, 2019). With this in mind, Benedet and colleagues evaluated the longitudinal relationship between NfL and established imaging biomarkers, including PET-based measures of amyloid-β (florbetapir) and tau (flortaucipir or MK6240) as well as volumetric measures. The comparisons were performed in two independent cohorts, from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Translational Biomarkers in Aging and Dementia (TRIAD) studies. In cognitively unimpaired individuals, there was a strong relationship between NfL levels and amyloid-β deposition in areas typically affected by Alzheimer's disease. Conversely, in

cognitively impaired individuals, NfL was most strongly associated with measures of tau deposition, also in a typical Alzheimer's disease topography. Notably, the association between NfL and amyloid-β in the cognitively unimpaired group was stronger than the association between NfL and measures of cerebral tau deposition in the cognitively impaired group. This implies that neurodegeneration is present early in the course of Alzheimer's disease. Moreover, the observed relationship between NfL and amyloid-β predates the occurrence of neurodegeneration as revealed by radiological biomarkers (e.g. atrophy). If this is true, then treatments will need to be initiated early to arrest or prevent neurodegeneration.

This study has several technical strengths, including the use of multimodal imaging. The most compelling feature of the analysis, however, is the fact that the reported effects were demonstrated in two independent cohorts. This methodological sophistication decreases the likelihood of a false positive result and increases generalizability. In a similar way, the study's use of longitudinal sampling improves model estimation and strengthens the conclusions regarding predictive power. There are also a few limitations to consider. Given that NfL is a non-specific marker of neurodegeneration, it is possible (and even likely) that non-Alzheimer's disease processes, such as cerebrovascular disease, influence serum concentrations of NfL. Moreover, the interpretation that NfL is more closely associated with amyloid-β than with tau in cognitively unimpaired individuals is contingent upon imaging markers of cerebral amyloid-β and tau deposition having equal variance and sensitivity to their respective pathologies—an assumption that has yet to be validated (Clark *et al.*, 2012; Fleisher *et al.*, 2020).

This study lends support to NfL as a practical measure of neuronal injury in Alzheimer's disease. The relationship between amyloid-β and NfL raises an important question about the time course of neuronal injury and suggests significant early damage, indicating that even earlier enrolment into clinical trials may be required. In the future, we expect to see NfL included as a biomarker of functional Alzheimer's disease pathological severity and as a biomarker outcome for therapeutic trials.

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Competing interests

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