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Original article

Association between sTREM2, an immune biomarker of microglial activation, and frontal lobe function in community-dwelling older adults: a cross-sectional study

Ryuzo Orihashi[1, 2], Yoshiomi Imamura[2], and Yoshito Mizoguchi[2]

[1]*Institute of Nursing, Faculty of Medicine, Saga University, Japan*
[2]*Department of Psychiatry, Faculty of Medicine, Saga University, Japan*

Abstract

Objective: Identifying the peripheral biomarkers related to the prevention or modification of unhealthy mental conditions in older adults is extremely beneficial. This study aimed to evaluate the serum levels of soluble triggering receptor expressed on myeloid cells 2 (sTREM2), a soluble form of an innate immune receptor expressed on microglia, in older adults living in a rural community, and their association with cognitive function.

Materials and Methods: This survey was conducted between November 2016 and September 2017 in Kurokawa-cho, Imari, Saga Prefecture, Japan, among people aged ≥65 years. Blood samples were collected from the participants for serum sTREM2 level analysis using a peptide enzyme immunoassay. The participants underwent cognitive function assessments, including the Mini-Mental State Examination, Clinical Dementia Rating, and Frontal Assessment Battery. Therefore, we examined the association between serum sTREM2 levels and cognitive function.

Results: Of the 95 participants, 25 were men and 70 were women with a mean age 78.24 ± 3.85 years and 77.96 ± 5.52 years, respectively. Serum sTREM2 levels were negatively associated with Frontal Assessment Battery scores, even after adjusting for age, sex, years of education, and serum high-sensitivity C-reactive protein levels.

Conclusion: Serum sTREM2 levels may be associated with frontal lobe function in adults aged ≥65 years.

Key words: cognitive function, frontal assessment battery (FAB), mental health, older adults, soluble triggering receptor expressed on myeloid cells 2 (sTREM2)

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Introduction

According to Japan's Ministry of Health, Labour and Welfare, Japan has one of the longest life expectancies in the world, and extending healthy life expectancy has become an important issue in the aging population. In 1990, local doctors, public health nurses, and volunteers initiated a dementia prevention project for the general residents of Kurokawa-cho, Imari, Saga Prefecture, Japan. Since 1994, brain MRI examinations, cognitive function assessments, and neuropsychological assessments have been performed in older adults, and lectures and gymnastics were provided through health classes. We have been participating in this project since 2004, longitudinally investigating older adults and conducting research on the existence of highly reliable biomarkers that indicate future risk of cognitive decline and depression. We studied how older adults maintain their mental health while living in familiar communities. To date, we have conducted many epidemiological studies in older adults living in rural communities and identified peripheral biomarkers associated with mental health maintenance[1–8]. In this study, we focused on triggering receptor expressed on myeloid cells 2 (TREM2), a surface receptor of microg-

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Correspondence: Yoshito Mizoguchi, Department of Psychiatry, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan
E-mail: ymizo@cc.saga-u.ac.jp

lial cells, and cognitive function. TREM2 has important roles in microglial functions including phagocytosis and modulation of neuroinflammation[9]. TREM2 has also been identified as one of the most potent genetic risk factors for Alzheimer's disease (AD)[10]. TREM2 is released into the extracellular space as a soluble form (sTREM2) and can be detected in the cerebrospinal fluid (CSF) and peripheral blood[11, 12]. The sTREM2 augments microglial viability and supports the physiological functions of microglia[13]. Insertion of sTREM2 in the brains of 5xFAD mice promotes amyloid-β uptake and degradation and provides a neuroprotective role against amyloid pathology[14]. Several studies reported an association between sTREM2 levels in the CSF or peripheral blood and AD[15–20]. However, the results of studies on the biological role of sTREM2 are inconsistent. We also analyzed the correlation between serum sTREM2 levels and brain volume. However, there was no correlation between serum sTREM2 levels and age-related volume changes in regions of the brain closely related to cognitive function[5]. Conversely, a large-scale cohort study reported that serum sTREM2 levels may serve as a novel biomarker for dementia[21]. Therefore, finding further evidence for an association between sTREM2 and cognitive function may contribute to the prediction of cognitive function decline and early intervention for such high-risk individuals in the future. This study evaluated serum sTREM2 levels in older adults living in a rural community and examined their association with cognitive function. If this study reveals an association between serum sTREM2 levels and cognitive function, it may strengthen the evidence that serum sTREM2 levels are one of the peripheral biomarkers related to the prevention or modification of mentally unhealthy conditions in older adults. Therefore, investigating the association between serum sTREM2 levels and cognitive function in older adults is expected to be beneficial in supporting aging communities in maintaining health and sociality.

Materials and Methods

Participant characteristics and survey procedure

This survey was conducted between November 2016 and September 2017 in Kurokawa-cho, Imari, Saga Prefecture, Japan, among people aged ≥65 years, as reported previously[1–8]. Kurokawa-cho is a rural town in northwestern Saga Prefecture that is somewhat isolated from urban areas. As of 2016, the population of Kurokawa-cho was 3,137, with 935 (29.8%) people aged ≥65 years. Approximately 100 participants were considered as a sample for the study. Power analysis using G*Power (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) showed that this sample size resulted in a medium effect size (α error prob, 0.05; Power, 0.8). The participants for this study were basically recruited from a list of participants from past surveys that were part of a longitudinal study. In addition, older adults who had not participated in past surveys but intended to participate in this survey were also recruited. When recruiting, sex ratio, cognitive function at that time, and activities of daily living were not considered. We asked a care manager belonging to Kurokawa-cho's in-home nursing care support project to confirm whether the participants could cooperate with the study. Ninety-seven participants then agreed to participate in the survey. Surveys were conducted once per week, with three participants each time. Of the 97 participants, 84 older adults participated in previous surveys and 13 were new participants. Two participants arbitrarily dropped out of the study, resulting in 95 participants completing the survey and were included in the cross-sectional analysis.

All methods were carried out in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Faculty of Medicine, Saga University, Japan. Written informed consent was obtained from all participants prior to participation.

Cognitive function assessments

All participants underwent cognitive function assessment using the Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR) and Frontal Assessment Battery (FAB). The MMSE is a simple screening index that estimates cognitive function[22]. The CDR is used for dementia evaluation and severity staging[23, 24]. The FAB consists of six subtests that measure cognitive function related to the frontal lobe[25].

Serum samples

To evaluate serum sTREM2 levels, blood samples were collected from participants between 13:00 and 15:00. On the same day, all samples were centrifuged at Saga University. Next, serum was extracted, transferred to a container, and immediately stored at −80°C.

Measurements of serum sTREM2 levels and risk factor

The serum was thawed at room temperature. All samples were analyzed in duplicate. Serum sTREM2 levels were analyzed using a commercially available human TREM2 ELISA kit (RayBiotech, Norcross, GA, USA) according to the manufacturer's instructions[5, 21, 26, 27]. The intra-assay coefficient of variation was 10% and the inter-assay coefficient of variation was 12%. Additionally, serum high-sensitivity C-reactive protein (hs-CRP) levels were analyzed using commercially available ELISA kits (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions[5]. The intra-assay coefficient of variation was 5.5% and the inter-assay coefficient of variation was 6.53%.

Statistical analysis

Statistical analyses were conducted using JMP statistical software (JMP 16.1.0; SAS Institute, Cary, NC, USA). Descriptive statistics were computed as mean and standard deviation (mean ± SD). Welch's t-test was used to compare the mean scores of the men and women. Fisher's exact test was used to compare CDR. Multiple regression analysis was used to examine the association between serum sTREM2 levels, and MMSE and FAB, respectively. Multiple logistic regression analysis was used to examine the association between serum sTREM2 levels and CDR (0 and 0.5 or more). The dependent variables were MMSE, FAB, and CDR, respectively, and the independent variables were serum sTREM2 levels, age, sex, years of education, and serum hs-CRP levels. Statistical significance was set at $P<0.05$.

Results

A total of 95 older adults (25 men and 70 women) were included in the study. The mean ages of men and women were 78.24 ± 3.85 years and 77.96 ± 5.52 years, respectively. There was no significant difference in the serum sTREM2 levels between men (1,155.7 ± 1,284.1 pg/mL) and women (791.7 ± 634.7 pg/mL). There was no correlation between age and serum sTREM2 levels. For serum sTREM2 levels, when we identified outliers based on quantile range (default setting), no outliers were detected. Furthermore, no significant differences was seen between men and women in serum hs-CRP levels, years of education, and cognitive function assessments (Table 1). Serum hs-CRP levels that fell below the lower limit of measurement were replaced with the lower limit, and similarly those above the upper limit of measurement were replaced with the upper limit. To analyze the association between serum sTREM2 levels and cognitive function, we adjusted for age, sex, years of education, and serum hs-CRP levels. Multiple regression analysis showed that serum sTREM2 levels were not associated with MMSE scores (Table 2) but were negatively associated with FAB scores (Table 3). Additionally, multiple logistic regression analysis showed that serum sTREM2 levels were not associated with CDR scores (0 and 0.5 or more) (Table 4). A simple regression analysis between serum sTREM2 levels and each cognitive function is shown in Figure 1.

Discussion

In this study, we focused on the association between serum sTREM2 levels and cognitive function assessments in people ≥65 years. Serum sTREM2 levels were negatively associated with the FAB scores, with a statistically significant difference even after adjusting for age, sex, years of education, and serum hs-CRP levels. On the FAB, the six subtest scores range from 0 to 3. These scores add up to a maximum score of 18. Higher scores indicated better performance. Although previous studies have shown that CSF sTREM2 levels are higher in patients compared than in healthy controls[17–19], others have reported no difference between healthy controls and patients with AD or mild cognitive impairment[16]. Additionally, previous studies on sTREM2 levels in peripheral blood have also shown no difference between healthy controls and patients with AD[20]. Furthermore, we analyzed the correlation between serum sTREM2 levels and brain volume using voxel-based morphometry implemented with Statistical Parametric Mapping. However, there was no correlation between serum sTREM2 levels and age-related volume changes in regions

Table 1 Participant demographics

	Overall	Men	Women	*P*
N	95	25	70	
Age (years), mean ± SD	78.03 ± 5.12	78.24 ± 3.85	77.96 ± 5.52	0.781[a]
sTREM2 (pg/mL), mean ± SD	887.5 ± 861.8	1,155.7 ± 1,284.1	791.7 ± 634.7	0.185[a]
hs-CRP (ng/mL), mean ± SD	1,364.9 ± 1,341.3	1,350.6 ± 1,386.7	1,369.9 ± 1,334.9	0.952[a]
Education (years), mean ± SD	10.01 ± 1.90	10.56 ± 2.20	9.81 ± 1.76	0.135[a]
BMI (kg/m^2), mean ± SD	23.90 ± 3.51	23.84 ± 3.04	23.93 ± 3.68	0.903[a]
MMSE, mean ± SD	27.11 ± 2.99	26.84 ± 2.94	27.20 ± 3.02	0.605[a]
FAB, mean ± SD	13.71 ± 2.79	13.68 ± 3.08	13.71 ± 2.70	0.961[a]
CDR, *n* (%)				
0	86 (90.53)	22 (88.0)	64 (91.43)	
0.5	8 (8.42)	3 (12.0)	5 (7.14)	
1	1 (1.05)	0 (0)	1 (1.43)	
0.5 or more	9 (9.47)	3 (12.0)	6 (8.57)	0.694[b]

[a]Welch's t-test and [b]Fisher's exact test.

BMI: body mass index; CDR: Clinical Dementia Rating; FAB: Frontal Assessment Battery; hs-CRP: high-sensitivity C-reactive protein; MMSE: Mini-Mental State Examination; sTREM2, soluble triggering receptor expressed on myeloid cells 2.

Table 2 Multiple regression analysis with MMSE as the dependent variable

Independent variable	Estimate	SE	β	*P*
sTREM2	–0.001	0.0003	–0.156	0.110
Age, years	–0.218	0.056	–0.372	0.0002
Sex (women)	0.161	0.317	0.048	0.613
Education, years	0.291	0.157	0.185	0.068
hs-CRP	–0.0002	0.0002	–0.082	0.369

R^2=0.290.

MMSE: mini-mental state examination; SE: standard error; β: standardized partial regression coefficient; sTREM2: soluble triggering receptor expressed on myeloid cells 2; hs-CRP: high-sensitivity C-reactive protein.

Table 3 Multiple regression analysis with FAB as the dependent variable

Independent variable	Estimate	SE	β	*P*
sTREM2	–0.001	0.0003	–0.307	0.004
Age, years	–0.089	0.055	–0.164	0.106
Sex (women)	–0.086	0.312	–0.027	0.783
Education, years	0.243	0.155	0.166	0.120
hs-CRP	0.0001	0.0002	0.039	0.688

R^2=0.209.

FAB: frontal assessment battery; SE, standard error; β, standardized partial regression coefficient; sTREM2: soluble triggering receptor expressed on myeloid cells 2; hs-CRP: high-sensitivity C-reactive protein.

Table 4 Multiple logistic regression analysis with CDR (0 and 0.5 or more) as the dependent variable

Independent variable	OR	Lower 95% CI	Upper 95% CI	*P*
sTREM2	1.000	0.999	1.001	0.770
Age, years	1.237	1.007	1.520	0.043
Sex (women)	0.359	0.061	2.106	0.256
Education, years	0.702	0.384	1.282	0.250
hs-CRP	0.999	0.999	1.001	0.744

R^2=0.196.

The odds ratio is calculated with p being the probability that the CDR is 0.5 or more.

CDR: clinical dementia rating; 95% CI: 95% confidence interval; OR: odds ratio; sTREM2: soluble triggering receptor expressed on myeloid cells 2; hs-CRP: high-sensitivity C-reactive protein.

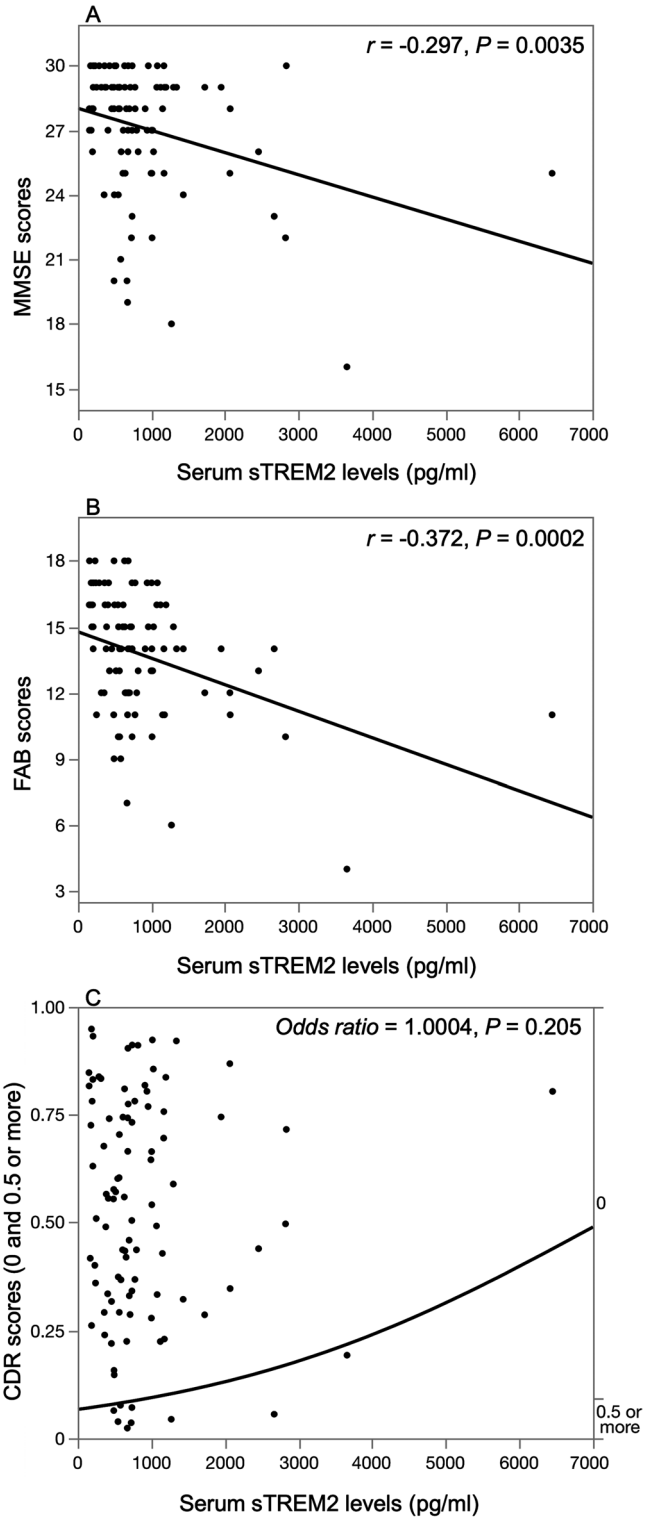

Figure 1 Simple regression analysis between serum sTREM2 levels and each cognitive function. In order, about (A) MMSE, (B) FAB, and (C) CDR.
sTREM2: soluble triggering receptor expressed on myeloid cells 2; MMSE: mini-mental state examination; FAB: frontal assessment battery; CDR: clinical dementia rating.

of the brain closely related to cognitive function[5]. From these studies, the association between sTREM2 and cognitive function seems inconsistent. However, a 10-year prospective follow-up study of approximately 1,300 community residents showed that high serum sTREM2 levels are associated with the development of dementia in the future[21]. Microglial activation in the frontal cortex has been reported

to predict cognitive decline in frontotemporal dementia[28]. The sTREM2 levels are thought to reflect the activation state of microglia. Our cross-sectional results are consistent with these findings. Additionally, the importance of sTREM2 as a blood biomarker for predicting dementia associated with diabetes has been revealed[29]. In the brains of patients with AD, TREM2 expression may have a protective effect at an early stage[30]. However, in the later stages, there may be pathogenic effects through the activation of the inflammatory response[31]. A meta-analysis showed that sTREM2 levels increase during the earlier course of AD development and are slightly attenuated at the dementia stage[20]. There may be differences in sTREM2 expression and its clinical relevance between healthy individuals and patients at early and late stages of AD. Although sTREM2 is thought to exert neuroprotective effects by improving the clearance effect of microglia[32], sTREM2 triggers the release of pro-inflammatory cytokines in microglia, which can adversely affect neuronal function[33]. Therefore, further studies based on disease stages and pathological features are needed to clarify the association between sTREM2 and the progression of AD. In this study, serum sTREM2 levels were negatively associated with the FAB scores. Our cross-sectional results may be novel and lead to future research, although it may be difficult to prove a causal relationship between serum sTREM2 levels and frontal lobe function in older adults. The prefrontal cortex is thought to be the cognitive center of the brain, in which humans understand abstract concepts such as language and numbers and are responsible for activities such as judgment, thinking, planning, behavior, and suppression of emotions. A functional test of the temporal lobe may not be sufficient to diagnose dementia, and a functional test of the frontal lobe may be necessary. In this study, we observed that serum sTREM2 levels were negatively associated with FAB scores, which assess frontal lobe function across cognitive functions. We believe that this contribution is novel. It may also be necessary to measure sTREM2 levels in the CSF and perform a similar analysis. The measurement of sTREM2 levels in the peripheral blood is minimally invasive, relatively easy, and may be applied clinically. Progress in research on the relationship between sTREM2 levels in peripheral blood and cognitive function may contribute to the prediction of cognitive function decline and early intervention for such high-risk individuals in the future.

This study had some limitations. As this was a cross-sectional study, the association between serum sTREM2 levels and FAB requires further analysis using longitudinal data. Moreover, compared with previous studies on serum sTREM2 levels[21], our sample size was smaller. The FAB is a simple and easy examination method that places minimal burden on participants, but it should be noted that it is difficult to evaluate frontal lobe function based on the FAB score alone. Details regarding activities and diets prior to the survey, and data on vascular risk factors such as hypertension, diabetes, and dyslipidemia were not obtained. In addition, older adults may often take various medications, including hormonal agents, to manage physical diseases. However, the details regarding these medications are unavailable. Therefore, the effects of these factors on sTREM2 levels could not be determined. Lifestyle influences, such as activities, diets, and social connections of older people may differ depending on rural or non-rural regions, and their effects on serum sTREM2 levels may also differ. Therefore, the current results may not be generalizable to non-rural regions.

Conclusion

In conclusion, we focused on the association between serum sTREM2 levels and cognitive function in older adults living in rural communities. We found that for people aged ≥65 years, serum sTREM2 levels were negatively associated with FAB scores. These results suggest that serum sTREM2 levels may be associated with frontal lobe function in adults aged ≥65 years.

Data availability statement: The data that support the findings of this study are available from the corresponding author (Yoshito Mizoguchi) but restrictions apply to the availability of these data, due to the restriction under the institutional ethical committee's policy and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the corresponding author (Yoshito Mizoguchi).

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Patient consent statement: Written informed consent was obtained from all participants prior to participation.

Author contributions: RO, YI, and YM designed this study and acquired the data. RO analyzed data. RO drafted and YM edited this manuscript.

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