doi:10.1093/brain/awab332 BRAIN 2021: 144; 3371–3380 | 3371

BRAIN
ORIGINAL ARTICLE

Plasma soluble TREM2 is associated with white matter lesions independent of amyloid and tau

Hsin-Hsi Tsai,[1,2] Ya-Fang Chen,[3] Ruoh-Fang Yen,[4] Yen-Ling Lo,[1] Kai-Chien Yang,[5] Jiann-Shing Jeng,[2] Li-Kai Tsai[2] and Che-Feng Chang[6]

See Rodriguez-Vieitez and Ashton (doi:10.1093/brain/awab399) for a scientific commentary on this article.

Cerebral small vessel disease is one of the most common causes of cognitive decline and stroke. While several lines of evidence have established a relationship between inflammation and cerebrovascular pathology, the mechanistic link has not yet been elucidated. Recent studies suggest activation of immune mediators, including the soluble form of triggering receptor expressed on myeloid cells 2 (TREM2), may be critical regulators.

In this study, we compared the plasma levels of soluble TREM2 and its correlations with neuroimaging markers and cerebral amyloid load in 10 patients with Alzheimer's disease and 66 survivors of spontaneous intracerebral haemorrhage with cerebral amyloid angiopathy or hypertensive small vessel disease, two of the most common types of sporadic small vessel disease. We performed brain MRI and ^{11}C-Pittsburgh compound B PET for all participants to evaluate radiological small vessel disease markers and cerebral amyloid burden, and ^{18}F-T807 PET in a subgroup of patients to evaluate cortical tau pathology.

Plasma soluble TREM2 levels were comparable between patients with Alzheimer's disease and small vessel disease ($P = 0.690$). In patients with small vessel disease, plasma soluble TREM2 was significantly associated with white matter hyperintensity volume ($P < 0.001$), but not with cerebral amyloid load. Among patients with Alzheimer's disease and cerebral amyloid angiopathy, plasma soluble TREM2 was independently associated with a tau-positive scan ($P = 0.001$) and white matter hyperintensity volume ($P = 0.013$), but not amyloid load ($P = 0.221$).

Our results indicate plasma soluble TREM2 is associated with white matter hyperintensity independent of amyloid and tau pathology. These findings highlight the potential utility of plasma soluble TREM2 as a strong predictive marker for small vessel disease-related white matter injury and hold clinical implications for targeting the innate immune response when treating this disease.

1 Department of Neurology, National Taiwan University Hospital Bei-Hu Branch, Taipei, Taiwan
2 Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan
3 Department of Medical Imaging, National Taiwan University Hospital, Taipei, Taiwan
4 Department of Nuclear Medicine, National Taiwan University Hospital, Taipei, Taiwan
5 Department and Graduate Institute of Pharmacology, National Taiwan University College of Medicine, Taipei, Taiwan
6 Department and Graduate Institute of Physiology, National Taiwan University College of Medicine, Taipei, Taiwan

Correspondence to: Che-Feng Chang
Department and Graduate Institute of Physiology, National Taiwan University College of Medicine
No. 1, Sec. 1, Jen-Ai Rd., Room 1038, Taipei 100, Taiwan
E-mail: chefengchang@ntu.edu.tw

Received May 22, 2021. Revised July 21, 2021. Accepted August 08, 2021. Advance access publication September 13, 2021

Keywords: cerebral amyloid angiopathy; cerebral small vessel disease; TREM2; white matter hyperintensity; neuroinflammation

Abbreviations: CAA = cerebral amyloid angiopathy; HTN = hypertension; ICH = intracerebral haemorrhage; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B; sTREM2 = soluble triggering receptor expressed on myeloid cells 2; SUVR = standardized uptake value ratio; SVD = cerebral small vessel disease; WMH = white matter hyperintensity

Introduction

Cerebral small vessel disease (SVD), the major cause of stroke and vascular cognitive impairment, is a disorder characterized by pathologies in the superficial and deep perforating arteries and arterioles in the brain.[1] Cerebral amyloid angiopathy (CAA) and hypertensive SVD (SVD-HTN) are the most common sporadic types of SVD. Typical radiological presentations that reflect parenchymal injury in SVD on conventional MRI include cerebral microbleeds, white matter hyperintensities (WMH), lacunes and dilated perivascular spaces.[2] The severity of CAA can also be evaluated *in vivo* by measuring the amount of cerebrovascular amyloid using amyloid PET.[3,4]

Inflammation associated with cerebrovascular pathology has been increasingly recognized in studies exploring the associations between inflammatory biomarkers and neuroimaging markers of SVD.[5,6] However, the differential contributions of CAA and hypertensive SVD to inflammatory responses are mostly unknown, as these pathologies frequently overlap. Additional evidence from preclinical studies also highlights the important contribution of neuroinflammation to the progression of CAA, and activated microglia specifically cluster around CAA vessels with gross amyloid deposits.[7,8] Targeting inflammation has been adopted as a novel therapeutic approach in SVD, and preclinical findings suggest that inhibition of cerebral vascular amyloid-induced microglial activation using pharmacological interventions alleviates the progression of CAA.[9,10] However, the mechanistic link between inflammation and SVD-mediated brain alterations is still largely unexplored.

Recent studies suggest that triggering receptor expressed on myeloid cells 2 (TREM2), an innate immune receptor of the immunoglobulin superfamily that is mainly expressed on the cell surface of myeloid cells, impacts a multitude of their functions including activation, inflammation, phagocytosis, proliferation and survival.[11,12] In the brain, TREM2 is mostly expressed on microglia and has been proposed to regulate both pro- and anti-inflammatory microglial activation in Alzheimer's disease-related conditions.[13,14] TREM2 contains an ectodomain that can be cleaved by sheddases, which results in release of the soluble form of TREM2 (sTREM2) into the extracellular space.[15] The presence of sTREM2 in CSF has been suggested as an alternative biomarker of microglial activation in many neurodegenerative diseases.[16,17] Soluble TREM2 can also be detected in the blood, and the levels of sTREM2 in peripheral blood correlate strongly with the levels of sTREM2 in CSF,[18,19] suggesting a potential role for peripheral sTREM2 in CNS pathologies. However, it remains unknown whether the peripheral levels of sTREM2 reflect the extent of parenchymal injury in SVD or correlate with brain pathology.

In this cross-sectional study, we aimed to elucidate the relationship between elevated plasma sTREM2 and the pathology of SVD. We first compared the plasma sTREM2 levels between patients with symptomatic SVD and patients with clinical Alzheimer's disease. We then explored the associations between plasma sTREM2 and changes in radiological SVD markers and vascular amyloid load using MRI and PET imaging of patients with cerebral amyloid angiopathy and hypertensive SVD. Finally, we investigated the association between the peripheral sTREM2 levels and the severity of SVD in subjects with amyloid-β disorders, while accounting for cerebral and cerebrovascular amyloid and tau pathology.

Materials and methods

Patient selection

For this cross-sectional analysis, we prospectively recruited patients from the stroke clinic and memory clinic of National Taiwan University Hospital (NTUH) and NTUH Bei-Hu Branch between June 2015 and July 2020. We included patients who were (i) clinically diagnosed with probable Alzheimer's disease dementia based on the diagnostic criteria of the National Institute on Aging-Alzheimer's Association[20]; and (ii) survivors of spontaneous ICH in which the underlying aetiology was attributed to SVD. Patients with SVD were further categorized as CAA (SVD-CAA) if the ICH and cerebral microbleeds were exclusively located in the lobar, cortical and/or cortical-subcortical areas according to the modified Boston criteria.[21] Patients with haemorrhage/cerebral microbleeds exclusively located in deep brain regions (basal ganglia, thalamus, pons) or patients with a combination of mixed lobar and deep bleeds were categorized as hypertensive SVD (SVD-HTN), as convincing data suggest these haemorrhages are caused by hypertensive microangiopathy.[22,23] We excluded patients with a history of neuroimmunological disorders. All survivors of ICH were recruited in the chronic phase (defined as at least 6 months after the index ICH event) to avoid the effect of potential inflammation associated with acute intracerebral haematoma, and patients who could not cooperate with the cognitive evaluation were also excluded. A total of 76 patients fulfilling the enrolment criteria agreed to participate in this study and underwent plasma sample collection and brain MRI and ^{11}C-Pittsburgh compound B (PiB)-PET scans. Patients with amyloid-β disorders, including Alzheimer's disease and SVD-CAA, also additionally received ^{18}F-T807-PET to evaluate cortical tau pathology (Fig. 1). Baseline clinical data and Mini-Mental State Examination (MMSE) scores were acquired through a standardized review of medical records and interviews with each participant. This study was performed with the approval of and in accordance with the guidelines of the institutional review board (201912003MINC) of NTUH; written informed consent was obtained from all participants or their family members according to the Declaration of Helsinki.

Plasma sample collection and sTREM2 measurement

Venous blood (10 ml) was drawn from each study participant at enrolment. Blood samples were centrifuged (2500*g* for 15 min) within

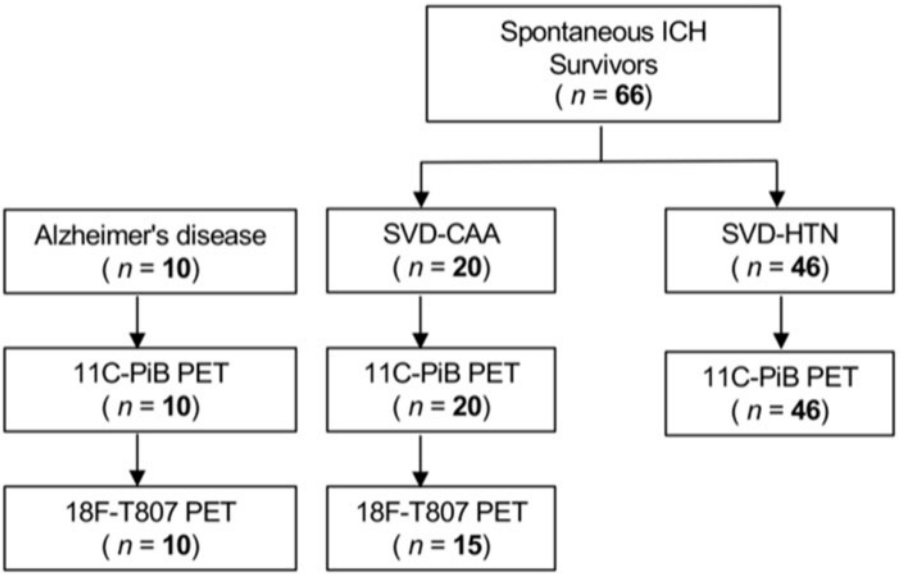

Figure 1 Flow chart of patient enrolment and imaging. We recruited 10 patients with Alzheimer's disease, 20 patients with SVD-CAA, and 46 patients with SVD-HTN in this study. All patients underwent ^{11}C-PiB PET scans to measure cerebral amyloid burden. Additionally, all patients with Alzheimer's disease and 15 patients with SVD-CAA underwent ^{18}F-T807 PET to evaluate cortical tau deposition.

3 h of collection. DNA was isolated from the buffy coat layer and genotyping of the *APOE* epsilon alleles (ε2, ε3 and ε4) was performed by PCR. The plasma was aliquoted and stored at –80°C before testing. Plasma levels of sTREM2 were analysed using the Meso Scale Discovery platform, as previously described.[17,24] In addition, plasma levels of total tau, amyloid-β_{1-42} and amyloid-β_{1-40} were measured using the Simoa immunoassay platform (Quanterix), as described previously.[25] Measurements were performed by board-certified laboratory technicians who were blinded to the clinical groups. All samples were run in duplicate, and the average concentrations were calculated.

MRI acquisition and analyses

Images were obtained using 3 T MRI scanners (Siemens Verio). The imaging protocol included T_1-weighted magnetization-prepared rapid gradient-echo imaging (MPRAGE, flip angle 9°, repetition time/echo time = 1460/2.39 ms, field of view = 25.6 cm, slice thickness = 1 mm), T_2-weighted imaging (repetition time/echo time = 3530/83 ms, field of view = 23 cm, slice thickness = 5 mm), FLAIR (repetition time/echo time = 10 000/89 ms, field of view = 23 cm, slice thickness = 5 mm), susceptibility-weighted imaging (flip angle 15°, repetition time/echo time = 28/20 ms, matrix number = 221 × 320, field of view = 23 cm, slice thickness = 2 mm), diffusion-weighted imaging, and apparent diffusion coefficient maps. Based on the Standards for Reporting Vascular Changes on Neuroimaging criteria,[2,26] we systemically evaluated relevant SVD markers on MRI, including the presence and location of cerebral microbleeds, cortical superficial siderosis, severity of WMH, and presence/absence of lacune. WMH volume was calculated as previously described.[23] The volume estimates were performed in the left hemisphere in patients with Alzheimer's disease and the ICH-free hemisphere in survivors of ICH, and multiplied by 2. All MRI scans were also processed using FreeSurfer software v6.0.0 (http://surfer.nmr.mgh.harvard.edu/ accessed 8 October 2021) to determine the mean cerebral cortex thickness and hippocampal volume using a T_1-weighted MPRAGE sequence.

PET acquisition and analyses

^{11}C-PiB and ^{18}F-T807 were prepared at the Cyclotron and Radiopharmaceutical Laboratory of NTUH. PET images (Discovery ST, GE Healthcare) were acquired over 30 min approximately 40 min after injection of 10 mCi ^{11}C-PiB or ^{18}F-T807. PET data were reconstructed via ordered set expectation maximization and corrected for attenuation. The PiB-PET data were semi-quantitatively analysed and expressed as standardized uptake value ratios (SUVRs) of the whole cerebral cortex using the cerebellar cortex as the reference region, as we previously described.[27,28] ^{18}F-T807 was visually rated as positive or negative by two investigators (R.-F.Y. and H.-H.T.) who were blinded to the clinical diagnosis. The image intensity was manually adjusted by each reader, so the mid range of the colour scale was defined as the value of the inferior cerebellar cortex. T807 retention was assessed at seven predefined regions (medial temporal, inferior temporal, medial parietal, lateral parietal, frontal, occipital, lateral temporal/cingulate) as previously proposed (0 = no binding; 1 = mild binding; 2 = intense binding).[29] In cases with asymmetrical uptake within the regions of interest between bilateral hemispheres, the higher signal intensity was chosen as the regional binding score. A global score (sum of the binding scores in the seven predefined regions) was calculated in each patient. We operationally defined the tau scan as positive if the global visual score was ⩾2. A consensus rating was achieved after discussion if there was disagreement in regards to the tau scan positivity. In addition to visual ratings, we also calculated the SUVR for the whole cerebral cortex and Braak stage V regions of interest using the cerebellar cortex as the reference region with PMOD software. The cerebral regions affected by the haematoma were excluded from the analysis to avoid the effect of off-target binding of T807 on haemosiderin deposition. All neuroimaging studies (MRI and PET scans) were performed within 3 months of enrolment of each participant.

Statistical analysis

Categorical variables are presented as percentages, and continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range, IQR) depending on their distribution.

Table 1 Demographics of study subjects

	SVD (*n* = 66)	SVD-CAA (*n* = 20)	SVD-HTN (*n* = 46)	Alzheimer's disease (*n* = 10)	P-value[b]
Female, %	16 (24.2%)	7 (35%)	9 (19.6%)	7 (70%)	0.007*
Age, years	65.5 ± 11.4	71.1 ± 9.8	63.1 ± 11.3	75.6 ± 8.1	0.007*
APOE ε4 frequency, %[a]	4 (6.3%)	2 (11.8%)	2 (4.3%)	4 (40%)	0.010*
APOE ε2 frequency, %[a]	9 (14.3%)	5 (29.4%)	4 (8.7%)	1 (10%)	1.000
Educational years	11.5 ± 4.3	11.2 ± 4.5	11.7 ± 4.3	9.8 ± 5.7	0.355
MMSE	24.0 ± 7.6	23.6 ± 7.8	24.1 ± 7.6	17.2 ± 6.1	0.004*
Chronic hypertension, %	52 (78.8%)	14 (70%)	38 (82.6%)	9 (90%)	0.676
Hyperlipidaemia, %	21 (31.8%)	5 (25%)	16 (34.8%)	4 (40%)	0.721
Diabetes mellitus, %	14 (21.2%)	2 (10%)	12 (26.1%)	0 (0%)	0.193
Soluble TREM2, ng/ml	8.13 (6.94–10.19)	7.70 (7.34–9.92)	8.45 (6.82–10.07)	8.75 (6.08–10.79)	0.690
Presence of microbleed					
Lobar microbleed, %	45 (68.2%)	13 (65%)	32 (69.6%)	4 (40%)	0.153
Deep microbleed, %	33 (50%)	0 (0%)	33 (71.7%)	2 (20%)	0.097
Total microbleed number	12.2 ± 21.0	11.6 ± 24.3	12.5 ± 19.6	0.9 ± 1.5	0.003*
WMH volume, ml	13.6 ± 12.6	12.5 ± 12.4	14.1 ± 12.8	3.1 ± 1.9	0.001*
Lacune, %	35 (53.0%)	7 (35%)	28 (60.9%)	3 (30%)	0.309
Cortical superficial siderosis, %	9 (13.6%)	8 (38.1%)	1 (2.2%)	0 (%)	0.598
Cortical amyloid load, global PiB SUVR	1.16 ± 0.22	1.35 ± 0.28	1.08 ± 0.11	1.48 ± 0.33	< 0.001*

Values are mean ± SD, median (IQR) or *n* (%).
[a]Three SVD-CAA patients did not have *APOE* allele data.
[b]P-value indicates significance level for comparison between SVD and Alzheimer's disease groups.
*$P < 0.05$.

In univariable analyses, we compared baseline demographic and neuroimaging variables and sTREM2 levels between patients with Alzheimer's disease and SVD using the Mann-Whitney test or Fisher's exact test, as appropriate. The correlations between plasma sTREM2 levels and the other plasma biomarkers (total tau, amyloid-β_{1-40}, amyloid-β_{1-42} and amyloid-β_{1-40}:amyloid-β_{1-42} ratio) were analysed using a multivariable linear regression model to adjust for age and sex in the Alzheimer's disease, SVD-CAA and SVD-HTN groups. Given the non-normal distribution, the plasma sTREM2 levels were log-transformed before entering all linear regression models.

We performed further univariate and multivariable linear regression analyses to investigate the independent correlations between plasma sTREM2 levels and relevant neuroimaging markers. For patients with Alzheimer's disease or SVD-CAA for whom tau PET scans were available, we compared the baseline demographics, neuroimaging variables, and sTREM2 levels between patients with tau PET-positive [PET(+)] and tau PET-negative [PET(–)] scans. The association between the sTREM2 level and a positive tau scan was further examined in a multivariable model with covariates including WMH volume, amyloid load, age and sex. To explore the effect of sTREM2 on cognitive performance, we then performed linear regression analysis to assess the association between the MMSE score and plasma sTREM2 in the whole cohort and predefined subgroups, including: (i) amyloid-β disorders with tau PET(+) and tau PET(–); and (ii) the SVD subgroups with high-grade WMH (overall Fazekas scale $\geqslant$ 2) and low-grade WMH (overall Fazekas scale 0–1), respectively. All statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). All tests of significance were two-tailed with a threshold for significance of $P < 0.05$.

Data availability

Any data not published within the article are available from the corresponding author upon reasonable request.

Results

Plasma sTREM2 levels are comparable in patients with SVD and Alzheimer's disease

Increased levels of sTREM2 in CSF have been reported in subjects across the Alzheimer's disease continuum[30,31]; however, only a few studies have investigated plasma sTREM2 in patients with Alzheimer's disease, and none to date of plasma sTREM2 in patients with SVD.[32] We first compared the plasma sTREM2 levels between patients with symptomatic SVD and patients with clinical Alzheimer's disease. We recruited 66 patients with SVD (20 SVD-CAA and 46 SVD-HTN) and 10 patients with Alzheimer's disease in the current study; the main demographic data are summarized in Table 1. Compared to patients with Alzheimer's disease (age 75.6 ± 8.1, 70% female), significantly fewer patients with SVD (age 65.5 ± 11.4, 24.2% female) had the *APOE* ε4 allele (6.3% versus 40%, Fisher's exact test: $P = 0.010$) and they performed better on the MMSE (MMSE score 24.0 ± 7.6 versus 17.2 ± 6.1, Mann-Whitney test: $P = 0.004$). The SVD group was associated with neuroimaging SVD markers, including a higher microbleed number (12.2 ± 21.0 versus 0.9 ± 1.5, Mann-Whitney test: $P = 0.003$) and larger WMH volume (13.6 ± 12.6 versus 3.1 ± 1.9, Mann-Whitney test: $P = 0.001$) compared with the Alzheimer's disease group. Conversely, patients with SVD had a lower amyloid load on PiB-PET scans (Global PiB SUVR = 1.16 ± 0.22 versus 1.48 ± 0.33, Mann-Whitney test: $P < 0.001$) than patients with Alzheimer's disease. Plasma sTREM2 levels were not significantly different between patients with SVD and Alzheimer's disease [8.13 (6.94–10.19) ng/ml versus 8.75 (6.08–10.79), Mann-Whitney test: $P = 0.690$]. Among the patients with SVD, plasma sTREM2 levels were comparable between the SVD-CAA and SVD-HTN subgroups [7.70 (7.34–9.92) versus 8.45 (6.82–10.07) ng/ml, Mann-Whitney test: P = 0.829, Fig. 2].

We next assessed the correlations between plasma sTREM2 levels and other plasma biomarkers (total tau, amyloid-β_{1-40}, amyloid-β_{1-42} and amyloid-β_{1-40}:amyloid-β_{1-42} ratio) in the Alzheimer's

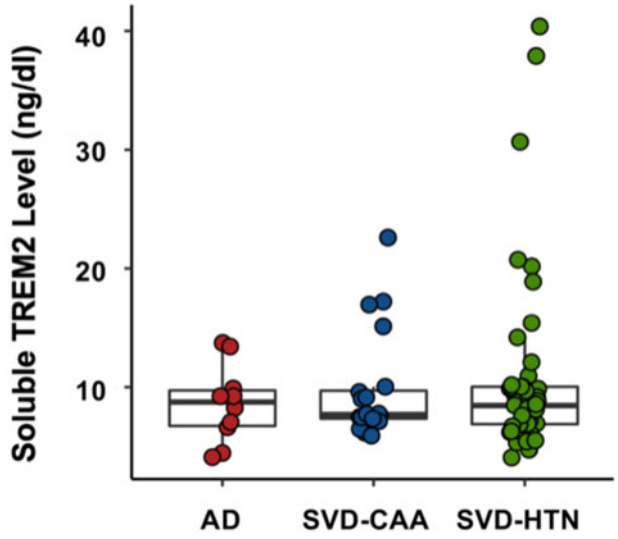

Figure 2 Box plots of plasma sTREM2 in patients with Alzheimer's disease, SVD-CAA, and SVD-HTN. Plasma sTREM2 levels were not significantly different between patients with SVD and Alzheimer's disease [8.13 (6.94–10.19) ng/ml versus 8.75 (6.08–10.79), $P = 0.690$]. Among patients with SVD, sTREM2 levels were not significantly different between the SVD-CAA and SVD-HTN subgroups [7.70 (7.34–9.92) versus 8.45 (6.82–10.07) ng/ml, $P = 0.829$].

disease, SVD-CAA and SVD-HTN groups (Supplementary Fig. 1). Plasma sTREM2 (log transformed) did not correlate with other plasma biomarkers in Alzheimer's disease (Supplementary Fig. 1A). However, in SVD-CAA, plasma sTREM2 level (log transformed) correlated positively with the plasma amyloid-$\beta_{1\text{-}40}$ level (standardized $\beta = 0.518$, $P = 0.033$; Supplementary Fig. 1B) and showed a strong correlative trend with the plasma amyloid-$\beta_{1\text{-}42}$ level (standardized $\beta = 0.442$, $P = 0.055$, Supplementary Fig. 1B). In SVD-HTN, plasma sTREM2 (log transformed) correlated positively with the total tau level (standardized $\beta = 0.330$, $P = 0.028$; Supplementary Fig. 1C).

Plasma sTREM2 levels are associated with WMH in SVD

Next, we evaluated the associations between sTREM2 and radiological biomarkers to identify whether any relevant SVD injury is associated with plasma sTREM2. Table 2 summarizes the univariate and multivariate linear regression analyses of the plasma sTREM2 level and neuroimaging variables (SVD subtype, cerebral microbleed number, WMH volume, lacune, amyloid burden, hippocampal volume and mean cortical thickness) for patients with SVD. Plasma sTREM2 (log transformed) correlated significantly with the WMH volume (standardized $\beta = 0.480$, $P < 0.001$; Fig. 3A), but not with the total microbleed number (standardized $\beta = 0.085$, $P = 0.495$; Fig. 3B) or the cerebral amyloid load (standardized $\beta = 0.069$; $P = 0.579$, Fig. 3C). The positive correlation between plasma sTREM2 and WMH volume remained significant when the linear regression model was adjusted for age and sex, and also in the full model including all of the neuroimaging variables as covariates (Table 2).

Plasma sTREM2 is independently associated with cortical tau pathology and WMH in amyloid-β disorders

To further investigate the independent contribution of small vessel pathology to the plasma sTREM2 level in the presence of amyloid and tau pathologies, we analysed patients with amyloid-β disorders, including Alzheimer's disease and SVD-CAA, for whom tau PET data were available ($n = 25$). Fifteen patients with SVD-CAA and 10 patients with Alzheimer's disease underwent a tau PET scan to measure cortical tau deposition. Twelve individuals (48%, five with SVD-CAA and seven with Alzheimer's disease) were categorized as tau PET(+) based on visual ratings. Representative images of tau PET(+) and tau PET(–) scans are shown in Fig. 4A. The inter-rater agreement for tau PET positivity was satisfactory ($\kappa = 0.76$, 95% confidence interval 0.51–1.0). Table 3 summarizes the comparison between patients with tau PET(+) and tau PET(–) scans. Patients with tau PET(+) scans had a comparable age, but lower MMSE scores (Mann-Whitney test: 16.6 ± 6.7 versus 23.1 ± 7.3, $P = 0.033$) than patients with tau PET(–) scans. Cerebral amyloid load was similar between the two subgroups, while higher tau tracer retention was observed in patients with tau PET(+) scans compared with patients with tau PET(–) scans using a semi-quantitative method (global ^{18}F-T807 SUVR = 1.36 ± 0.24 versus 1.08 ± 0.09, Mann-Whitney test: $P < 0.001$; Braak stage V SUVR = 1.29 ± 0.23 versus 1.05 ± 0.08, Mann-Whitney test: $P < 0.001$).

The plasma sTREM2 levels of patients with tau PET(+) and tau PET(–) scans are shown in Fig. 4B. Patients with tau PET(+) scans had higher plasma sTREM2 levels than patients with tau PET(–) scans [9.96 (8.50–14.76) versus 7.45 (6.55–7.76) ng/ml, Mann-Whitney test: $P = 0.002$]. Additionally, we performed multivariate linear regression analysis to investigate the associations between plasma sTREM2, tau scan positivity, WMH volume and amyloid load with further adjustment for age and sex. Plasma sTREM2 (log transformed) remained independently associated with a positive tau scan (standardized $\beta = 0.653$, $P = 0.001$) and higher WMH volume (standardized $\beta = 0.461$, $P = 0.013$), but not with amyloid load (standardized $\beta = -0.234$, $P = 0.221$).

Plasma sTREM2 correlates with better cognition in patients with cortical tau pathology only

We next examined if plasma sTREM2 is associated with cognitive status. In the entire cohort, including both the patients with Alzheimer's disease and SVD, there was no significant correlation between the MMSE score and plasma sTREM2 level (standardized $\beta = -0.164$, $P = 0.160$). Interestingly, among patients with amyloid-β disorders (Alzheimer's disease and SVD-CAA), the MMSE score only positively correlated with plasma sTREM2 in patients with tau PET(+) scans (standardized $\beta = 0.647$, $P = 0.023$), but not in patients with tau PET(–) scans (standardized $\beta = -0.112$, $P = 0.716$; Fig. 5A). The correlation between the MMSE score and plasma sTREM2 level in patients with tau PET(+) scans remained significant after adjusting for age and years of education (standardized $\beta = 0.632$, $P = 0.049$). We further assessed the correlation between plasma sTREM2 and the MMSE score in patients with SVD (SVD-CAA and SVD-HTN) stratified by the WMH severity scale. We found that the MMSE score and plasma sTREM2 were not significantly correlated to each other in subjects with either high-grade WMH or low-grade WMH (both $P > 0.05$; Fig. 5B), suggesting no association between plasma sTREM2 and cognitive performance irrespective of SVD stage.

Discussion

In the present study, we explored the associations between plasma sTREM2 and the neuroimaging features of SVD in a cohort of 76 patients. First, we showed the plasma sTREM2 levels are comparable between patients with SVD and patients with Alzheimer's disease. Second, plasma sTREM2 correlated positively with the WMH volume independent of amyloid-β load in patients

Table 2 Correlation between plasma sTREM2 and neuroimaging markers in SVD patients (SVD-CAA and SVD-HTN)

	Model 1 (Univariate)		Model 2 (Age, sex)		Model 3 (full model)	
	Standardized β	*P*-value	Standardized β	*P*-value	Standardized β	*P*-value
Small vessel disease subtype (SVD-CAA versus SVD-HTN)	–0.019	0.877	–	–	0.096	0.571
Total microbleed number	0.085	0.495	–	–	0.007	0.962
WMH volume	0.480	<0.001*	0.451	<0.001*	0.374	0.013*
Lacune presence	0.147	0.240	–	–	0.313	0.058
Amyloid burden	0.069	0.579	–	–	–0.004	0.997
Hippocampal volume	0.002	0.986	–	–	0.168	0.302
Mean cortical thickness	–0.030	0.871	–	–	1.371	0.177

*$P < 0.05$.

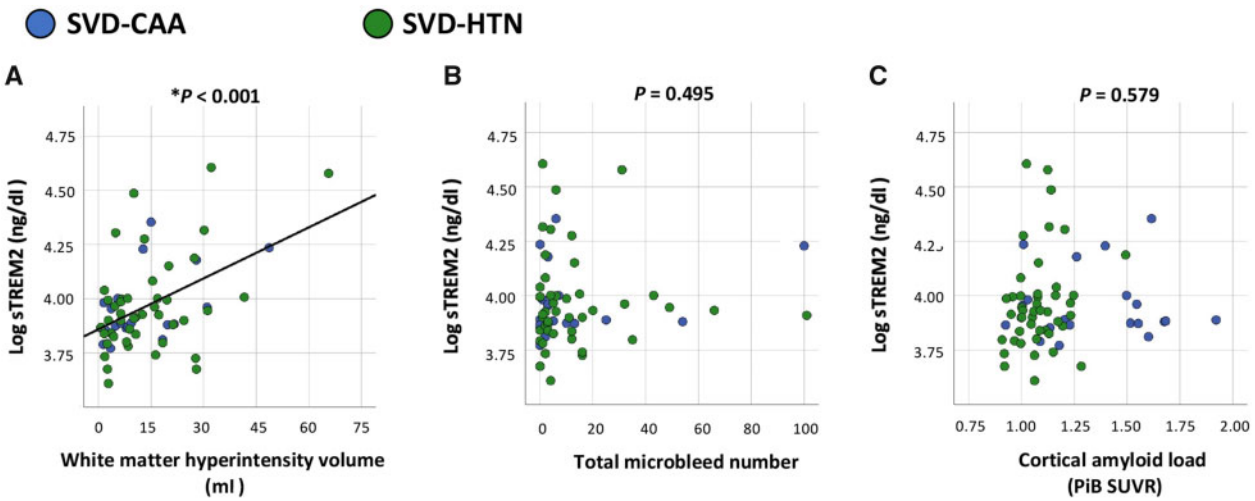

Figure 3 Correlations between plasma sTREM2 and neuroimaging markers. (**A**) Positive correlation was observed between plasma sTREM2 (log transformed) and WMH volume (standardized β = 0.480, $P < 0.001$). (**B**) No correlation was observed between plasma sTREM2 (log transformed) and microbleed burden (standardized β = 0.085, $P = 0.495$). (**C**) No correlation was observed between plasma sTREM2 (log transformed) and cerebral amyloid load (standardized β = 0.069, $P = 0.579$).

with SVD, implicating increased myeloid cell-associated inflammation and TREM2 signalling occur during the progression of SVD in a cerebral amyloid-β deposition-independent manner, and plasma sTREM2 is likely to be associated with white matter lesions in SVD. Finally, we demonstrate that higher plasma sTREM2 was independently associated with higher WMH volume and positive cortical tau pathology, but not with amyloid deposition in amyloid-β disorders. Taken together, our results suggest SVD-related white matter injury is associated with elevated plasma sTREM2, independent of cerebral amyloid and tau pathologies.

Cerebral SVDs are pathologies in small superficial and deep penetrating arteries of the brain that result in a multitude of clinical manifestations, including gait disturbance, cognitive impairment, mood disorders, and strokes such as spontaneous ICH.[33] Studies investigating the underlying pathogenic mechanisms in SVD have identified impaired blood–brain barrier integrity and extravasation of plasma constituents such as fibrinogen. This blood protein may in turn activate the innate immune response and subsequently promote cellular or humoral immune responses, which ultimately lead to neuron and oligodendrocyte injury.[34] Here, we demonstrate that plasma sTREM2 levels significantly correlate with WMH, a marker of SVD severity and white matter injury. While the function of TREM2-dependent inflammation in SVD is mostly unknown, our findings suggest that peripheral sTREM2 is an essential immune response implicated in neurovascular compromise in SVD. We investigated the correlation between plasma sTREM2 and cognitive scores in SVD as sTREM2 and TREM2 signalling have been proposed to exert potential neuroprotective effects[17,35,36]; however, we did not detect any association in either early or advanced-stage SVD. It should be noted that the patients in the SVD group were recruited as survivors of ICH; thus, their cognitive function may be significantly affected by the previous stroke event, which may therefore confound our results. Future longitudinal follow-up cohort studies are needed to elucidate the prognostic value of plasma sTREM2 for long-term outcomes. Approaches such as *in vivo* cerebral PET for neuroinflammation may also help delineate the dynamics of microglial activation during the progression of SVD.

While CSF sTREM2 has been extensively studied, only a handful of studies have investigated circulatory (plasma or serum) sTREM2 and its role in CNS pathology remains controversial. Patients with early Alzheimer's disease were suggested to have higher levels of CSF sTREM2, but no significant difference in plasma sTREM2 was detected between patients with Alzheimer's disease and control subjects.[32,37] Additionally, Piccio and colleagues[38] showed the serum level of sTREM2 did not differ between patients with multiple sclerosis and other neurological disorders. Studies have proposed that circulatory sTREM2 could be of peripheral origin, given

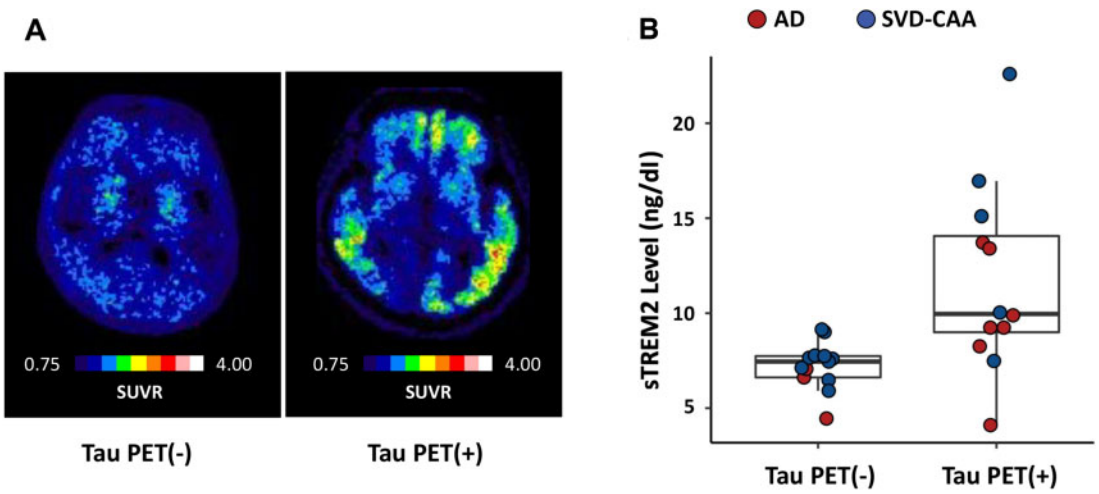

Figure 4 Box plots of plasma sTREM2 in patients with tau PET(–) and tau PET(+) scans. In 25 patients with SVD-CAA and Alzheimer's disease, 12 (48%) patients were visually rated as tau PET(+). (**A**) Representative images of positive and negative tau PET scans. (**B**) Patients with tau PET(+) scans had higher plasma sTREM2 than patients with tau PET(–) scans [9.96 (8.50–14.76) versus 7.45 (6.55–7.76) ng/ml, $P = 0.002$].

Table 3 Comparison between tau PET(+) and tau PET(–) in amyloid-β disorders (SVD-CAA and Alzheimer's disease)

	Tau PET(+) ($n = 12$)	Tau PET(–) ($n = 13$)	P-value
Female, %	7 (58.3%)	5 (38.5%)	0.434
Age, years	76.8 ± 8.2	73.4 ± 6.6	0.231
Educational years	9.1 ± 4.7	10.2 ± 4.6	0.448
MMSE	16.6 ± 6.7	23.1 ± 7.3	0.033*
CAA/AD	5/7	10/3	0.111
Soluble TREM2, ng/ml	9.96 (8.50–14.76)	7.45 (6.55–7.76)	0.002*
Presence of microbleed			
Lobar microbleed, %	7 (58.3%)	9 (69.2%)	0.688
Deep microbleed, %	1 (8.3%)	1 (7.7%)	1.0
Total microbleed number	10.8 ± 28.3	8.5 ± 15.4	0.717
WMH volume, ml	7.3 ± 7.8	10.3 ± 9.4	0.341
Lacune, %	5 (41.7%)	4 (30.8%)	0.688
Cortical superficial siderosis, %	4 (33.3%)	4 (30.8%)	1.0
Global PiB retention, SUVR	1.49 ± 0.30	1.44 ± 0.26	0.913
Global T807 retention, SUVR	1.36 ± 0.24	1.08 ± 0.09	< 0.001*
Braak stage V T807 retention, SUVR	1.29 ± 0.23	1.05 ± 0.08	< 0.001*

Values are mean ± SD, median (IQR) or *n* (%).
*$P < 0.05$.

that TREM2 is highly expressed in myeloid lineage cells such as monocytes, macrophages and osteoclasts.[11] In line with this idea, post-mortem data also suggested that TREM2 in the human brain could represent a marker of recruitment of monocytes, rather than the resident microglia.[39] In fact, multiple studies have reported strong correlations between levels of peripheral sTREM2 and CSF sTREM2.[18,19] Moreover, additional evidence suggests central TREM2 activation potentially leads to blood–brain barrier dysfunction, and therefore elevates the peripheral levels of sTREM2.[18] A population-based study by Ohara *et al.*[40] found increased serum sTREM2 was a risk factor for developing incident dementia. Collectively, this evidence suggests a potential role for peripheral sTREM2 in CNS pathology. Our findings support this hypothesis by showing that the plasma sTREM2 level correlates strongly with white matter lesions and tau pathology in the brain.

Previous research has suggested major roles for sTREM2 in the development of neurodegenerative disorders, especially in Alzheimer's disease. A cross-sectional study of the CSF of patients with Alzheimer's disease reported that the CSF sTREM2 level peaked at the early symptomatic stages and correlated with other CSF markers of neurodegeneration, including t-tau and p-tau.[31] Another study found CSF sTREM2 was elevated in patients with Parkinson's disease with a positive tau signature,[41] suggesting the level of sTREM2 in CSF can be considered as a marker of neuronal injury in neurodegenerative disorders. In line with previous studies, we observed elevated plasma sTREM2 was associated with cortical tau pathology in both Alzheimer's disease and CAA. We also demonstrated that plasma sTREM2 correlated positively with the level of plasma t-tau in the SVD-HTN subgroup. Tau proteins are primarily expressed in CNS neurons, and the plasma t-tau levels are thought to reflect neuronal damage and subsequent drainage of tau from the brain parenchyma to the CSF and blood.[42,43] Our results strengthen the idea of utilizing plasma sTREM2 as a biomarker of neuronal injury and neurodegeneration.[19] Interestingly, TREM2 signalling in the CNS is thought to exert opposing functions, and whether TREM2 is beneficial or detrimental to brain pathology depends on the disease

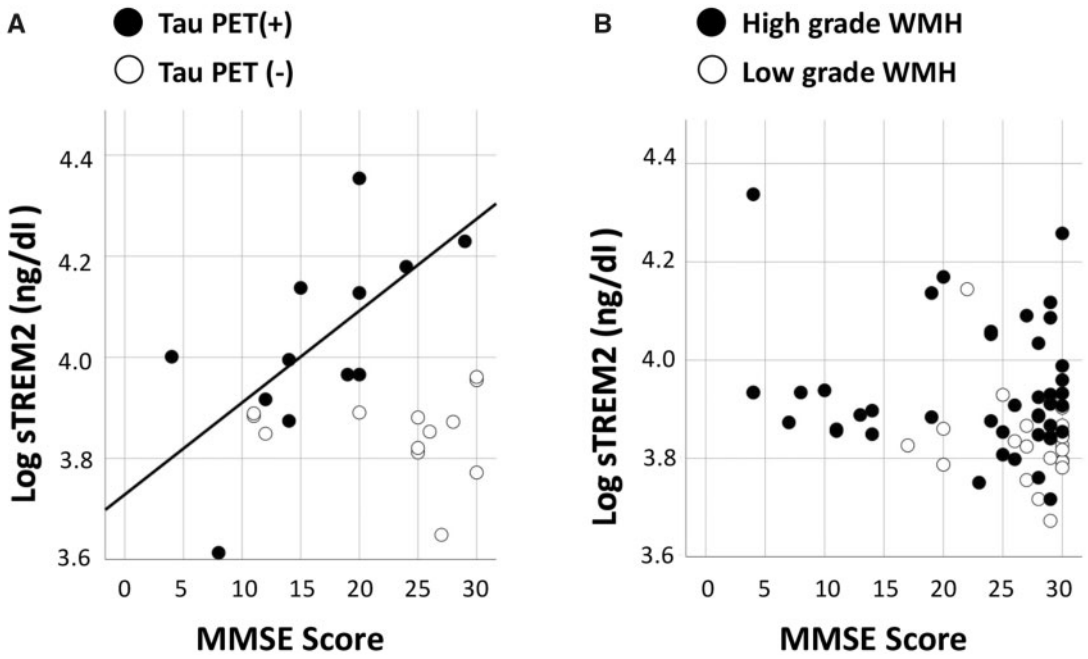

Figure 5 Correlations between plasma sTREM2 and cognitive scores. (**A**) In patients with amyloid-β disorders, a positive correlation was observed between plasma sTREM2 and the cognitive scores of patients with tau PET(+) scans (standardized β = 0.647, $P = 0.023$; adjusted for age and years of education, $P = 0.049$), but not in patients with tau PET(–) scans ($P = 0.84$). (**B**) In patients with SVD, no correlation was observed between plasma sTREM2 and cognitive score in the subgroups with high-grade WMH or low-grade WMH (both $P > 0.05$).

type and disease stage. Some studies have suggested that increased CSF sTREM2 is associated with slower cognitive decline in Alzheimer's disease.[17,36] The current study reveals the interesting observation that a positive correlation exists between plasma sTREM2 and cognition status in patients with Alzheimer's disease or CAA with a positive tau scan. A similar correlation was observed in a previous study investigating CSF sTREM2 in Parkinson's disease, in which the sTREM2 level correlated positively with the cognitive scores in patients with a positive CSF tau signature.[41] Despite the low numbers of patients and the cross-sectional design, our findings based on plasma samples suggest high levels of sTREM2 may be a potentially prognostic marker when tau-mediated neurodegeneration occurs in Alzheimer's disease or CAA.

One of the strengths of this study is the inclusion of SVD-CAA in addition to Alzheimer's disease in the study cohort. This allowed us to examine the individual contribution of SVD, amyloid-β and tau pathology to elevated plasma sTREM2, as the clinical manifestations and cerebral pathologies of CAA and Alzheimer's disease often overlap with each other.[44] Previous preclinical studies suggest TREM2 plays an important role in signalling to contain and clear cerebral amyloid-β.[45,46] Only one animal study specifically focused on CAA and described impaired TREM2 signalling in the early stage of CAA, suggesting that reduced inflammation may be associated with early vascular pathology. Unfortunately, the function of TREM2-dependent signalling in the clearance of amyloid-β cannot be demonstrated in most clinical studies. In patients with Alzheimer's disease, CSF sTREM2 has been shown to correlate with total and phosphorylated tau levels, but not with the levels of amyloid-β_{42}.[47] Another preclinical study in Alzheimer's disease also observed increased CSF sTREM2 in the presence of tau deposition, rather than amyloid-β pathology.[48] Our results based on plasma samples from subjects across the SVD and Alzheimer's disease spectrum are in agreement with the previous literature, and provide additional evidence that elevated plasma sTREM2 occurs independently of both parenchymal and cerebrovascular amyloid-β deposition. We detected a positive correlation between plasma sTREM2 and plasma amyloid-$\beta_{1\text{-}40}$ or plasma amyloid-$\beta_{1\text{-}42}$ in SVD-CAA in this study. Elevated plasma amyloid-β levels have been suggested as a marker that reflects cerebrovascular lesions, including white matter lesions and cerebral microbleeds.[49–52] Our findings support the idea that neurovascular compromise in CAA, rather than the vascular amyloid deposits, is associated with an enhanced peripheral TREM2 response.

Another important strength of our study is the use of *in vivo* molecular imaging to measure cerebral amyloid-β and tau pathologies, which allowed us to investigate their relationships with plasma sTREM2 in real time. This approach also provides accurate estimates of cerebral pathologies. Amyloid PET can detect both parenchymal and cerebrovascular amyloid-β in Alzheimer's disease and CAA.[3,23] Amyloid PET has been applied to identify the presence of CAA in survivors of ICH, and this methodology is essential as many patients may harbour a dual SVD pathology (i.e. coexisting CAA and hypertensive SVD).[27] Amyloid PET can also provide quantitative data that correlates with plaque density and the severity of CAA.[4,53] Our analysis of this cohort provides valuable information regarding cerebral amyloid-β load in patients with SVD, and therefore helps to elucidate the association between SVD and plasma sTREM2 when the effect of cerebral amyloid-β burden, especially CAA, is also taken into consideration.

There are limitations to this study. First, we only measured plasma sTREM2, and not the levels in CSF. Plasma sTREM2 could be of peripheral origin and be affected by other systemic diseases.[54] However, plasma samples are generally more accessible, and therefore have a broader clinical application. Second, patients with SVD were recruited from survivors of spontaneous ICH, and not from patients presenting with other clinical manifestations. We believe this is the best selection strategy to recruit patients with CAA, as CAA can be accurately diagnosed after symptomatic lobar ICH in clinical practice using the modified Boston criteria.[55] However, we could not completely rule out the possibility that the observed sTREM2 levels reflect inflammation caused by unresolved haematoma. To minimize this confounding factor, we only

included patients at least 6 months after their index ICH event. Lastly, the lack of sTREM2 data from normal healthy controls and the cross-sectional design of this current study limit our interpretation of causality between plasma sTREM2, WMH and tau deposition within our cohort. Future longitudinal studies with neuroimaging follow-up and detailed neuropsychological profiling are essential to clarify whether sTREM2 provides a disease-protective effect in SVD.

In conclusion, our findings suggest SVD-related WMH on MRI is associated with plasma sTREM2, independently of cerebral amyloid-β and tau deposition. Since small vessel pathology plays a major role in stroke and other neurodegenerative disorders, our findings related to inflammation in advanced SVD should prompt further investigations to clarify the intricate relationship between TREM2-related inflammation, neurovascular unit compromise and, ultimately, neurodegeneration. Our results also imply the innate immune response may represent a potential target to effectively treat this disease.

Acknowledgements

We thank the Second Core Lab, Department of Medical Research, National Taiwan University Hospital, for providing technical support. We thank PET/Cyclotron Center, Department of Nuclear Medicine, National Taiwan University Hospital, for preparing the radiopharmaceuticals and performing the PET imaging. We thank Jhih Syuan Lin for assisting with plasma sample preparation. We thank Danye Jiang for editing the manuscript and insightful input. We thank Bo-Ching Lee for assisting with figure production. We thank the patients and families who graciously participated in the clinical study.

Funding

This work was supported by National Taiwan University Hospital Bei-Hu branch (H.-H.T., 11002), National Taiwan University (C.-F.C., NTUCC-110L891203), and the Ministry of Science and Technology, Taiwan (H.-H.T., MOST 109–2628-B-002–025 and 110–2628-B-002–063; C.-F.C., MOST 109–2628-B-002–024 and 110–2628-B-002–030).

Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

References

1. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: Mechanisms and clinical implications. *Lancet Neurol*. 2019;18(7):684–696.
2. Wardlaw JM, Smith EE, Biessels GJ, et al.; STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822–838.
3. Chen SJ, Tsai HH, Tsai LK, et al. Advances in cerebral amyloid angiopathy imaging. *Ther Adv Neurol Disord*. 2019;12:1756286419844113.
4. Tsai HH, Pasi M, Tsai LK, et al. Centrum semiovale perivascular space and amyloid deposition in spontaneous intracerebral hemorrhage. *Stroke*. 2021;52(7):2356–2362.
5. Low A, Mak E, Malpetti M, et al. In vivo neuroinflammation and cerebral small vessel disease in mild cognitive impairment and Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2020;92(1):45–52.
6. Low A, Mak E, Rowe JB, Markus HS, O'Brien JT. Inflammation and cerebral small vessel disease: A systematic review. *Ageing Res Rev*. 2019;53:100916.
7. Carrano A, Hoozemans JJ, van der Vies SM, van Horssen J, de Vries HE, Rozemuller AJ. Neuroinflammation and blood-brain barrier changes in capillary amyloid angiopathy. *Neurodegener Dis*. 2012;10(1-4):329–331.
8. Zhu X, Hatfield J, Sullivan JK, Xu F, Van Nostrand WE. Robust neuroinflammation and perivascular pathology in rTg-DI rats, a novel model of microvascular cerebral amyloid angiopathy. *J Neuroinflammation*. 2020;17(1):78.
9. Fan R, Xu F, Previti ML, et al. Minocycline reduces microglial activation and improves behavioral deficits in a transgenic model of cerebral microvascular amyloid. *J Neurosci*. 2007;27(12):3057–3063.
10. Bath PM, Wardlaw JM. Pharmacological treatment and prevention of cerebral small vessel disease: A review of potential interventions. *Int J Stroke*. 2015;10(4):469–478.
11. Colonna M. TREMs in the immune system and beyond. *Nat Rev Immunol*. 2003;3(6):445–453.
12. Yang J, Fu Z, Zhang X, Xiong M, Meng L, Zhang Z. TREM2 ectodomain and its soluble form in Alzheimer's disease. *J Neuroinflammation*. 2020;17(1):204.
13. Xue F, Du H. TREM2 mediates microglial anti-inflammatory activations in Alzheimer's disease: Lessons learned from transcriptomics. *Cells*. 2021;10(2):321.
14. Walter J. The triggering receptor expressed on myeloid cells 2: A molecular link of neuroinflammation and neurodegenerative diseases. *J Biol Chem*. 2016;291(9):4334–4341.
15. Wunderlich P, Glebov K, Kemmerling N, Tien NT, Neumann H, Walter J. Sequential proteolytic processing of the triggering receptor expressed on myeloid cells-2 (TREM2) protein by ectodomain shedding and gamma-secretase-dependent intramembranous cleavage. *J Biol Chem*. 2013;288(46):33027–33036.
16. Zhong L, Chen XF. The emerging roles and therapeutic potential of soluble TREM2 in Alzheimer's disease. *Front Aging Neurosci*. 2019;11:328.
17. Ewers M, Franzmeier N, Suarez-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.
18. 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.
19. Ferri E, Rossi PD, Geraci A, Ciccone S, Cesari M, Arosio B. The sTREM2 concentrations in the blood: A marker of neurodegeneration? *Front Mol Biosci*. 2020;7:627931.
20. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to 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(3):263–269.
21. Linn J, Halpin A, Demaerel P, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology*. 2010;74(17):1346–1350.
22. Pasi M, Charidimou A, Boulouis G, et al. Mixed-location cerebral hemorrhage/microbleeds: Underlying microangiopathy and recurrence risk. *Neurology*. 2018;90(2):e119–e126.
23. Tsai HH, Pasi M, Tsai LK, et al. Microangiopathy underlying mixed-location intracerebral hemorrhages/microbleeds: A PiB-PET study. *Neurology*. 2019;92(8):e774–e781.

24. Banerjee G, Ambler G, Keshavan A, et al. Cerebrospinal fluid biomarkers in cerebral amyloid angiopathy. *J Alzheimers Dis*. 2020;74(4):1189–1201.
25. Rissin DM, Kan CW, Campbell TG, et al. Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations. *Nat Biotechnol*. 2010;28(6): 595–599.
26. Pasi M, Boulouis G, Fotiadis P, et al. Distribution of lacunes in cerebral amyloid angiopathy and hypertensive small vessel disease. *Neurology*. 2017;88(23):2162–2168.
27. Tsai HH, Tsai LK, Chen YF, et al. Correlation of cerebral microbleed distribution to amyloid burden in patients with primary intracerebral hemorrhage. *Sci Rep*. 2017;7:44715.
28. Tsai HH, Pasi M, Tsai LK, et al. Distribution of lacunar infarcts in Asians with intracerebral hemorrhage: A magnetic resonance imaging and amyloid positron emission tomography study. *Stroke*. 2018;49(6):1515–1517.
29. Sonni I, Lesman Segev OH, Baker SL, et al.; Alzheimer's Disease Neuroimaging Initiative. Evaluation of a visual interpretation method for tau-PET with (18)F-flortaucipir. *Alzheimers Dement (Amst)*. 2020;12(1):e12133.
30. Heslegrave A, Heywood W, Paterson R, et al. Increased cerebrospinal fluid soluble TREM2 concentration in Alzheimer's disease. *Mol Neurodegener*. 2016;11:3.
31. Suarez-Calvet M, Kleinberger G, Araque Caballero MA, 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(5): 466–476.
32. Liu D, Cao B, Zhao Y, et al. Soluble TREM2 changes during the clinical course of Alzheimer's disease: A meta-analysis. *Neurosci Lett*. 2018;686:10–16.
33. Ter Telgte A, van Leijsen EMC, Wiegertjes K, Klijn CJM, Tuladhar AM, de Leeuw FE. Cerebral small vessel disease: From a focal to a global perspective. *Nat Rev Neurol*. 2018;14(7):387–398.
34. Fu Y, Yan Y. Emerging role of immunity in cerebral small vessel disease. *Front Immunol*. 2018;9:67.
35. Ulrich JD, Ulland TK, Colonna M, Holtzman DM. Elucidating the role of TREM2 in Alzheimer's disease. *Neuron*. 2017;94(2): 237–248.
36. Hu WT, Ozturk T, Kollhoff A, Wharton W, Christina Howell J; Alzheimer's Disease Neuroimaging Initiative. Higher CSF sTNFR1-related proteins associate with better prognosis in very early Alzheimer's disease. *Nat Commun*. 2021;12(1):4001.
37. Ashton NJ, Suarez-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.
38. Piccio L, Buonsanti C, Cella M, et al. Identification of soluble TREM-2 in the cerebrospinal fluid and its association with multiple sclerosis and CNS inflammation. *Brain*. 2008;131(11): 3081–3091.
39. Fahrenhold M, Rakic S, Classey J, et al.; MRC-CFAS. TREM2 expression in the human brain: A marker of monocyte recruitment? *Brain Pathol*. 2018;28(5):595–602.
40. Ohara T, Hata J, Tanaka M, et al. Serum soluble triggering receptor expressed on myeloid cells 2 as a biomarker for incident dementia: The Hisayama study. *Ann Neurol*. 2019;85(1):47–58.
41. Wilson EN, Swarovski MS, Linortner P, et al. Soluble TREM2 is elevated in Parkinson's disease subgroups with increased CSF tau. *Brain*. 2020;143(3):932–943.
42. Mattsson N, Zetterberg H, Janelidze S, et al.; ADNI Investigators. Plasma tau in Alzheimer disease. *Neurology*. 2016;87(17): 1827–1835.
43. Schraen-Maschke S, Sergeant N, Dhaenens CM, et al. Tau as a biomarker of neurodegenerative diseases. *Biomark Med*. 2008; 2(4):363–384.
44. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease – one peptide, two pathways. *Nat Rev Neurol*. 2020;16(1):30–42.
45. Gratuze M, Leyns CEG, Holtzman DM. New insights into the role of TREM2 in Alzheimer's disease. *Mol Neurodegener*. 2018; 13(1):66.
46. Yuan P, Condello C, Keene CD, et al. TREM2 haplodeficiency in mice and humans impairs the microglia barrier function leading to decreased amyloid compaction and severe axonal dystrophy. *Neuron*. 2016;90(4):724–739.
47. Suarez-Calvet M, Morenas-Rodriguez 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-beta pathology. *Mol Neurodegener*. 2019;14(1):1.
48. Ma LZ, Tan L, Bi YL, et al. Dynamic changes of CSF sTREM2 in preclinical Alzheimer's disease: The CABLE study. *Mol Neurodegener*. 2020;15(1):25.
49. Gurol ME, Irizarry MC, Smith EE, et al. Plasma beta-amyloid and white matter lesions in AD, MCI, and cerebral amyloid angiopathy. *Neurology*. 2006;66(1):23–29.
50. Tsai HH, Tsai LK, Lo YL, Lin CH. Amyloid related cerebral microbleed and plasma Abeta40 are associated with cognitive decline in Parkinson's disease. *Sci Rep*. 2021;11(1):7115.
51. Janelidze S, Stomrud E, Palmqvist S, et al. Plasma beta-amyloid in Alzheimer's disease and vascular disease. *Sci Rep*. 2016;6: 26801.
52. Hilal S, Akoudad S, van Duijn CM, et al. Plasma amyloid-beta levels, cerebral small vessel disease, and cognition: The Rotterdam study. *J Alzheimers Dis*. 2017;60(3):977–987.
53. Amadoru S, Dore V, McLean CA, et al. Comparison of amyloid PET measured in Centiloid units with neuropathological findings in Alzheimer's disease. *Alzheimers Res Ther*. 2020;12(1):22.
54. Neumann H, Takahashi K. Essential role of the microglial triggering receptor expressed on myeloid cells-2 (TREM2) for central nervous tissue immune homeostasis. *J Neuroimmunol*. 2007; 184(1-2):92–99.
55. Charidimou A, Farid K, Baron JC. Amyloid-PET in sporadic cerebral amyloid angiopathy: A diagnostic accuracy meta-analysis. *Neurology*. 2017;89(14):1490–1498.