



Plasma sTREM2: a potential marker of cerebrovascular injury in neurodegenerative disorders

This scientific commentary refers to ‘Plasma soluble TREM2 is associated with white matter lesions independent of amyloid and tau’ by Tsai et al. (doi:10.1093/brain/awab332).

A common pathological finding across neurodegenerative disorders is protein aggregation in the brain. In particular, amyloid- β plaques and tau neurofibrillary tangles are the hallmarks of Alzheimer’s disease, the most common cause of dementia. However, there is growing consensus that the innate immune system and neurovascular mechanisms play key roles in triggering and/or exacerbating neurodegeneration.¹ Accumulating evidence linking immune-related genes to increased risk of neurodegenerative disorders has stimulated research on neuroinflammation as a therapeutic target. As a prominent example, mutations in the ‘triggering receptor expressed on myeloid cells 2’ (TREM2) gene, which encodes a receptor specific to microglia in the brain and myeloid cells in the periphery, are strongly associated with increased risk of Alzheimer’s disease.² Moreover, studies in animal models have shown that impaired TREM2 function in myeloid cells results in less efficient phagocytosis of amyloid- β and cell debris, suggesting a role for TREM2 in Alzheimer’s disease pathogenesis.²

Recent advances in ultra-sensitive biochemical techniques have translated the established CSF measurements of amyloid- β and phosphorylated tau to blood.³ Now, building on this success, there is a quickly evolving field of research to measure other molecules circulating in blood that can better characterize the complex pathology of Alzheimer’s disease, including inflammation, axonal injury, astroglial activation and synaptic dysfunction.

In particular, soluble fragments from TREM2 receptors that are shed by proteases into the brain parenchyma can be detected in the CSF.² For the most part, soluble TREM2 (sTREM2) is elevated in the CSF of patients with Alzheimer’s disease; however, levels change throughout the development of Alzheimer’s pathology, peaking in the early symptomatic phases of the disease.^{2,4} Notably, CSF sTREM2 is positively correlated with plasma sTREM2 in neurodegenerative disorders,⁵ and this has motivated research into blood assays for sTREM2 that could be used to track innate immune system changes in Alzheimer’s disease.

However, there is a paucity of studies comparing sTREM2 levels in the blood between control subjects and patients with neurodegenerative disorders, and the available results are mixed. Some of the initial studies found no difference between plasma sTREM2 levels in healthy controls versus patients with Alzheimer’s disease⁵ or TREM2 mutation carriers.⁶ More recently, significant

increases in serum sTREM2 have been reported in Alzheimer’s disease and other neurodegenerative disorders compared with healthy controls,⁷ but many of these results suggest that blood sTREM2 is unlikely to have value as a diagnostic biomarker in the traditional sense.

Nonetheless, the association between plasma sTREM2 and *in vivo* neuroimaging markers of amyloid- β , tau or cerebrovascular injury, as well as the relationship between plasma sTREM2 and cognition, remain poorly understood. In particular, no studies on plasma sTREM2 have included patients with small vessel disease (SVD), a common cause of cognitive impairment and dementia in older adults, and a frequent co-pathology in Alzheimer’s disease.⁸ In this issue of *Brain*, Tsai and co-workers⁹ address these issues, and identify cerebrovascular injury as quantified by white matter lesions on MRI as an *in vivo* neuropathological correlate of plasma sTREM2 independent of amyloid- β and tau.

Plasma sTREM2 is associated with white matter lesions in SVD

In this cross-sectional study, Tsai et al.⁹ included 66 patients with SVD pathology who were survivors of spontaneous intracerebral haemorrhage, and 10 patients with Alzheimer’s disease dementia. Based on the type of cerebrovascular pathology, SVD patients were further categorized as SVD with cerebral amyloid angiopathy (SVD-CAA, $n = 20$) or hypertensive SVD (SVD-HTN, $n = 46$). All patients underwent multimodal neuroimaging including MRI and ¹¹C-Pittsburgh compound-B PET scans, plasma sTREM2 quantified using the Meso Scale Discovery platform, cognitive evaluation and APOE genotyping.

No difference was found between the plasma sTREM2 levels in patients with SVD versus Alzheimer’s disease dementia. Within the SVD group, plasma sTREM2 levels were not associated with global amyloid- β burden as measured by ¹¹C-Pittsburgh compound-B PET, but were positively correlated with white matter hyperintensities, a well-validated MRI marker of cerebrovascular injury (Fig. 1A), even after correcting for demographics and global amyloid- β burden. Given the paucity of studies on plasma sTREM2, the new data from Tsai et al.⁹ provide a first indication that plasma sTREM2 may be a marker of cerebrovascular injury in SVD. The absence of a control group, however, limits the possibility of assessing whether plasma sTREM2 has diagnostic value for differentiating patients with SVD or Alzheimer’s disease dementia from healthy control subjects.

Received October 16, 2021. Accepted October 16, 2021

© The Author(s) (2021). Published by Oxford University Press on behalf of the Guarantors of Brain.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

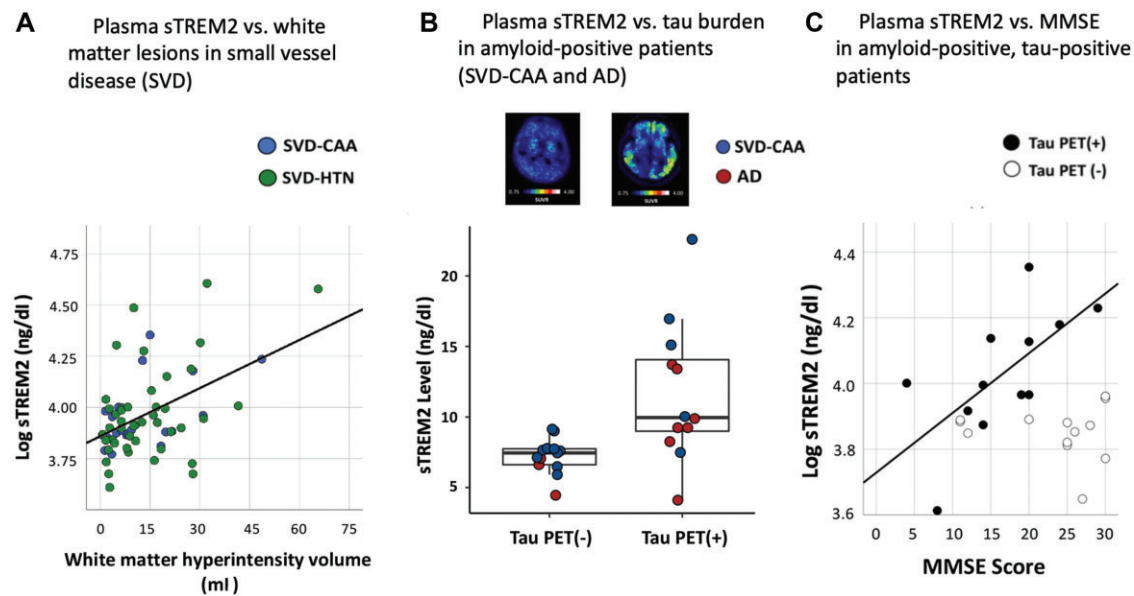


Figure 1 Associations of plasma sTREM2 with white matter lesions, tau burden and cognition. AD = Alzheimer's disease; MMSE = Mini-Mental State Examination; sTREM2 = soluble TREM2; SVD = small vessel disease; SVD-CAA = small vessel disease with cerebral amyloid angiopathy; SVD-HTN = hypertensive small vessel disease. Adapted from Tsai et al.⁹

Plasma sTREM2 is associated with white matter lesions and tau positivity in amyloid-positive patients

To investigate the association of plasma sTREM2 with neuroimaging in the context of amyloid- β disorders, Tsai and co-workers⁹ then performed secondary analyses in a smaller subset of 25 amyloid-PET positive patients comprising 15 patients with SVD-CAA and 10 patients with Alzheimer's disease dementia, who also had accompanying tau PET imaging with ¹⁸F-flortaucipir. Visual evaluation of the ¹⁸F-flortaucipir PET scans revealed that approximately half of the patients were tau-positive and the other half were tau-negative. Across these 25 patients, plasma sTREM2 was associated with both higher volume of white matter hyperintensities and tau-PET positivity (Fig. 1B), but not with global amyloid- β burden, corrected for demographic variables.

This association between plasma sTREM2 and *in vivo* tau positivity in the brain is consistent with previous findings that CSF sTREM2 is positively associated with CSF total and phosphorylated tau.⁴ Another study found that, in plasma from patients with Alzheimer's disease, sTREM2 is positively associated with neurofilament light (NFL),⁶ a non-specific marker of neurodegeneration and white matter pathology. Together with these previous reports, the new data from Tsai et al.⁹ in patients with amyloid- β disorders reinforce the idea that sTREM2 may be coupled with tau aggregation and neurodegeneration, while adding a novel association with cerebrovascular injury.

Plasma sTREM2 and cognition

No correlation was observed between plasma sTREM2 and Mini-Mental State Examination (MMSE) in SVD patients, irrespective of their disease severity, as measured by high or low-grade white matter hyperintensity. Interestingly, however, among the group of 25 patients with elevated brain amyloid- β pathology, plasma sTREM2 levels were correlated with higher MMSE only within the tau-positive subgroup (Fig. 1C).

This suggests that plasma sTREM2 may have a protective effect on cognition in patients with advanced Alzheimer's disease pathology as defined by both positive amyloid- β and tau burden in the brain. This potentially protective effect of plasma sTREM2 is in line

with previous findings in Alzheimer's disease patients where, for a given age and neuropathological burden, higher CSF sTREM2 at baseline is associated with slower subsequent cognitive decline and clinical progression.¹⁰ Given the cross-sectional design and limited sample size in the study by Tsai et al.,⁹ their results should be considered with caution, but should motivate further replication in larger cohorts with longitudinal data.

Future perspectives

This study by Tsai et al.⁹ thus provides both confirmatory and novel multimodal neuroimaging, plasma and cognition data that shed light on the neuroimaging and neuropsychological correlates of plasma sTREM2. Given the growing recognition that vascular and inflammatory mechanisms are key players in neurodegenerative diseases, this study has strong clinical relevance.


It also raises many unanswered questions. Perhaps the most difficult concerns the interpretation of biomarkers in plasma versus CSF. For example, while CSF sTREM2 is considered highly specific for brain microgliosis, sTREM2 in blood is likely a marker of a great variety of myeloid cells including circulating monocytes and macrophages,² and therefore a marker of peripheral inflammation. Supporting this interpretation, plasma sTREM2 was previously found to be correlated with C-reactive protein.^{5,6} While both CNS and peripheral inflammatory mechanisms may be highly relevant in neurodegenerative disorders, it is important to keep in mind that CSF and blood measures of sTREM2 likely carry different information.

Lastly, the immunoassays that determine sTREM2 concentration cannot distinguish the source (CNS or peripheral), thus sTREM2 leaking into the blood from the CNS in response to cerebrovascular or tau pathology, will have to be sufficiently abundant to avoid being diluted by peripheral sTREM2 with a different biological meaning.

This research adds to efforts to derive biological definitions of neurodegenerative disorders that will lead to more personalized treatments.³ In this context, there is increasing interest in markers beyond amyloid- β and tau, in particular reflecting inflammation and vascular components—towards a more comprehensive ATX(N) biomarker system.⁸ Could plasma markers such as sTREM2 be useful

in the future as biomarkers of vascular and/or inflammatory mechanisms? Future longitudinal studies in larger cohorts will be required to answer this question. Such studies should also test sTREM2 against NfL or other putative blood biomarkers that could demonstrate a similar response with a potentially greater magnitude.

Plasma biomarkers that carry information on inflammation or vascular pathology have promising implications for future clinical trials targeting the innate immune response in Alzheimer's disease, but further validation studies are urgently needed.

 Elena Rodriguez-Vieitez¹ and Nicholas J. Ashton^{2,3,4,5}

¹ Division of Clinical Geriatrics, Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden

² Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden

³ Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Gothenburg, Sweden

⁴ King's College London, Institute of Psychiatry, Psychology and Neuroscience, Maurice Wohl Clinical Neuroscience Institute, London, UK

⁵ NIHR Biomedical Research Centre for Mental Health and Biomedical Research Unit for Dementia at South London and Maudsley NHS Foundation, London, UK

Correspondence to: Elena Rodriguez-Vieitez

E-mail: elena.rodriguez-vieitez@ki.se

doi:10.1093/brain/awab399

Advance access publication October 21, 2021

Funding

E.R.-V. and N.J.A. receive funding from the Swedish Alzheimer Foundation (Alzheimerfonden), the Swedish Dementia Association (Demensfonden), the Gun & Bertil Stohne's Foundation, and the Gamla Tjänarinnor Foundation.

Competing interests

The authors report no competing interests.

References

1. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: Where do we go from here? *Nat Rev Neurol.* 2021;17(3):157–172.
2. Jay TR, von Saucken VE, Landreth GE. TREM2 in neurodegenerative diseases. *Mol Neurodegener.* 2017;12(1):56.
3. Hansson O. Biomarkers for neurodegenerative diseases. *Nat Med.* 2021;27(6):954–963.
4. Suárez-Calvet M, Morenas-Rodríguez E, Kleinberger G, et al.; Alzheimer's Disease Neuroimaging Initiative. Early increase of CSF sTREM2 in Alzheimer's disease is associated with tau related-neurodegeneration but not with amyloid- β pathology. *Mol Neurodegener.* 2019;14(1):1.
5. Bekris LM, Khrestian M, Dyne E, et al. Soluble TREM2 and biomarkers of central and peripheral inflammation in neurodegenerative disease. *J Neuroimmunol.* 2018;319:19–27.
6. Ashton NJ, Suárez-Calvet M, Heslegrave A, et al. Plasma levels of soluble TREM2 and neurofilament light chain in TREM2 rare variant carriers. *Alzheimers Res Ther.* 2019;11(1):94.
7. Schulz I, Kruse N, Gera RG, et al. Systematic assessment of 10 biomarker candidates focusing on α -synuclein-related disorders. *Mov Disord.* Published online 7 August 2021. <https://doi.org/10.1002/mds.28738>
8. Hampel H, Cummings J, Blennow K, Gao P, Jack CR, Vergallo A. Developing the ATX(N) classification for use across the Alzheimer disease continuum. *Nat Rev Neurol.* 2021;17(9):580–589.
9. Tsai H, Chen Y, Yen R, et al. Plasma soluble TREM2 is associated with white matter lesions independent of amyloid and tau. *Brain.* 2021;144(11):3371–3380.
10. Ewers M, Franzmeier N, Suárez-Calvet M, et al.; Alzheimer's Disease Neuroimaging Initiative. Increased soluble TREM2 in cerebrospinal fluid is associated with reduced cognitive and clinical decline in Alzheimer's disease. *Sci Transl Med.* 2019; 11(507):eaav6221.