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SHORT COMMUNICATION OPEN ACCESS

Serum sTREM2 Levels and Disability Progression in Patients With Primary Progressive Multiple Sclerosis

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ABSTRACT

Background: Triggering receptor expressed on myeloid cells 2 (TREM2) is a microglia surface receptor that aids in tissue repair and debris clearance. The soluble form, sTREM2, found in both blood and cerebrospinal fluid, is considered a biomarker for microglial activation. Based on the central role of microglia in MS pathogenesis, we aimed to investigate whether serum sTREM2 levels could predict disability progression in patients with primary progressive MS.

Methods: Serum levels of sTREM2 were measured at baseline using a single-molecule array assay in a multicenter cohort of 137 primary progressive multiple sclerosis (PPMS) patients. Univariable and multivariable linear models evaluated the association between sTREM2 levels and EDSS change at 2 years, 6 years, and last follow-up.

Nicolás Fissolo and Pascal Benkert have contributed equally to this article.

Results: While an association was observed at 2 years only in non-inflammatory PPMS patients, no consistent relationship was found between sTREM2 levels and disability progression over longer follow-up.
Conclusions: These findings suggest that serum sTREM2 may have limited value as a biomarker of disability progression in PPMS.

1 | Introduction

Triggering receptor expressed on myeloid cells 2 (TREM2) is a surface receptor expressed on microglia that facilitates the clearance of myelin debris and the removal of apoptotic cells, thereby supporting tissue repair and regeneration [1]. Blocking TREM2 aggravated experimental autoimmune encephalomyelitis [2], whereas TREM2 overexpression enhanced recovery [3]. TREM2 is also present in a soluble form (sTREM2), which can be detected in peripheral blood and cerebrospinal fluid (CSF) and may act as a negative regulator of membrane-bound TREM2 activity [1, 4]. CSF sTREM2 levels are considered a biomarker of microglial activation [5] and have been found to be elevated in patients with both relapsing and progressive forms of multiple sclerosis (MS) compared to neurological controls [4, 6]. Recently, CSF sTREM2 levels were found to correlate with EDSS scores [7] and to predict disease severity, as assessed by the MS Severity Score, in MS patients [8]. Considering the central role of microglia in MS pathogenesis, we aimed to investigate whether serum sTREM2 levels could predict disability progression in patients with primary progressive MS (PPMS).

2 | Methods

sTREM2 levels were determined in blood samples from a multicentric cohort of 137 patients with PPMS, which was part of a previously published study by our group [9]. The study was approved by the corresponding Hospital Ethics Committee. Table S1 summarizes the demographic and clinical information of the PPMS cohort.

Disability progression was evaluated at 2 years, 6 years, and at the time of the last visit, based on annualized changes in relevant EDSS units, as previously described [9]. Briefly, relevant changes in EDSS from baseline to the other three time points were defined as ≥ 1 unit for baseline EDSS < 6.0 and ≥ 0.5 unit for baseline EDSS ≥ 6.0. Changes crossing EDSS 6.0 were calculated as the sum of partial changes (e.g., EDSS 4.5 to 6.5 equals $1.5 + 1 = 2.5$ relevant units). Patients were classified into inflammatory and non-inflammatory according to clinical and MRI activity at baseline and during follow-up [9]. Briefly, PPMS patients were considered inflammatory if they had relapses within 3 months before sampling, contrast-enhancing lesions on baseline MRI (≤ 3 months from sampling), or new T2 or contrast-enhancing lesions on follow-up MRI. The presence of activity in any MRI was sufficient to classify the patient as inflammatory, whereas patients without radiological activity at baseline and during follow-up were classified as non-inflammatory.

Serum sTREM2 levels were measured using a commercially available immunoassay kit (cat#104542, Quanterix, Billerica, MA) run on the fully automated ultrasensitive Simoa HD-X Analyzer (Quanterix). Samples were run in duplicate in accordance with manufacturers' instructions with appropriate standards and internal controls. The intra-assay and inter-assay coefficients of variation were 5% and 3%, respectively.

Statistical analysis was performed as previously described [9]. Briefly, a linear regression model was used to identify factors associated with sTREM2 levels (dependent variable; log-transformed). Univariable and multivariable analyses (adjusted for age, sex and baseline EDSS) were conducted to evaluate the association between annualized EDSS change over the three different time intervals (dependent variable) and baseline sTREM2 levels. sTREM2 levels were log2-transformed; estimates therefore represent the additive effect on annualized EDSS change per doubling of sTREM2 levels. All analyses were performed using R version 4.3.1.

3 | Results

At baseline, median serum sTREM2 levels were 1058.9 pg/mL (IQR, 793.1–1403.2 pg/mL) (Table S1). In multivariable analysis, serum sTREM2 levels increased by 1.2% per year (estimate: 1.012; 95% CI: (1.004, 1.020); $p = 0.0040$). Gender, disease duration, and EDSS at baseline did not influence serum sTREM2 levels (Table S2).

Median follow-up time of PPMS patients was 9.1 (IQR, 7.2–13.0) years. Median EDSS scores at 2 years, 6 years, and at last visit were 4.5 (IQR, 3.5–6.0), 6.0 (IQR, 4.5–7.0), and 6.5 (IQR, 5.5–7.5) respectively. Nine (6.6%) PPMS patients received treatment during follow-up (Table S1). Serum sTREM2 levels were not associated with disability progression at 2 years, 6 years, or at the time of the last visit in either univariable or multivariable analyses, after adjustment for age, sex, and EDSS at baseline (Figure 1; Table S3). Excluding the 9 patients who received treatment during follow-up in a sensitivity analysis did not change the results (data not shown).

Sixty-two (41.9%) PPMS patients were classified as non-inflammatory, and baseline median serum sTREM2 levels were 1065.3 pg/mL (IQR, 809.7–1358.7 pg/mL) (Table S4). At 2 years, both univariable and multivariable analyses showed a significant association between serum sTREM2 levels and disability progression. A doubling of baseline serum sTREM2 levels was associated with an increase of 0.17 relevant EDSS units per year (estimate 0.17; 95% CI: (0.02, 0.31); $p = 0.023$) in the univariable analysis, and an increase of 0.18 relevant EDSS units per year (estimate 0.18; 95% CI: (0.02, 0.34); $p = 0.030$) in the multivariable analysis (Figure 2; Table S5). Similar to the entire cohort, in non-inflammatory PPMS patients, serum sTREM2 levels were not associated with disability progression at 6 years or at the time of the last visit (Figure 2; Table S5).

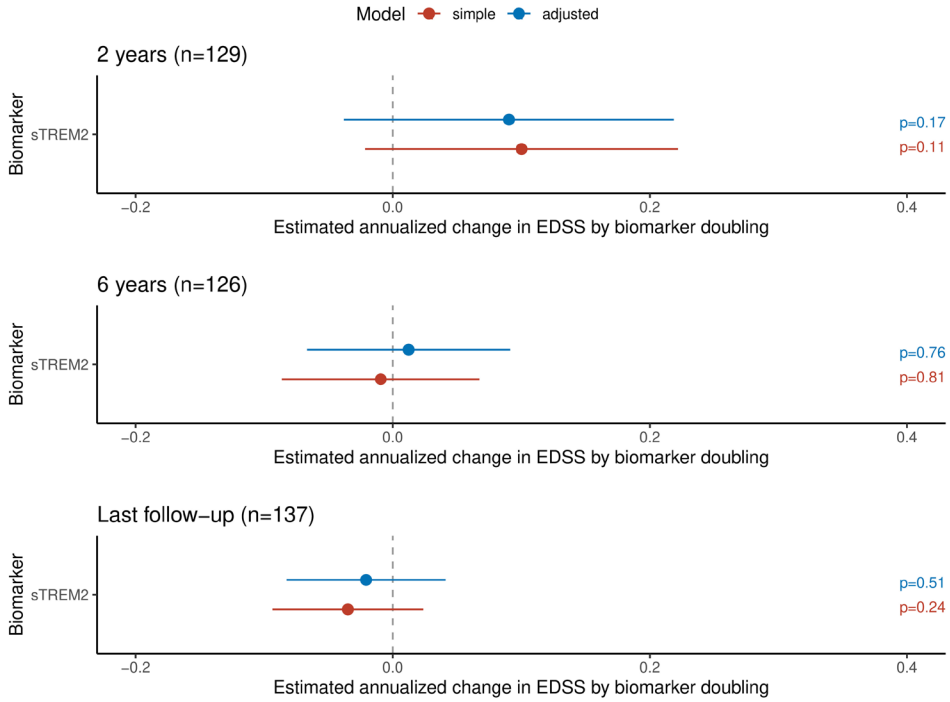

FIGURE 1 | Association between serum sTREM2 levels and disability progression in PPMS patients. Forest plots show the marginal effects per doubling of sTREM2 concentration on disability progression, expressed as the annualized change in EDSS between baseline and three time points: 2 years, 6 years, and the time of the last visit. The graphs display mean effects with 95% confidence intervals from univariable ("simple") and multivariable ("adjusted") models after adjusting for age, sex, and baseline EDSS. EDSS: Expanded Disability Status Scale. sTREM2: Soluble triggering receptor expressed on myeloid cells 2.

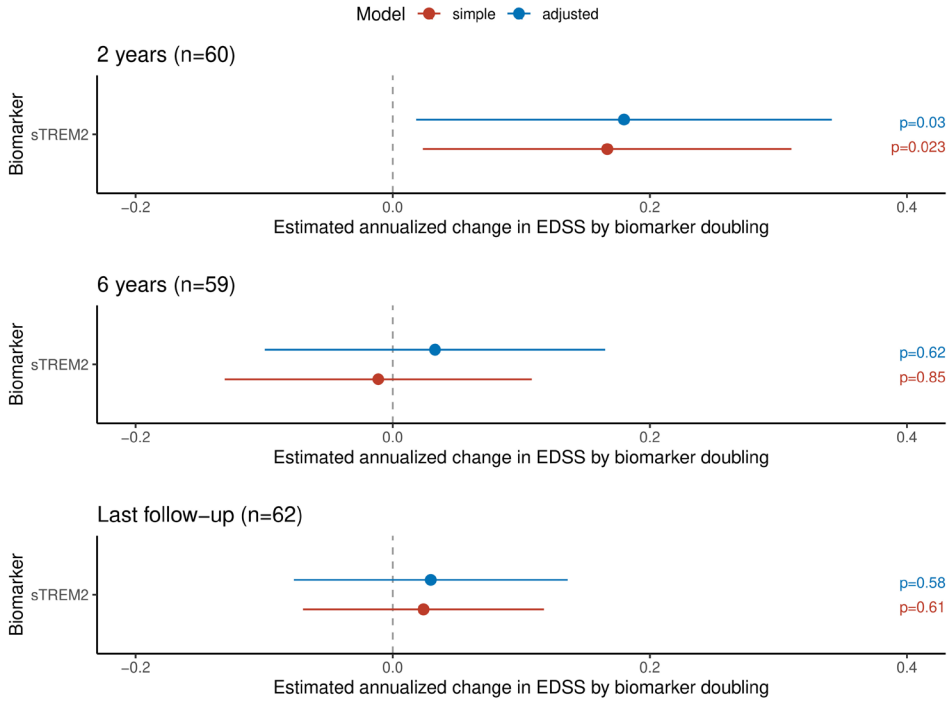

FIGURE 2 | Association between serum sTREM2 levels and disability progression in non-inflammatory PPMS patients. Forest plots show the marginal effects per doubling of sTREM2 concentration on disability progression, expressed as the annualized change in EDSS between baseline and three time points: 2 years, 6 years, and the time of the last visit. The graphs display mean effects with 95% confidence intervals from univariable ("simple") and multivariable ("adjusted") models after adjusting for age, sex, and baseline EDSS. EDSS: Expanded Disability Status Scale. sTREM2: Soluble triggering receptor expressed on myeloid cells 2.

4 | Discussion

In a previous study conducted by our group [9], serum levels of neurofilament light chain, glial fibrillary acidic protein, and chitinase 3-like 1 (CHI3L1) were found to be associated with disability progression in a cohort of 141 PPMS patients. Interestingly, in non-inflammatory PPMS patients, only CHI3L1, a biomarker of microglial activation [10], remained significantly associated with disability progression. In the present study, we explored whether sTREM2, which is also considered a biomarker of microglial activation [5], was measured in 137 of the 141 PPMS patients from the original cohort [9]. Except for the finding of a significant association of serum sTREM2 levels with disability progression at 2 years in the non-inflammatory cohort, serum sTREM2 levels were generally not associated with disability progression in PPMS patients.

TREM2 can be expressed by a wide variety of cell types [1], and similar to CHI3L1, serum sTREM2 levels may reflect multiple cellular sources beyond microglia. Although serum CHI3L1 levels were associated with disability progression in the entire PPMS cohort and in non-inflammatory patients, serum sTREM2 levels do not appear to show a similar pattern. The association found between serum sTREM2 levels and disability progression at 2 years, restricted to the non-inflammatory group, may suggest that sTREM2 levels specifically reflect the neurodegenerative component associated with disability progression, and that this effect may be diluted when more inflammatory patients are included. However, this short-term predictive value in non-inflammatory PPMS patients was lost with longer follow-up.

It should be emphasized that studies in large cohorts correlating sTREM2 levels in blood and CSF are lacking, and it cannot be ruled out that CSF sTREM2 levels may be associated with disability progression in patients with PPMS. In this context, a previous study in a small patient cohort found no correlation between serum and CSF sTREM2 levels, and differences between MS patients and controls with non-inflammatory neurological diseases were observed only in the CSF, not in the blood [4].

In conclusion, these findings indicate that serum sTREM2 is unlikely to serve as a reliable biomarker of disability progression in PPMS.

Author Contributions

Nicolás Fissolo and Pascal Benkert: conceptualization, investigation, formal analysis, writing – review and editing. Andreu Vilaseca-Jolonch, Yolanda Blanco, Harald Hegen, Klaus Berek, Francisco Pérez-Miralles, Konrad Rejdak, Luisa M Villar, Enric Monreal, Roberto Alvarez-Lafuente, Franziska Bachhuber, Hayrettin Tumani, Sergio Martínez-Yelamos, Antonio J Sánchez-López, Antonio García-Merino, Tamara Castillo-Triviño, Jan Lycke, Igal Rosenstein, Nieves Téllez, Roberto Furlan, Jan D. Lünemann, Michael Khalil, Jens Kuhle: investigation, writing – review and editing. Lucía Gutiérrez: investigation, formal analysis. Xavier Montalban: conceptualization, investigation, writing – review and editing, supervision. Manuel Comabella: conceptualization, investigation, formal analysis, writing – original draft, supervision.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1.**