Neurodegenerative dementias: screening for major threats to healthy longevity with blood biomarkers

Clinical screening tests are readily available for most major age-associated diseases, including cardiovascular disease, type 2 diabetes, and common cancers. However, one of the most common causes of death in older adults—dementia—lacks a readily available early screening test that can be used in primary care. According to WHO, approximately 50 million people currently have dementia, and it is a leading cause of disability, dependency, and death among older people worldwide, making it a major threat to healthy human longevity. Reducing dementia prevalence and ensuring appropriate care will require access to readily implemented tools for detecting the disease processes underlying dementia in older adults. In *The Lancet Healthy Longevity*, Inge M W Verberk and colleagues provide evidence that such tools might be available in the form of blood biomarkers that can predict future dementia and disease progression among individuals who were free of dementia at the time of blood sampling.[1]

A major challenge to dementia screening has been the lack of easily deployed tests that are capable of early disease detection. Accordingly, biomarker development efforts have focused on developing assays for specific disease pathologies that can be detected before cognitive decline. Alzheimer's disease—by far the most common cause of dementia—has been a major focus of biomarker development. In Alzheimer's disease, the first detectable pathology occurs two to three decades before clinical symptom onset[2] and involves accumulation of extracellular amyloid plaques, which have a 42 amino acid-long amyloid β protein ($A\beta_{42}$) as their core. This pathology can be detected in living humans by use of amyloid PET imaging and by measuring aggregation-prone $A\beta_{42}$ (alone or as a ratio with water-soluble 40 amino acid-long Aβ) in cerebrospinal fluid (CSF) and blood.[3] Phosphorylation and secretion of tau, a microtubule-associated axonal protein that is highly expressed in cortical neurons, follows amyloid pathology in Alzheimer's disease, and this process is reflected in CSF and blood concentrations of phosphorylated tau and by the eventual development of neurofibrillary tangles, which can be assessed by use of tau PET.[3] Although these tools represent major advances in the field, they

only reflect one cause of dementia; biomarkers for neurodegenerative dementias other than Alzheimer's disease, characterised by proteins such as TAR DNA-binding protein 43 and misfolded α-synuclein,[4] are still in development. Likewise, cerebrovascular disease, which is a common primary cause of dementia, does not have a biomarker that could be easily implemented in primary care.

Therefore, although disease-specific features have often been the primary targets for biomarker development, these might not be the clinical tools of choice when an individual first presents to primary care with a memory complaint. In their study, Verberk and colleagues[1] tested the utility of blood biomarkers that reflect processes common to most causes of dementia. Per definition, neurodegenerative diseases show progressive neuroaxonal loss, a process captured by the blood biomarker for neurofilament light (NfL),[3] which was assessed by Verberk and colleagues. Additionally, given that a broad range of neurodegenerative diseases are also characterised by the activation of astrocytes—abundant support cells that ensure homeostasis of the CNS[5]—Verberk and colleagues examined blood levels of glial fibrillary acidic protein (GFAP) that is expressed and released by activated astrocytes.[3] While these biomarkers are not indicators of any specific neurodegenerative disease, both NfL and GFAP are specific to the nervous system and represent minimally invasive tools for assessing brain health that might further inform risk of progression to dementia. In Verberk and colleagues' study, NfL and GFAP were measured in 300 individuals without cognitive impairment who were controls in a memory clinic-based study of neurodegenerative dementias.[1] These individuals received extensive screening for dementia at first visit and annual follow-up visits, and serum GFAP and NfL levels were measured at baseline for all participants and at follow-up for a subset of participants. Mean baseline age was 61 years (SD 9), 125 (42%) of participants were women, and mini-mental state examination was 29 (IQR 27–29). Median follow-up time was 3·0 years (IQR 1·9–4·2), and and 27 (9%) of the 300 participants developed dementia.

Already at baseline, GFAP levels were approximately 1·7-times higher and NfL levels approximately 1·4-times higher in individuals who developed dementia during follow-up than in those who did not (age and sex adjusted p<0·0001 GFAP, p=0·0031 NfL). After testing for independent associations, only GFAP remained associated with an increased risk of dementia (hazard ratio 3·3, 95% CI 1·9–5·5; p<0·0001). Additionally, GFAP performed well in predicting dementia prognosis when used simultaneously with $A\beta_{42/40}$, suggesting that it might be useful in combination with disease-specific biomarkers. Both neurodegeneration and astrocytic activation appear to differentiate patients who are more or less susceptible to Aβ and tau pathology regarding clinical expression of Alzheimer's disease.[6] NfL was not as sensitive as GFAP, but in a subgroup of individuals with repeated sampling, the slope of NfL increase was higher in participants with cognitive deterioration than in those with preserved cognition. This finding resembles the pattern observed in familial Alzheimer's disease and Huntington's disease, where NfL change appears to be a more sensitive marker of eventual disease progression than baseline NfL alone.[7,8]

Neurodegenerative dementias are common, and disease-modifying treatments and other effective interventions are urgently needed to ensure healthy ageing. With access to such treatments, careful history-taking and clinical examination need to be enhanced by tests that alert a clinician to the potential presence of neurodegenerative processes. The results presented by Verberk and colleagues suggest that such generic blood-based biomarkers with potential for use in clinical practice might be close at hand.

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