J Neurol (2017) 264:139–151
DOI 10.1007/s00415-016-8333-7

ORIGINAL COMMUNICATION

Myelin-oligodendrocyte-glycoprotein (MOG) autoantibodies as potential markers of severe optic neuritis and subclinical retinal axonal degeneration

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Received: 22 July 2016 / Revised: 2 November 2016 / Accepted: 3 November 2016 / Published online: 14 November 2016

Abstract Antibodies against conformation-dependent epitopes of myelin-oligodendrocyte-glycoprotein (MOG-abs) are present in subgroups of neuromyelitis optica spectrum disorder (NMOSD), recurrent optic neuritis (rON), multiple sclerosis (MS), and anti-NMDAR encephalitis. Using optical coherence tomography (OCT) we assessed whether MOG-abs might serve as potential marker of retinal axonal degeneration. We investigated a clinically heterogeneous cohort of 13 MOG-abs-positive patients (4 MOG-abs-positive rON, 4 MOG-abs-positive adult MS, 3 MOG-abs-positive relapsing encephalomyelitis, 2 MOG-abs-positive aquaporin-4-abs-negative NMOSD). As controls, we studied 13 age, sex and ON episode(s)-matched MOG-abs and aquaporin-4-abs-negative (AQP4-abs-negative) MS patients and 13 healthy controls (HC). In addition, we investigated 19 unmatched AQP4-abs-positive MOG-abs-negative NMOSD subjects. Considering all eyes, global pRNFL [in µm, mean (SD)] was significantly reduced in MOG-abs-positive patients [72.56 (22.71)] compared to MOG-abs-negative MS [80.81 (13.55), $p = 0.0128$], HCs [103.54 (8.529), $p = 0.0014$] and NMOSD [88.32 (18.43), $p = 0.0353$]. Non ON eyes from MOG-abs-positive subjects showed significant subclinical atrophy of temporal pRNFL quadrants. Microcystic macular edema (MME) was observed only in eyes of MOG-abs-positive (24%) and AQP4-abs-positive NMOSD (5.6%), but not in MOG-abs-negative MS or HC ($p < 0.01$). MOG-abs may serve as potential marker of retinal degeneration. Specifically, MOG-abs-related OCT features predominate in temporal pRNFL quadrants (resembling the MS retinal pattern), might be more severe than AQP4-abs-positive NMOSD, indicate subclinical pathology, and may be associated with MME.

Keywords Myelin-oligodendrocyte-glycoprotein · Neuromyelitis optica spectrum disorder · Multiple sclerosis · Optical coherence tomography · Microcystic macular edema

Introduction

Antibodies against conformation-dependent epitopes of myelin-oligodendrocyte-glycoprotein (MOG-abs) have been described in several autoimmune CNS diseases with partly overlapping clinical features. MOG-abs can be found in bilateral recurrent optic neuritis (rON), Aquaporin-4-abs-negative neuromyelitis optica spectrum disease (NMOSD), childhood multiple sclerosis (MS) and, rarely, anti-NMDA-receptor encephalitis [1]. Additionally, MOG is an emerging confirmed antibody target in a small subgroup of adult MS patients and MOG-abs have been detected in single patients with neuropathological MS pattern II more recently [1–5]. Due to the bouquet of diseases associated with MOG-abs, it is tempting to speculate

Electronic supplementary material The online version of this article (doi:10.1007/s00415-016-8333-7) contains supplementary material, which is available to authorized users.

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that MOG-abs-associated CNS disease might be a distinct entity, tentatively called MOG-antibody-associated encephalomyelitis, MOG-antibody-associated demyelination or AQP4-abs-negative MOG-abs-positive NMOSD [1]. The clinical features in all cases seem to overlap with MS and NMOSD, but the pathogenetic relevance of the MOG-abs remains still unclear [1].

In some animal models, immunization with MOG causes features of experimental autoimmune encephalitis with dominant optic nerve and spinal cord involvement. Therefore, an association between ON and MOG-abs can be suggested [6, 7]. ON is characterized by visual loss and pain with eye movement due to inflammation of the optic nerve and can be observed in different neuroimmunological diseases. MS associated ON (MS-ON) has been intensively investigated by optical coherence tomography (OCT) in recent years [8]. This technique played a crucial role in analyzing retinal changes and proved to be a precise and reproducible method for noninvasive visualization of axons of the CNS. Whereas in OCT studies of MS mostly temporal pRNFL quadrants were affected after ON episodes, OCT studies of AQP-4-abs-positive NMOSD demonstrated retinal axonal loss in all pRNFL quadrants after ON episodes [9]. Additionally, subclinical retinal atrophy has been reported in MS and, to a lesser extent, in NMOSD [8, 9]. Therefore, OCT might be helpful for differentiating between ON types of different etiology [8, 10, 11]. Unilateral ON [12–15] and maybe more specifically, bilateral rON [14] can occur in patients with MOG-abs, but in contrast to MS and AQP4-abs-positive NMOSD [9, 16], characteristic OCT phenotype patterns have not been clearly described in MOG-abs-positive CNS disease.

Here we used OCT to evaluate MOG-abs as a potential marker of clinical and subclinical retinal axonal degeneration in a clinically heterogeneous group of MOG-abs-positive patients.

Materials and methods

Study populations

Patients were seen and followed up at two university hospitals specialized in neuroimmunological diseases (The Institute of Clinical Neuroimmunology, LMU, Munich, Germany and the University Hospital of Lille, Lille, France). During the study period (2013–2015) all patients tested positive for MOG-abs were included. Three groups of patients were evaluated: group (1), 13 MOG-abs-positive patients (4 MOG-abs-positive rON, 4 MOG-abs-positive adult MS (patients described in [2]), 3 MOG-abs-positive relapsing encephalomyelitis (partly described in [3]), 2 AQP4-abs-negative MOG-abs-positive NMOSD); group (2), 13 relapsing remitting MS (RRMS) patients (without MOG-abs and AQP4-abs) strictly matched to group (1) according to age, sex and number of ON episodes (Table 1) [17]; and group (3), 19 unmatched AQP4-abs-positive MOG-abs-negative NMOSD patients. Additionally, we analyzed 13 healthy controls (HC, group 4) matched to group (1) according to age and sex. We collected demographics (gender, age) and clinical data (disease duration, number and side of clinical ON episodes, duration since last ON episode). Subjects with concomitant potentially OCT-confounding diseases (glaucoma, diabetes mellitus, retinal surgery, retinal disease, ametropia >6 diopters), or with a recent relapse (ON <6 months) were excluded. Evaluation criteria for this study were retinal thickness/volume, presence of microcystic macular edema (MME), and visual disability measured by high contrast visual acuity (VA).

Detection of antibodies to MOG and AQP4

For detection of abs to MOG, serum samples from all patients were analyzed by a cell-based flow cytometric assay as previously described [2, 3, 18, 19]. HeLa cells were transiently transfected with human full-length MOG fused C-terminally to EGFP-N1 (CLONTECH Laboratories, Mountain View, CA) or with EGFP alone (control cells). For the determination of anti-MOG IgG, 50,000 unfixed live cells were incubated 24 h after transfection with a 1:50 dilution of the serum sample for 45 min at 4 °C. As secondary reagents a 1:500 dilution of a biotin-SP-conjugated goat anti-human IgG (Jackson ImmunoResearch, West Grove, PA, USA) and a 1:2000 dilution of Alexa Fluor® 647-conjugated Streptavidin (Jackson ImmunoResearch, West Grove, PA, USA) were applied. For the determination of anti-MOG reactivity we gated on cells with a FITC-fluorescence intensity above 500 (details and picture in [19]) and determined their mean channel fluorescence intensity (MFI) in the allophycocyanin channel. Then we calculated the MFI ratio between MOG-EGFP-transfected cells and cells transfected with EGFP alone. Sera that scored positive for anti-MOG IgG were also analyzed for the presence of anti-MOG IgM using allophycocyanin-labeled anti-human IgM (Clone: SA-DA4, eBioscience San Diego, CA). Diagnosis and clinical data were unknown to the testing person. The threshold for MOG reactivity was set to the mean plus 3 SDs (MFI ratio 2.27) of 39 adult healthy controls as described before [3]. All MOG-abs-positive patients showed a MFI ratio over 2.27 (Suppl. Fig.). One of the 13 MOG-abs-positive patients was tested positive with commercial standard cell-based immunofluorescence

Table 1 Description of study participants

Variables	MOG-abs-positive ($n = 13$)	MOG-abs-negative RRMS ($n = 13$)	MOG-abs-negative, AQP4-abs-positive NMOSD ($n = 19$)	HC ($n = 13$)
Age, mean (SD)	41.38 (14.03)	39.85 (12.5)	48.32 (8.94)	41.46 (13.81)
Females, *n* (%)	6 (46.2)	6 (46.2)	15 (78.9)	6 (46.2)
Disease duration (in months), mean (SD)	97.77 (80.79)	140.77 (96.51)	63.16 (52.33)	–
EDSS score, median (min–max)	2.5 (0–5)	2 (0–6.5)	3.5 (1–7)	–
No unilateral ON episode, *n* (%)	10 (76.93)	10 (76.93)	14 (73.69)	–
No bilateral ON episode, *n* (%)	3 (23.07)	3 (23.07)	5 (26.31)	–
Positive AQP-4-Ab, *n* (%)	0 (0)	0 (0)	19 (100)	–
Positive MOG-Ab, *n* (%)	13 (100)	0 (0)	0 (0)	–
Analysis using eyes, *N*	25	26	38	26
No ON episode, *n* (%)	12 (48)	13 (50)	23 (60.5)	–
More than one ON episode, *n* (%)	6 (24)	5 (19.2)	3 (7.9)	–
Number of ON episode [all eyes; mean (SD)]	0.92 (1.11)	0.81 (1.02)	0.53 (0.79)	
Number of ON episode [ON eyes; mean (SD)]	1.77 (0.92)	1.61 (0.87)	1.33 (0.72)	
Time (in months) since last ON episode, mean (SD)	60.00 (72.38)	101.85 (69.14)	63.00 (31.14)	–
Median (range)	21 (6;242)	90 (6–228)	79 (6–96)	–

HC healthy controls, *MOG*-abs-positive: myelin-oligodendrocyte-glycoprotein antibody positive patients, *MOG-abs-negative* myelin-oligodendrocyte-glycoprotein antibody negative patients, *RRMS* relapsing remitting multiple sclerosis, *NMOSD* neuromyelitis optica spectrum disorder, *EDSS* Expanded Disability Status Scale, *AQP-4-Ab* aquaporin-4-antibody, *ON* optic neuritis

technique prior plasmapheresis (MOG IFT, EUROIMMUN, Laboratory Stöcker, Germany, Suppl. Fig.). After plasmapheresis we noted disappearance of the anti-MOG response in our MOG assay as well as in the MOG IFT (EUROIMMUN) assay. However, it is known, that the anti-MOG reactivity is fluctuating with disappearances and reappearances over time and the correlation with clinical disease activity is inconsistent [2]. AQP4-abs testing was performed with commercial standard cell-based Anti-Aquaporin-4-IIFT assay (e.g., EUROIMMUN, Germany [20].

Optical coherence tomography

OCT examination was performed using a SD-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) at both centers. The OCT protocol included a peripapillary ring scan for measuring peripapillary RNFL (pRNFL; 12°, 3.4 mm circular scan around the optic nerve with a minimum of 50 automatic real time (ART), respecting (OSCAR-IB) criteria [21], and a macular scan consisting of 25 vertical scans centered on the fovea. Studied OCT parameters were global pRNFL, temporal (T) pRNFL, nasal (N) pRNFL, temporo-superior (TS) pRNFL, temporo-inferior (TI) pRNFL, naso-superior (NS) pRNFL, naso-inferior (NI) pRNFL, nasal/temporal (N/T) pRNFL ratio, total macular volume (TMV) and all intra-retinal layer volumes obtained with macular segmentation. In Fig. 1 exemplary peripapillary and macular scans in a patient with MOG associated bilateral severe ON are shown.

Intra-retinal layer segmentation

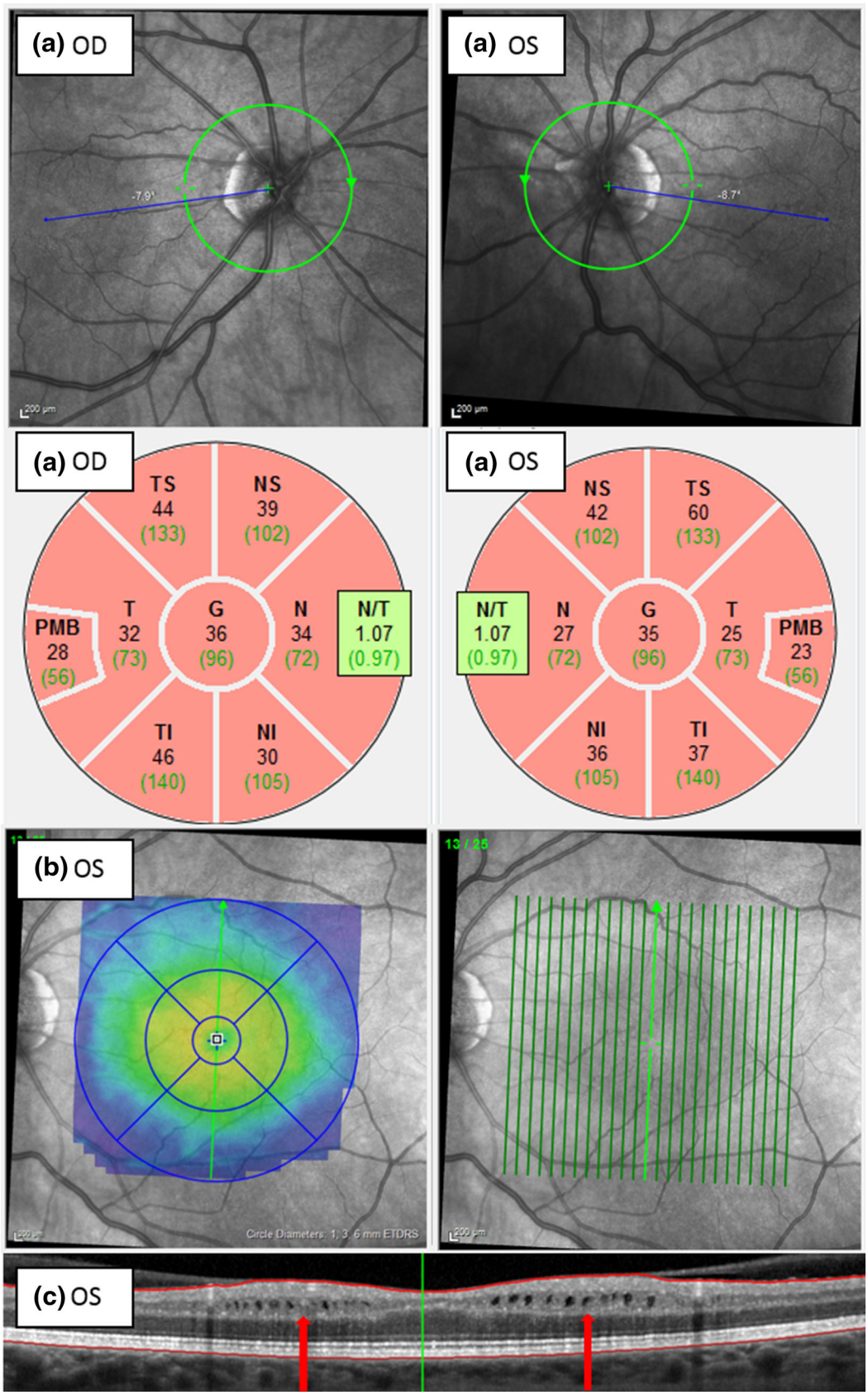
Macular segmentation was performed with Spectralis Viewing Module V. 6.0.9.0 provided by Heidelberg Engineering (Fig. 1). As already described [22], the mean volume within perifoveal rim [Early Treatment Diabetic Retinopathy Study (ETDRS) 3 mm] was calculated for the macular RNFL (mRNFL), mGCL (macular ganglion cells layer), mIPL (macular inner plexiform layer), mINL (macular inner nuclear layer), mOPL (macular outer plexiform layer) and mONL (macular outer nuclear layer). MME was defined as the presence of cystic lesions on at least one scan. We defined mRNFL, mGCL and mIPL as inner retinal layers.

Visual function testing

In a well-lit room, we monocularly evaluated high contrast visual acuity (VA) of both eyes (Snellen scale).

Clinical parameters

All patients had been seen at the respective center, clinical data collected and all patients neurologically examined at


(a) OD
(a) OS
(a) OD
TS 44 (133)
NS 39 (102)
T 32 (73)
G 36 (96)
N 34 (72)
N/T 1.07 (0.97)
PMB 28 (56)
TI 46 (140)
NI 30 (105)
(a) OS
NS 42 (102)
TS 60 (133)
N/T 1.07 (0.97)
N 27 (72)
G 35 (96)
T 25 (73)
PMB 23 (56)
NI 36 (105)
TI 37 (140)
(b) OS
Circle Diameters: 1, 3, 6 mm ETDRS
(c) OS

◀**Fig. 1** Peripapillary and macular scans in a patient with MOG associated bilateral severe optic neuritis (ON); **a** *left* (oculus sinister, OS) and *right* (oculus dexter, OD) peripapillary optical coherence tomography (OCT) scan showing severe peripapillary retinal nerve fiber layer (pRNFL) atrophy in terms of global value and all quadrants; **b** *left* macular OCT scan with *25 vertical lines*, calculation of macular volume was made according to the ETDRS 3 mm perifoveal rim; **c** microcystic macular edema (MME) located in inner nuclear layer (INL)

the time of the OCT examination. Clinical disability was evaluated by the Expanded Disability Status Scale (EDSS).

Statistical analysis

Clinical features and OCT results were evaluated in all patients and HC. Data descriptions report both mean and standard deviation for continuous parameters or frequency and proportion for categorical variables. For comparison of OCT measures between subpopulations, HC were matched to MOG-abs-positive patients according to age and gender, and MS patients were matched to MOG-abs-positive patients according to age, gender and the number of ON episode(s). Owing to the scarcity of MOG-abs-positive patients, it was not possible to match NMOSD patients to MOG-abs-positive patients.

To consider within-patient inter-eye correlation, we used generalized estimation equation models (GEEs) in which the correlation matrix parameter was set to 'exchangeable'. In these models, OCT measures were the dependent variables while patient's disease status was the (main) independent variable. Furthermore, in adjusted GEE analyses, the following additional independent variables were added: gender, age, disease duration, as well as ON episode (multiple ON episodes/1 ON <12 months ago/1 ON ≥12 months ago). MME frequencies in MOG-abs-positive patients vs. other groups were compared using Fisher's exact test. Statistical significance was achieved at $p < 0.05$. In this observational study, we acknowledge an increased risk of type I (alpha) error due to multiple testing. All analyses should be interpreted as constituting exploratory data analyses. In consideration of Bonferroni correction for multiple testing, statistical significance was achieved at $p < 0.001$. Data were analyzed with SAS version 9.3 (SAS institute, Cary, NC, USA) by a statistician.

Results

Clinical characteristics of patients and HC

Clinical characteristics of all patients and HC are summarized in Table 1. Differences in gender distribution and age between MOG-abs-positive and NMOSD patients were not statistically significant ($p = 0.072$ and $p = 0.097$, respectively). One eye of a MOG-abs-positive patient was excluded because of a past history of retinal detachment.

MOG-abs-positive eyes vs. matched HC eyes

Considering all eyes together (Table 2), global pRNFL, all temporal pRNFL quadrants (TI/T/TS), mRNFL, mGCL, and mIPL were significantly reduced in MOG-abs-positive eyes compared to HC. Considering ON eyes (Table 3), all pRNFL parameters (except N/T RNFL ratio), TMV, mRNFL, mGCL and mIPL were significantly reduced in MOG-abs-positive eyes, whereas mINL and mONL were significantly thickened. Considering NON eyes (Table 4), global pRNFL, all temporal quadrants (TI/T/TS), TMV, mRNFL, mGCL and mIPL were also significantly reduced in MOG-abs-positive eyes.

MOG-abs-positive eyes vs. matched MOG-abs-negative RRMS eyes

Considering all eyes together (Table 2), global pRNFL, TI/TS/NS pRNFL and mRNFL were significantly reduced and mINL significantly thickened in MOG-abs-positive eyes. Considering ON eyes (Table 3), TI/TS pRNFL and mRNFL were significantly reduced in MOG-abs-positive eyes. Considering NON eyes (Table 4), TI/NS pRNFL and N/T pRNFL ratios were also significantly reduced in MOG-abs-positive eyes. Interestingly, subgroup analysis between the four MOG-abs-positive MS patients (group 1) and matched MOG-abs-negative MS patients (group 2) yielded a more pronounced retinal atrophy in MOG-abs-positive MS than in classical MOG-abs-negative MS (all eyes or ON eyes or NON eyes; Table 5).

MOG-abs-positive eyes vs. unmatched AQP4-abs-positive MOG-abs-negative NMOSD eyes

Considering all eyes together (Table 2), all pRNFL values (except N/T pRNFL ratio) and all inner retinal layers were lower in MOG-abs-positive eyes, but only global pRNFL, TI/TS pRNFL quadrants and mRNFL were significantly reduced in MOG-abs-positive eyes. Only a trend towards significance was observed for temporal pRNFL. Considering ON eyes (Table 3), global pRNFL, T/TS/NS/N pRNFL, and mRNFL were significantly reduced in MOG-abs-positive eyes. Considering NON eyes (Table 4), TI/T pRNFL quadrants, mRFNL, mGCL and mIPL were significantly reduced in MOG-abs-positive eyes.

In Fig. 2, we illustrated results concerning the global pRNFL thickness in ON and NON eyes according to each diseases' group and in HC. Within ON eyes, global pRNFL

Table 2 Comparison of OCT measures and visual acuity after matching eyes using gender and age

Number of eyes	MOG-abs-positive ($N = 25$)	HC ($N = 26$)	p value MOG-abs-positive vs. HC	MOG-abs-negative RRMS ($N = 26$)	p value MOG-abs-positive vs. MOG-abs-negative RRMS	MOG-abs-negative, AQP4-abs-positive NMOSD ($N = 38$)	p value MOG-abs-positive vs. MOG-abs-negative, AQP4-abs-positive NMOSD
Parameters	Mean ± SD	Mean ± SD	Adj. GEE	Mean ± SD	Adj. GEE	Mean ± SD	Adj. GEE
pRNFL_G	72.560 ± 22.714	103.538 ± 8.529	**0.0014**	80.808 ± 13.553	**0.0128**	88.316 ± 18.429	**0.0353**
pRNFL_TI	104.800 ± 38.607	152.269 ± 15.881	**0.0021**	120.500 ± 20.745	**0.0107**	130.921 ± 30.284	**0.0307**
pRNFL_T	48.920 ± 18.039	75.077 ± 9.465	**0.0002**	51.269 ± 13.334	0.3895	61.737 ± 14.130	0.0950[#]
pRNFL_TS	97.400 ± 30.965	137.731 ± 16.496	**0.0008**	112.308 ± 19.495	**0.0060**	122.474 ± 29.707	**0.0157**
pRNFL_NS	80.960 ± 26.984	112.385 ± 26.341	0.0565[#]	93.269 ± 24.502	**0.0031**	91.289 ± 20.500	0.6863
pRNFL_N	58.640 ± 19.866	81.269 ± 15.473	0.0550[#]	63.923 ± 15.902	0.1582	70.816 ± 19.193	0.2956
pRNFL_NI	83.040 ± 29.889	114.500 ± 26.861	0.3149	90.538 ± 19.574	0.2066	97.000 ± 28.487	0.2902
pRNFL_ratio	1.257 ± 0.347	1.155 ± 0.278	0.1670	1.308 ± 0.355	0.8216	1.161 ± 0.306	0.5521
TMV	2.048 ± 0.107	2.168 ± 0.071	0.1210	2.020 ± 0.127	0.3379	2.065 ± 0.205	0.8388
mRNFL	0.128 ± 0.020	0.160 ± 0.013	**<0.0001**	0.141 ± 0.017	**0.0012**	0.139 ± 0.021	**0.0220**
mGCL	0.225 ± 0.078	0.333 ± 0.034	**0.0001**	0.240 ± 0.066	0.3453	0.278 ± 0.071	0.1116
mIPL	0.208 ± 0.041	0.272 ± 0.018	**0.0007**	0.218 ± 0.043	0.4458	0.237 ± 0.048	0.2050
mINL	0.276 ± 0.074	0.240 ± 0.023	0.1591	0.248 ± 0.020	**0.0452**	0.243 ± 0.037	0.6817
mOPL	0.197 ± 0.023	0.203 ± 0.022	0.7781	0.205 ± 0.030	0.2001	0.198 ± 0.021	0.2149
mONL	0.481 ± 0.073	0.455 ± 0.027	0.8435	0.473 ± 0.043	0.3354	0.479 ± 0.042	0.9758
VA	0.666 ± 0.348	1.127 ± 0.104	**<0.0001**	0.887 ± 0.310	**0.0289**	0.844 ± 0.327	0.1067

pRNFL thicknesses are expressed in μm and macular volumes in μm^3

MOG-abs-positive myelin-oligodendrocyte-glycoprotein antibody positive patients, *MOG-abs-negative*: myelin-oligodendrocyte-glycoprotein antibody negative patients, *AQP4-abs-positive* aquaporin 4 antibody positive, *NMOSD* neuromyelitis optica spectrum disorder, *RRMS* relapsing remitting multiple sclerosis, *HC* healthy controls, *pRNFL* peripapillary retinal nerve fiber layer, *T* temporal, *TS* temporo-superior, *TI* temporo-inferior, *N* nasal, *NS* naso-superior, *NI* naso-inferior, *N/T* nasal/temporal, *TMV* total macular volume, *mRNFL* macular RNFL, *mGCL* macular ganglion cell layer, *mIPL* macular inner plexiform layer, *mINL* macular inner nuclear layer, *mOPL* macular outer plexiform layer, *mONL* macular outer nuclear layer

Significant results ($p < 0.05$) are indicated in bold. [#] $p < 0.1$. Significant results after Bonferroni correction are underlined

Table 3 Comparison of OCT measures and visual acuity after matching eyes using gender and age in subpopulations of eyes with clinical episode of optic neuritis

Number of eyes	MOG-abs-pos ($N = 13$)	HC ($N = 26$)	p value MOG-abs-positive vs. HC	MOG-abs-negative RRMS ($N = 13$)	p value MOG-abs-positive vs. MOG-abs-negative RRMS	MOG-abs-negative, AQP4-abs-positive NMOSD ($N = 15$)	p value MOG-abs-positive vs. MOG-abs-negative, AQP4-abs-positive NMOSD
Parameters	Mean ± SD	Mean ± SD	Adj. GEE	Mean ± SD	Adj. GEE	Mean ± SD	Adj. GEE
pRNFL_G	59.000 ± 20.112	103.538 ± 8.529	**<0.0001**	71.154 ± 11.268	0.0873#	76.267 ± 22.670	**0.0264**
pRNFL_TI	85.154 ± 35.679	152.269 ± 15.881	**<0.0001**	107.154 ± 18.667	**0.0452**	113.333 ± 37.947	0.1182
pRNFL_T	41.154 ± 17.492	75.077 ± 9.465	**<0.0001**	46.231 ± 14.811	0.3240	51.867 ± 15.075	**0.0462**
pRNFL_TS	77.923 ± 27.069	137.731 ± 16.496	**<0.0001**	106.077 ± 23.078	**<0.0001**	106.400 ± 36.081	**0.0208**
pRNFL_NS	65.077 ± 23.128	112.385 ± 26.341	**<0.0001**	80.000 ± 21.455	0.1138	86.933 ± 24.315	**0.0081**
pRNFL_N	46.462 ± 16.205	81.269 ± 15.473	**<0.0001**	53.538 ± 12.633	0.2472	60.400 ± 23.886	**0.0391**
pRNFL_NI	68.231 ± 23.644	114.500 ± 26.861	**<0.0001**	77.000 ± 14.048	0.3605	79.533 ± 23.781	0.3052
pRNFL_ratio	1.203 ± 0.355	1.155 ± 0.278	0.6815	1.255 ± 0.418	0.5572	1.169 ± 0.401	0.9938
TMV	2.003 ± 0.089	2.168 ± 0.071	**<0.0001**	1.968 ± 0.115	0.7132	1.973 ± 0.250	0.9003
mRNFL	0.123 ± 0.022	0.160 ± 0.013	**<0.0001**	0.140 ± 0.022	**0.0244**	0.127 ± 0.024	**0.0146**
mGCL	0.180 ± 0.072	0.333 ± 0.034	**<0.0001**	0.205 ± 0.063	0.5817	0.232 ± 0.081	0.0923#
mIPL	0.187 ± 0.034	0.272 ± 0.018	**<0.0001**	0.195 ± 0.036	0.6306	0.205 ± 0.053	0.2352
mINL	0.288 ± 0.070	0.240 ± 0.023	**0.0135**	0.257 ± 0.014	0.1467	0.239 ± 0.045	0.0941#
mOPL	0.194 ± 0.023	0.203 ± 0.022	0.1329	0.205 ± 0.028	0.7249	0.194 ± 0.022	0.0685#
mONL	0.496 ± 0.047	0.455 ± 0.027	**0.0080**	0.474 ± 0.038	0.6138	0.486 ± 0.044	0.1128
VA	0.612 ± 0.350	1.127 ± 0.104	**<0.0001**	0.735 ± 0.346	0.6042	0.799 ± 0.346	0.0722#

pRNFL thicknesses are expressed in μm and macular volumes in μm^3

MOG-abs-positive myelin-oligodendrocyte-glycoprotein antibody positive patients, *MOG-abs-negative* myelin-oligodendrocyte-glycoprotein antibody negative patients, *AQP4-abs-positive* aquaporin 4 antibody positive, *NMOSD* neuromyelitis optica spectrum disorder, *RRMS* relapsing remitting multiple sclerosis, *HC* healthy controls, *pRNFL* peripapillary retinal nerve fiber layer, *T* temporal, *TS* temporo-superior, *TI* temporo-inferior, *N* nasal, *NS* naso-superior, *NI* naso-inferior, *N/T* nasal/temporal, *TMV* total macular volume, *mRNFL* macular RNFL, *mGCL* macular ganglion cell layer, *mIPL* macular inner plexiform layer, *mINL* macular inner nuclear layer, *mOPL* macular outer plexiform layer, *mONL* macular outer nuclear layer

Significant results ($p < 0.05$) are indicated in bold. # $p < 0.1$. Significant results after Bonferroni correction are underlined

Table 4 Comparison of OCT measures and visual acuity after matching eyes using gender and age in subpopulations of eyes without clinical episode of optic neuritis

Number of eyes	MOG-abs-pos ($N = 12$)	HC ($N = 26$)	p value MOG-abs-positive vs. HC	MOG-abs-negative RRMS ($N = 13$)	p value MOG-abs-positive vs. MOG-abs-negative RRMS	MOG-abs-negative, AQP4-abs-positive NMOSD ($N = 23$)	p value MOG-abs-positive vs. MOG-abs-negative, AQP4-abs-positive NMOSD
Parameters	Mean ± SD	Mean ± SD	Adj. GEE	Mean ± SD	Adj. GEE	Mean ± SD	Adj. GEE
pRNFL_G	87.250 ± 15.220	103.538 ± 8.529	**0.0014**	90.462 ± 7.333	0.7905	96.174 ± 8.978	0.0548[#]
pRNFL_TI	126.083 ± 30.216	152.269 ± 15.881	**0.0017**	133.846 ± 12.733	**0.0110**	142.391 ± 16.662	**0.0336**
pRNFL_T	57.333 ± 15.090	75.077 ± 9.465	**0.0002**	56.308 ± 9.801	0.6406	68.174 ± 9.023	**0.0199**
pRNFL_TS	118.500 ± 18.938	137.731 ± 16.496	**0.0025**	118.538 ± 13.233	0.0521[#]	132.957 ± 19.099	0.0506[#]
pRNFL_NS	98.167 ± 19.595	112.385 ± 26.341	0.1045	106.538 ± 20.222	**<0.0001**	94.130 ± 17.584	0.7230
pRNFL_N	71.833 ± 14.471	81.269 ± 15.473	0.0717[#]	74.308 ± 11.557	0.9130	77.609 ± 11.587	0.1918
pRNFL_NI	99.083 ± 28.273	114.500 ± 26.861	0.1971	104.077 ± 14.274	0.8982	108.391 ± 25.715	0.3671
pRNFL_ratio	1.315 ± 0.345	1.155 ± 0.278	0.2152	1.361 ± 0.287	**0.0019**	1.156 ± 0.236	0.1933
TMV	2.096 ± 0.107	2.168 ± 0.071	**0.0398**	2.072 ± 0.121	0.6263	2.131 ± 0.138	0.3624
mRNFL	0.133 ± 0.016	0.160 ± 0.013	**<0.0001**	0.142 ± 0.011	0.1150	0.147 ± 0.015	**0.0094**
mGCL	0.273 ± 0.053	0.333 ± 0.034	**0.0013**	0.275 ± 0.049	0.7728	0.310 ± 0.039	**0.0115**
mIPL	0.231 ± 0.037	0.272 ± 0.018	**0.0010**	0.241 ± 0.036	0.7898	0.260 ± 0.026	**0.0046**
mINL	0.262 ± 0.079	0.240 ± 0.023	0.3072	0.240 ± 0.021	0.3545	0.246 ± 0.031	0.5941
mOPL	0.200 ± 0.024	0.203 ± 0.022	0.5123	0.204 ± 0.033	0.9807	0.200 ± 0.021	0.4499
mONL	0.465 ± 0.093	0.455 ± 0.027	0.8482	0.472 ± 0.048	0.4495	0.475 ± 0.042	0.8242
VA	0.726 ± 0.352	1.127 ± 0.104	**0.0001**	1.038 ± 0.176	**0.0054**	0.873 ± 0.318	**0.0056**

pRNFL thicknesses are expressed in μm and macular volumes in μm^3

MOG-abs-positive myelin-oligodendrocyte-glycoprotein antibody positive patients, *MOG-abs-negative* myelin-oligodendrocyte-glycoprotein antibody negative patients, *AQP4-abs-positive* aquaporin 4 antibody positive, *NMOSD* neuromyelitis optica spectrum disorder, *RRMS* relapsing remitting multiple sclerosis, *HC* healthy controls, *pRNFL* peripapillary retinal nerve fiber layer, *T* temporal, *TS* temporo-superior, *TI* temporo-inferior, *N* nasal, *NS* naso-superior, *NI* naso-inferior, *N/T* nasal/temporal, *TMV* total macular volume, *mRNFL* macular RNFL, *mGCL* macular ganglion cell layer, *mIPL* macular inner plexiform layer, *mINL* macular inner nuclear layer, *mOPL* macular outer plexiform layer, *mONL* macular outer nuclear layer

Significant results ($p < 0.05$) are indicated in bold. [#] $p < 0.1$. Significant results after Bonferroni correction are underlined

Table 5 Global peripapillary retinal nerve fiber layer thickness in multiple sclerosis patients according to presence of anti-MOG antibody and optic neuritis occurrence

	MOG-abs-positive RRMS	MOG-abs-negative RRMS patients
All eyes	68.1 ± 17.5 ($n = 8$)	80.8 ± 13.6 ($n = 26$)
ON eyes	55.7 ± 16.1 ($n = 4$)	71.2 ± 11.3 ($n = 13$)
NON eyes	80.5 ± 7.1 ($n = 4$)	90.5 ± 7.3 ($n = 13$)

pRNFL thicknesses are expressed in µm

MOG-abs-positive myelin-oligodendrocyte-glycoprotein antibody positive patients, *MOG-abs-negative* myelin-oligodendrocyte-glycoprotein antibody negative patients, *NMOSD* neuromyelitis optica spectrum disorder, *RRMS* relapsing remitting multiple sclerosis, *pRNFL* peripapillary retinal nerve fiber layer, *MME* microcystic macular edema, *ON* optic neuritis, *NON* non optic neuritis

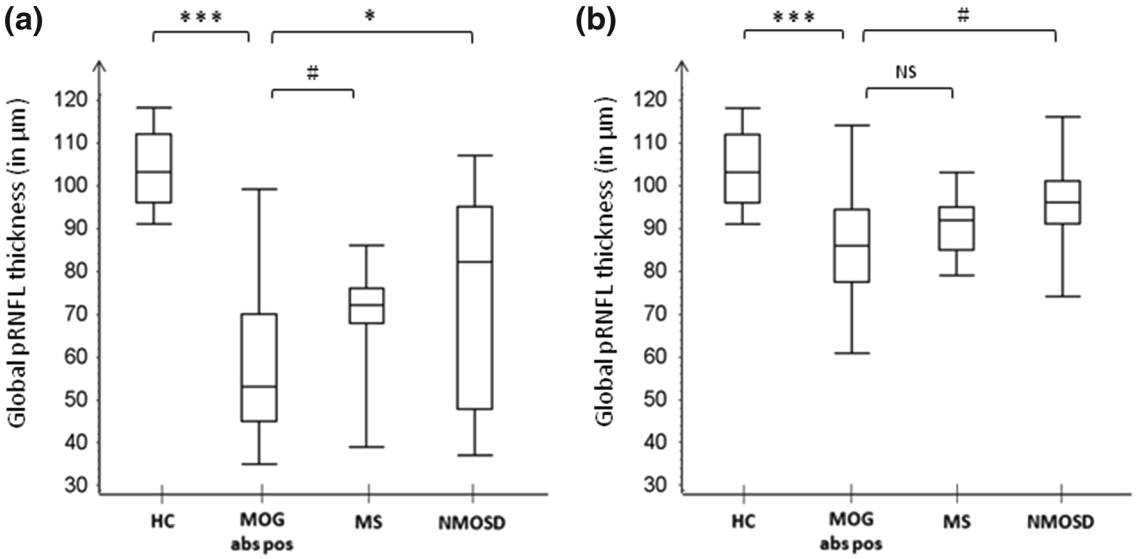


Fig. 2 Global peripapillary retinal nerve fiber layer thickness in healthy controls, optic neuritis eyes (**a**) and non optic neuritis eyes (**b**) of MOG-abs-positive patients, MS patients and AQP4-abs-positive NMOSD patients; *pRNFL* peripapillary retinal nerve fiber layer, *MOG abs pos* myelin-oligodendrocyte-glycoprotein antibody positive patients, *H* healthy controls, *NMOSD* neuromyelitis optica spectrum disorder, *MS* multiple sclerosis, *NS* non significant; $^{\#}p < 0.1$; $^{*}p < 0.05$; $^{***}p < 0.001$

Table 6 Global peripapillary retinal nerve fiber layer thickness according to microcystic macular edema presence and optic neuritis occurrence

	MOG-abs-positive	MOG-abs-negative MS	MOG-abs-negative, AQP4-abs-positive NMOSD
MME eyes	44.7 ± 10.2 ($n = 6$)	–	71 ± 32.5 ($n = 2$)
Non MME eyes	81.4 ± 17.8 ($n = 19$)	80.8 ± 13.6 ($n = 26$)	89.3 ± 17.3 ($n = 36$)
Non MME ON eyes	70 ± 17.5 ($n = 8$)	71.2 ± 11.3 ($n = 13$)	78.3 ± 22.1 ($n = 14$)
Non MME NON eyes	89.6 ± 13.4 ($n = 11$)	90.5 ± 7.3 ($n = 13$)	96.3 ± 9.2 ($n = 22$)

pRNFL thicknesses are expressed in µm

MOG-abs-positive myelin-oligodendrocyte-glycoprotein antibody positive patients, *MOG-abs-negative* myelin-oligodendrocyte-glycoprotein antibody negative patients, *AQP4-abs-positive* aquaporin 4 antibody positive, *NMOSD* neuromyelitis optica spectrum disorder, *MS* relapsing remitting multiple sclerosis, *pRNFL* peripapillary retinal nerve fiber layer, *MME* microcystic macular edema, *ON* optic neuritis, *NON* non optic neuritis

thickness of MOG-abs-positive eyes was significantly reduced vs. HC and NMOSD. A trend towards significance was observed vs. MS. Within NON eyes, global pRNFL thickness of MOG-abs-positive patients was significantly reduced vs. HC. A trend towards significance was observed vs. NMOSD. No difference was observed vs. MS.

Microcystic macular edema

There was no MME in HC or RRMS patients, but MME was observed in two ON eyes of two AQP-4-positive patients and in six ON eyes of three MOG-abs-positive patients (one RRMS, one rON, one relapsing encephalomyelitis). The difference in MME frequency between MOG-abs-positive eyes and MS eyes is statistically significant ($p = 0.0098$), whereas for MOG-abs-positive eyes vs. NMOSD eyes, statistical significance was not reached ($p = 0.0544$). MME (Fig. 1) was always located in INL, and always associated with a past history of severe clinical ON and with severe pRNFL atrophy as shown in Table 6. In correlation to this finding, INL thickening was observed in MOG-abs-positive ON eyes (Table 3). Due to the low number of MME in our patient cohorts, no statistical correlation between MME and visual impairment could be confirmed. However, patients with MME had more severe ON and low VA ranging from 0.0 to 0.8 (mean 0.3 ± 0.4).

Visual acuity

Considering all eyes together (Table 2), VA was significantly lower in MOG-abs-positive eyes than HC or MS. Considering ON eyes, a lower VA was seen in MOG-abs-positive eyes in comparison to MS and NMOSD, but statistical significance was not reached (Table 3). Considering NON eyes (Table 4), MOG-abs-positive eyes presented a significant lower VA in comparison to HC, MS and NMOSD (Table 4).

Discussion

MOG-abs have been described in several neuroimmunological CNS diseases with partly overlapping clinical features [1], and recently also in a small proportion of adult MS patients [2, 5]. The clinical features of MOG-abs-positive CNS disease seem to partly overlap with NMOSD and MS, but the clinical significance and pathogenetic relevance of MOG-abs remains to be further defined [1]. MOG-abs associated ON has been thought to show a more favorable outcome [13, 23–26], however, OCT data regarding MOG-abs associated retinal degeneration are scarce [14, 24]. Here we are able to show MOG-abs as a potential emerging marker of ON and NON retinal axonal degeneration in 13 clinically MOG-abs-positive patients. Atrophy seems to be the consequence of clinical episode(s) of ON as well as subclinical involvement of visual pathways, and is associated with MME in 24% of ON eyes. Overall retinal damage was most pronounced in MOG-abs-positive patients compared to MS patients and patients with AQP-4-abs-positive NMOSD in clinically affected and non-affected eyes. Concerning OCT atrophy patterns, all pRNFL quadrants and inner macular layers showed atrophy, but mostly temporal pRNFL quadrants were affected. OCT atrophy patterns in MOG-abs-positive patients were similar compared to OCT patterns already described in MS patients [8]. In MS-ON the papillomacular bundle (PMB) is especially affected. The PMB consists of the so called parvocellular axons, which are more vulnerable to inflammation, due to their thin diameter [27].

Several reasons may account for the differences between our results presented here and the published favorable clinical outcome of MOG-abs associated ON [13, 23, 24]. One explanation could be the longer follow-up analysis of our cohort with a mean of 60 months between last ON and OCT. Peripapillary RNFL atrophy classically occurs within 6 months after ON [28], but ongoing degeneration may occur beyond 6 months. Furthermore, involvement of the anterior part of the optic nerve [29] and severe optic nerve swelling [14] have been reported more frequently in MOG-abs-positive ON than in AQP4-abs-positive ON. Thus, pRNFL thicknesses measured at an early stage of axonal retinal degeneration ($\leq$6 months post ON) might be overestimated, potentially leading to an underestimation of retinal axonal loss in MOG-abs-positive ON eyes. Additionally, our data are supported by the fact that along with a higher retinal atrophy level, visual acuity (VA) testing in our MOG-abs-positive cohort was worse than in MS-ON eyes or NMOSD-ON eyes. We are aware that VA is not very sensitive for quantifying visual disability in neuroinflammatory CNS disorders, and low contrast VA (LCVA) scale would have been more sensitive [30]. Published optic nerve MRI studies reported longer optic nerve lesions in MOG-abs-positive patients than in MS or NMOSD [24, 26, 29, 31] and a positive correlation between optic nerve inflammatory lesion length and retinal atrophy [32]. Thus, it is comprehensible that post ON retinal atrophy may be of greater extent in MOG-abs-positive patients. Finally, a recent study comparing retinal thicknesses of MOG-abs-positive ON patients and AQP4-abs-positive ON patients reported severe and similar atrophy in these two populations [33]. In our study, MOG-abs-positive patients showed more retinal atrophy than AQP4-abs-positive NMOSD patients. However, in contrast to our matched cohorts (MS vs. MOG-abs-positive), the AQP4-abs-positive NMOSD patients were not matched according to the number of ON episodes and showed a lower number of clinical ON episodes per eye.

Consistent with the pronounced atrophy pattern in MOG-abs-positive ON, we found MME in six eyes (24%) of MOG-abs-positive patients with a history of severe ON. MME has been described in severe MS-ON [8, 34] and NMOSD-ON [35], but until now there are no reports of

MME in patients with MOG-abs. In our study, MME was more frequently observed in MOG-abs-positive patients than in AQP-4-abs positive NMOSD patients and—contrary to what is reported in MS [34] and in accordance to what is reported in NMOSD [9]—MME in MOG-abs-positive patients could be detected only in ON eyes. MME seems to be linked to Müller cell pathology [36] but is not specific to inflammatory optic nerve diseases. MME can mainly be observed in the INL, but it has been reported in ONL as well [37, 38]. This could partly explain the observed INL thickening in our MOG-abs-positive patients. Interestingly, we found additional ONL thickening in MOG-abs-positive ON eyes, which has already been described after acute ON [39, 40]. ONL thickening has also been associated with the presence of MME [41].

The pathogenetic relevance of the MOG-abs remains still unclear, although a pathophysiological role of MOG-abs in ON can be assumed [42]. Our subgroup analysis is supporting this, since we found a more pronounced retinal atrophy in MOG-abs-positive MS patients compared to MS patients without MOG-abs. However, since MOG-abs are only rarely seen in adult MS patients, the number of patients is too low for statistical analysis and needs further confirmation.

Subclinical retinal atrophy as it occurs in MS and to a lesser extent in AQP-4-abs-positive NMOSD [8, 9] has so far not been reported in MOG-abs-positive patients [15, 24, 29]. Interestingly, in NON eyes of MOG-abs-positive patients, atrophy can—as it is known for MS—be observed only in temporal pRNFL quadrants. All lesions in the optic pathway from the optic nerve to the visual cortex can contribute to this subclinical retinal degeneration. Our dataset lacks detailed MRI data such as optic nerve imaging. In future studies, MRI data on optic nerve lesion volume and whole brain lesion volume should help to further evaluate subclinical retinal atrophy in MOG-abs-positive patients.

Our study has several limitations. The main limitation is the small number and heterogeneity of MOG-abs-positive patients, but MOG-abs-positive CNS disease is very rare. Additional limitations include the lack of LCVA data, VEP and magnetic resonance imaging (MRI), including optic nerve imaging which would be important for a better understanding of subclinical retinal axonal loss and demyelination in the MOG-abs-positive group.

In conclusion, we show evidence that MOG-abs may serve as potential markers of retinal degeneration. Specifically, MOG-abs-related OCT features (a) show atrophy that predominates in temporal pRNFL quadrants (resembling the MS retinal pattern), (b) show slightly more atrophy than NMOSD, (c) indicate subclinical pathology in NON eyes, and (d) may be associated with MME, a biomarker of severe optic neuropathy.

Acknowledgements We are grateful to Dr. F. Thaler and Dr. S. Liebscher for helpful comments on the manuscript. We thank A. Bamberger for technical support.

Compliance with ethical standards

Conflicts of interest JH received speaker honoraria, travel expenses, and personal compensations from Merck, Biogen, Bayer-Healthcare, Sanofi Genzyme and Novartis Pharma. TK has received travel expenses and speaking honoraria from Bayer-Healthcare, Genzyme, Teva-Pharma, Merck, Novartis-Pharma, Sanofi, and Biogen and grant support from Bayer-Schering AG and Novartis-Pharma. RS, MS and ES have nothing to disclose. EM has received grant support from Novartis-Pharma and personal compensations from Roche. RH is supported by the Deutsche Forschungsgemeinschaft, Munich Cluster for Systems Neurology (SYNERGY) and the KKNMS and has received personal compensations from Bayer-Healthcare, Teva-Pharma, Merck, Biogen, Novartis-Pharma, Sanofi and Genzyme. OO reports grant for research from Novartis-Pharma; grants and personal fees from Biogen, Genzyme, Merck, Novartis-Pharma and Teva-Pharma, outside the submitted work.

Ethical standards The study was approved by the local ethics committee (Ethikkommission bei der LMU München, 427-14) in compliance with the Declaration of Helsinki. All patients and HC gave written consent to participate in the study.

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