Quantitative myelin imaging is associated with Eomesodermin-expressing CD4+ Th cells in secondary progressive multiple sclerosis

Theodoros Ladopoulos[1,2] , Zainab Abbas[1] , Marleen Münnig[1], Paulina Trendelenburg[1], Emelie Schönauer[1], Marielena Bongert[1], Britta Krieger[2], Barbara Bellenberg[2], Simon Faissner[1], Carsten Lukas[2], Ralf Gold[1] , Ruth Schneider[1,2*]

1 Department of Neurology, St. Josef Hospital, Ruhr-University Bochum, Bochum, Germany

2 Institute for Neuroradiology, St. Josef Hospital, Ruhr-University Bochum, Bochum, Germany

Introduction

A great proportion of patients with relapsing remitting multiple sclerosis (RRMS) transitions to the secondary progressive (SPMS) form, which is accompanied by continuous deterioration of disease-related physical and cognitive disability (1). The pathophysiology of SPMS involves both inflammatory and neurodegenerative components, but remains incompletely understood. The lack of validated biomarkers leads to delayed, mainly retrospective diagnosis. Recent studies demonstrated crucial involvement of Eomesodermin expressing(Eomes+) CD4+ Th cells in the pathogenesis of SPMS. Increased levels of these cells were detected in SPMS patients with disability progression and predicted disease worsening with high accuracy(2). However, it remains to be deciphered if increased levels of Eomes+ CD4+ Th cells are associated with pathophysiological hallmarks in MS, such as brain demyelination and atrophy.

Objectives and Aims

To investigate possible associations between Eomes+ CD4+ Th cells with brain demyelination and atrophy in patients with RRMS and SPMS, using a time-efficient quantitative MRI sequence for myelin imaging and brain volumetry.

Methods

SyMRI using a multiecho, saturation recovery pulse sequence (QRAPMASTER), provides automatic brain tissue and myelin volumetry based on R1 and R2 relaxation rates and proton density quantification (3). 30 RRMS and 42 SPMS patients received QRAPMASTER on a 1.5 Tesla MRI scanner. Myelin and brain volumes as fractions (%) of intracranial volume (Myelin volume fraction: MVF, brain parenchymal fraction: BPF) were estimated. Peripheral blood mononuclear cells (PBMCs) were isolated and proportions of Eomes+Th-cells were analyzed using flow cytometry (BD FACS-Canto TMII). ANOVA and Mann-Whitney u test were used for parametric and non parametric group comparisons. Spearman‘s correlation method was used for the correlation analysis.

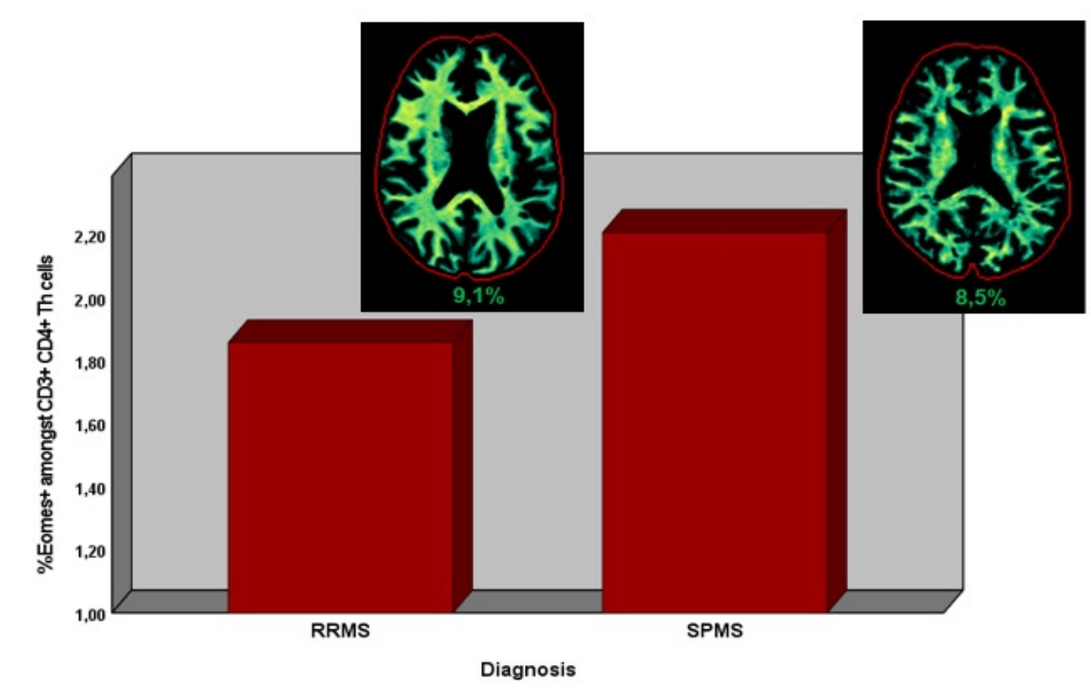

Figure 1. Bar charts depicting proportions of Eomes+ CD4+ T-cells amongst CD3+ CD4+ Th cells in RRMS and SPMS patients. Representative myelin maps and mean intracranial MVFs (%) of RRMS and SPMS patients are shown next to the charts.

Results

Age and disease duration significantly differed between the relapsing and the progressive group. In SPMS intracranial MVF and BPF (mean values, SDs) were significantly ($p<0,001$) lower compared to RMS. Frequencies of Eomes+Th-cells (median values, IQRs) were significantly ($p<0,001$) increased in SPMS compared to RMS. The proportion of Eomes+Th-cells amongst CD3+ CD4+ Th cells correlated with intracranial MVF and with BPF in SPMS patients (age as covariate, Spearman’s correlation, $p<0.001$). No associations between Eomesodermin expressing CD4+ cells and MRI measures were observed in the RRMS group.

	RRMS	SPMS
N (%female)	30 (60)	42 (62)
Age (years, mean, SD)	43 (31-55)	55 (46-64) *
Disease duration (years, mean, SD)	12 (3-21)	23 (14-32) *
MVF (%, mean, SD)	9.1 (8.3-9.9)	8.5 (7.1-9.9) *
BPF (%, mean, SD)	80 (74.5-85.5)	75 (70.4-79.6) *
Eomes+ amongst CD3+ CD4+ (median, IQR)	1.85 (0.96-2.82)	2.21 (1.29-3.25) *

Table 1. Demographics and group comparisons. *significant differences with a $p<0.05$.

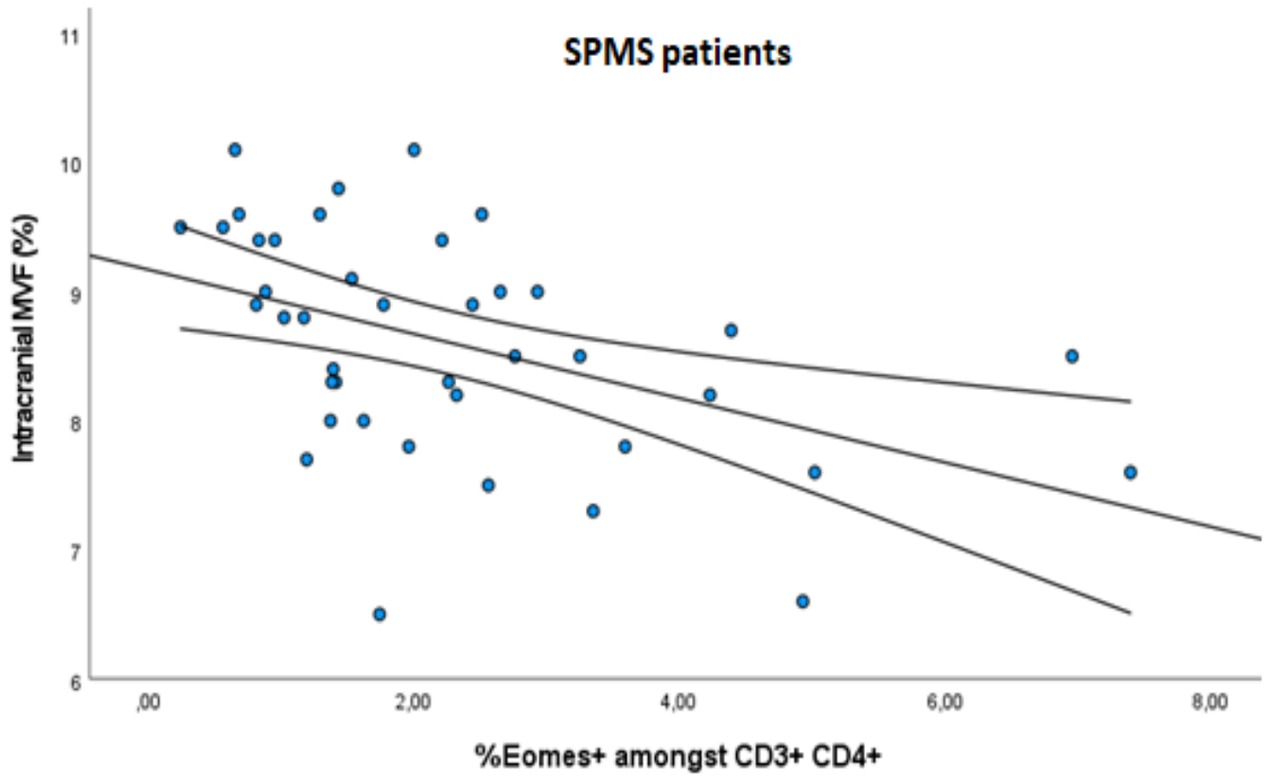

Figure 2. Scatterplot of the association between intracranial MVF and proportion of eomesodermin expressing cells among CD4+ T-cells in SPMS patients.

Conclusions

Confirming recent literature, Eomes+Th-cells were increased in patients with SPMS compared to RMS. Quantitative synthetic MRI revealed lower myelin and total brain volume fractions in SPMS compared to RRMS. Intriguingly, a correlation of MVF with Eomes+Th-cells could be demonstrated only in SPMS. It could be hypothesized that Eomes+Th-cells mediated processes might be in part associated with the extent of myelin loss in SPMS.

Disclosures Theodoros Ladopoulos: has received research scientific grant support from Novartis Pharma. Zainab Abbas: nothing to disclose. Marleen Münnig: nothing to disclose. Paulina Trendelenburg: nothing to disclose. Emelie Schönauer: nothing to disclose. Marielena Bongert: nothing to disclose. Britta Krieger: nothing to disclose. Barbara Bellenberg: nothing to disclose. Simon Faissner: has received speaker’s and/or scientific board honoraria and/or congress travel support from Biogen, BMS, Celgene, Genesis Pharma, Janssen, Merck, Novartis and Roche and grant support from Ruhr-University Bochum, DMSG, Stiftung für therapeutische Forschung, Lead Discovery Center GmbH and Novartis; none related to this manuscript. Carsten Lukas: received a research grant by the German Federal Ministry for Education and Research, BMBF, German Competence Network Multiple Sclerosis (KKNMS), grant no.01GI1601I, has received consulting and speaker’s honoraria from Biogen Idec, Bayer Schering, Daiichi Sanykyo, Merck Serono, Novartis, Sanofi, Genzyme and TEVA. Ralf Gold: has received compensation for serving as a consultant or speaker from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis, and Teva Neuroscience; he, or the institution he works for, has received research support from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis and Teva Neuroscience; he has also received honoraria as a Journal Editor from SAGE and Thieme Verlag. Ruth Schneider: has received speaker’s honoraria from Biogen Idec GmbH, Alexion Pharma, Novartis Pharma and Roche Pharma AG, congress travel support from Merck, Biogen Idec GmbH and has received research scientific grant support from Novartis Pharma

***Corresponding Author:**
Ruth.Schneider@rub.de
Department of Neurology, NiRiMS Research group, St. Josef Hospital, Ruhr University Bochum, Germany

References

1. Tedeholm H et al. Effectiveness of first generation disease-modifying therapy to prevent conversion to secondary progressive multiple sclerosis. Mult Scler Relat Disord. 2022 Oct 5;68:104220.
2. Raveney BJE et al. Involvement of cytotoxic Eomes-expressing CD4+ T cells in secondary progressive multiple sclerosis. Proc Natl Acad Sci U S A. 2021 Mar 16;118(11):e2021818118.
3. Ouellette R et al. Validation of Rapid Magnetic Resonance Myelin Imaging in Multiple Sclerosis. Ann Neurol. 2020 May;87(5):710-724.