Retinal Layer Thinning After Optic Neuritis is Associated With Future Relapse Remission in Relapsing Multiple Sclerosis

Author(s):
Gabriel Bsteh, PD, MD, PhD; Nik Krajnc, MD; Katharina Riedl; Patrick Altmann, MD, PhD; Barbara Kornek, Univ.-Prof., MD; Fritz Leutmezer, Univ.-Prof., MD; Stefan Macher, MD, PhD; Christoph Mitsch, PD, MD, PhD; Philip Pruckner, MD; Paulus Stefan Rommer, Assoz.-Prof. MD; Gudrun Zulehner, MD; Berthold Pemp, Assoz.-Prof. MD; Thomas Berger, Univ.Prof., MD, MSc on behalf of Vienna Multiple Sclerosis Database Study Group

Corresponding Author:
Gabriel Bsteh, gabriel.bsteh@meduniwien.ac.at

Affiliation Information for All Authors: 1. Department of Neurology, Medical University of Vienna, Vienna, Austria; 2. Department of Ophthalmology, Medical University of Vienna, Vienna, Austria

Equal Author Contribution:

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Contributions:
Gabriel Bsteh: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Nik Krajnc: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Katharina Riedl: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Patrick Altmann: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Barbara Kornek: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Fritz Leutmezer: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Stefan Macher: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Christoph Mitsch: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Philip Pruckner: Drafting/revision of the manuscript for content, including medical writing for content
Paulus Stefan Rommer: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Gudrun Zulehner: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Berthold Pemp: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Thomas Berger: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design

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Abstract

Introduction: Remission of relapses is an important contributor to both short- and long-term prognosis in relapsing multiple sclerosis (RMS). In MS-associated acute optic neuritis (MS-ON), retinal layer thinning measured by optical coherence tomography (OCT) is a reliable biomarker of both functional recovery and the degree of neuroaxonal damage. However, prediction of non-ON relapse remission is challenging. We aimed to investigate whether retinal thinning after ON is associated with relapse remission after subsequent non-ON relapses.

Methods: For this longitudinal observational study from the Vienna MS database (VMSD), we included MS patients with 1) an episode of acute ON, 2) available spectral-domain OCT scans within 12 months before ON onset (OCTbaseline), within 1 week after ON onset (OCTacute) and 3-6 months after ON (OCTfollow-up), and 3) at least one non-ON relapse after the ON episode. Subsequent non-ON relapses were classified as displaying either complete or incomplete remission based on change in expanded disability status scale (EDSS) assessed 6 months post-relapse. Association of retinal
thinning in peripapillary retinal nerve fiber layer (ΔpRNFL) and macular ganglion-cell-and-inner-plexiform-layer (ΔGCIPL) with incomplete remission was tested by multivariate logistic regression models adjusting for age, sex, disease duration, relapse severity, time to steroid treatment, and DMT status.

**Results:** We analyzed 167 MS patients (mean age 36.5 years [SD 12.3], 71.3% female, mean disease duration 3.1 years [SD 4.5]) during a mean observation period of 3.4 years (SD 2.8) after the ON episode. In 61 patients (36.5%) at least one relapse showed incomplete remission. In the multivariable analyses, incomplete remission of non-ON relapse was associated with ΔGCIPL thinning both from OCT\textsubscript{baseline} to OCT\textsubscript{follow-up} and from OCT\textsubscript{acute} to OCT\textsubscript{follow-up} (odds ratio [OR] 2.4 per 5µm, p<0.001, respectively), independently explaining 29% and 27% of variance respectively. ΔpRNFL was also associated with incomplete relapse remission when measured from OCT\textsubscript{baseline} to OCT\textsubscript{follow-up} (OR 1.9 per 10µm, p<0.001) independently accounting for 22% of variance, but not when measured from OCT\textsubscript{acute} to OCT\textsubscript{follow-up}.

**Conclusions:** Retinal layer thinning after optic neuritis may be useful as a marker of future relapse remission in RMS.

**Introduction**

Multiple sclerosis (MS) is characterized by a highly heterogenic disease course on an individual level \(^1\). The currently pathophysiological concept of MS encompasses a disease process that involves both inflammatory and neurodegenerative components, which are currently viewed as a largely overlapping continuum with neuroaxonal damage already occurring in very early stages, and, while clinically often silent, mainly determining long-term prognosis \(^2\).

Recovery (i.e. remission) from relapses, the clinical hallmark of MS particularly in early disease phases, predicts long-term disability and is therefore used as a prognostic factor in clinical practice \(^3\text{--}^7\). Remission of early relapses seems to be similar within individual patients
as the trajectory of recovery stays similar with subsequent demyelinating events pointing to individual specific factors responsible for a “good” vs “poor” recovery paradigm. While younger age and lower severity of relapse are well established predictors of relapse remission, complete recovery may mask the accumulation of neuroaxonal damage below the clinical threshold creating the necessity for reliable biomarkers reflecting subclinical processes. Optical coherence tomography (OCT) enables non-invasive, inexpensive, well tolerated high-resolution in-vivo imaging of distinct layers of the retina with excellent reproducibility. Peripapillary retinal nerve fiber layer (pRNFL) and macular ganglion-cell-and-inner-plexiform-layer (GCIPL) thinning have been established as markers of neuroaxonal degeneration in MS. MS-associated acute optic neuritis (ON), a typical presentation of MS relapse, displays rates of remission comparable to other types of relapses, similarly depending on age and severity. ON causes a reduction in both RNFL and GCIPL thickness corresponding to the degree of neuroaxonal damage. Based on the proposed concept of similar trajectory of recovery from subsequent demyelinating events in individual patients, we aimed to investigate in this study whether retinal thinning after ON is associated with relapse remission after subsequent non-ON relapses.

Methods

Patients and definitions

For this longitudinal observational study, we used the Vienna MS database (VMSD), which is established at the MS Clinic of the Department of Neurology, Medical University of Vienna, serving as both primary and reference center mainly for Vienna and its geographical catchment area. By July 2021, a cohort of 1428 MS patients diagnosed according to respective McDonald criteria had been included. VMSD case reports include
demographic data, details of MS course (disease onset, time to diagnosis, relapses, Expanded Disability Status Scale [EDSS] and onset of secondary progression), diagnostic investigations (MRI, OCT, cerebrospinal fluid findings) and DMT history (including initiation, interruption, changes and adverse effects). Data are collected retrospectively at first visit and prospectively whenever the patient returns for scheduled (every 3-6 months) follow-up or unscheduled visits.

We included MS patients aged >18 years at onset with 1) an episode of acute ON, 2) available spectral-domain OCT scans within 12 months before ON onset and within 1 week after ON onset, 3) available spectral-domain OCT scan 3-6 months after ON, and 4) at least one non-ON MS relapse after the ON episode. Patients with bilateral ON were excluded from the study. The detailed in/exclusion process is depicted in Figure 1. All patients included had been tested for antibodies against AQP4 and MOG and patients with NMOSD/MOGAD were excluded.

**Placeholder Figure 1. Inclusion and exclusion flow diagram.**

The endpoint of this study was relapse remission from non-ON relapse. All non-ON relapses occurring after an episode of ON recorded in the VMSD were extracted and classified based on change in Expanded Disability Status Scale (EDSS) assessed 6 months post-relapse compared to the last documented EDSS before relapse in the VMSD. Incomplete remission was defined as EDSS post-relapse $\geq 0.5$ points compared to EDSS before relapse.$^{24}$ Similarly, recovery from ON was classified based on the visual EDSS functional score (FS) with incomplete recovery defined as $\geq 1$ point increase in the visual FS post-relapse compared to before relapse. ON onset was defined as the first day of noticeable visual change or eye pain, whichever occurred first. Generally, a relapse was defined as patient-reported symptoms or
objectively observed signs typical of an acute CNS inflammatory demyelinating event, current or prior to the visit, with a duration of at least 24 hours in the absence of fever or infection, separated from the last relapse by at least 30 days. Relapse severity was defined as mild (if EDSS increase at relapse was <2 points compared to the last documented EDSS before relapse) or severe (EDSS increase ≥2 points compared to last documented EDSS before relapse) 8. Relapses were subclassified according to EDSS FS involved as pyramidal, cerebellar, brainstem, sensory or polysymptomatic. All relapses included (ON and non-ON) were treated with high-dose methylprednisolone (HDMP; 3000-5000mg over 3-5 days) and time to HDMP was defined as the time from the reported first day of symptoms to the first day of HDMP in days.

DMT status at every respective relapse was classified as: 1) “no DMT” (N-DMT) defined as patients receiving no DMT at the occurrence of relapse, 2) “moderately effective DMT” (M-DMT) defined as patients receiving either dimethyl fumarate, glatiramer acetate, interferon-beta preparations, or teriflunomide, and 3) “highly effective DMT” (H-DMT) defined as patients receiving either alemtuzumab, antiCD20 monoclonal antibodies (ocrelizumab, ofatumumab, rituximab), cladribine, natalizumab, or sphingosine-1-phosphate receptor modulators (fingolimod, ozanimod, siponimod).

Optical coherence tomography

OCT imaging was performed by experienced neuro-ophthalmologists at the Department of Ophthalmology and Optometry of the same institution using the same spectral-domain OCT (Heidelberg Engineering, Heidelberg, Germany; software Heidelberg eye explorer software version 6.9a) without pupil dilatation in a dark room. For pRNFL measurement, a custom 3.4 mm ring scan (12°) centered on the optic nerve head was used (1536 A-scans, automatic real-time tracking [ART]: 100 averaged frames). For GCIPL measurement, a 20°×20° macular volume scan (512 A-scans, 25 B-scans, vertical alignment, ART: 16 averaged frames)
centered on the macula was performed. GCIPL thickness was defined as the mean layer thickness of the four inner and outer quadrants of the circular grid centered around the foveola corresponding to the 3mm and 6mm rings as defined by the Early Treatment Diabetic Retinopathy Study. Semiautomated image processing was conducted using the built-in proprietary software for automated layer segmentation with manual correction of obvious errors. All examinations were performed in accordance with the OSCAR-IB quality control criteria and described according to the APOSTEL criteria. ON associated thinning of pRNFL (ΔpRNFL) and GCIPL (ΔGCIPL) was calculated as the difference between pRNFL/GCIPL thicknesses of the ON affected eye in the OCT scans within 12 months before ON onset (OCT_{baseline}) and 3-6 months after ON (OCT_{follow-up}). We also calculated the difference between pRNFL/GCIPL thicknesses in the OCT scans within 1 week after ON onset (OCT_{acute}) and 3-6 months after ON (OCT_{follow-up}). Patients with bilateral ON were excluded from the study. Other exclusion criteria were previous diagnoses of ophthalmological (i.e. myopia greater than -4 diopters, optic disc drusen), neurological, or drug-related causes of vision loss or retinal damage not attributable to MS. The investigators performing the OCT were blinded to clinical parameters and vice versa.

**Standard Protocol Approvals, Registrations, and Patient Consents**

The study was approved by the ethics committee of the Medical University Vienna (ethical approval number: 1707/2020). As this was retrospective study, the need for written informed consent from study participants was waived by the ethics committee.

**Data Availability Statement**

Data supporting the findings of this study are available from the corresponding author upon reasonable request by a qualified researcher and upon approval by the ethics committee of the Medical University Vienna.
Statistics

Statistical analysis was performed using SPSS 26.0 (SPSS Inc, Chicago, IL, USA) and R-Statistical Software (Version 4.0.0). Univariate group comparisons were done by Chi-square-test, Mann-Whitney U test or independent t-test (with Welch’s correction in case of unequal standard deviations between the groups) as appropriate. Univariate correlations were analyzed by Pearson or Spearman test as appropriate.

Association of retinal thinning with incomplete remission was tested by multivariate logistic regression models with relapse remission as the dependent variable and $\Delta$pRNFL/$\Delta$GCIPL as the independent variable adjusting for age, sex, disease duration, incomplete relapse remission before ON, relapse severity, polysymptomatic relapse, time to HDMP, and DMT status both at ON and at the non-ON relapse. Contribution of variables of interest to explanation of variance was assessed by change in $R^2$ through step-wise removal from the regression models.

A predefined subgroup analysis was conducted with the same model set-up including only patients with complete recovery from ON to determine the additional value of retinal thinning beyond clinical recovery from ON.

We performed sensitivity analyses including absolute values of pRNFL and GCIPL at OCT$_\text{baseline}$ as additional covariates into the regression models.

We tested all variables for normal distribution by Lilliefors-test and for collinearity by variance inflation factor (VIF) and excluded all variables from the regression analysis if the VIF was $>2.0$ corresponding to an $R^2$ of 0.60. Missing values were handled by multiple (20 times) imputation using the missing not at random (MNAR) approach with pooling of estimates according to Rubin’s rules.$^{28}$ A two-sided p-value $<0.05$ was considered statistically significant.

Results
We analyzed 167 MS patients during a mean observation period of 3.4 years (SD 2.8) after the ON episode. Detailed characteristics of the study cohort are given in Table 1.

**Placeholder Table 1. Cohort characteristics**

Mean retinal thinning from OCT\textsubscript{baseline} to OCT\textsubscript{follow-up} was 25.3µm (SD 22.7) in pRNFL and 13.2µm (SD 7.9) in GCIPL, while from OCT\textsubscript{acute} to OCT\textsubscript{follow-up} it was 43.1µm (SD 45.2) in \Delta pRNFL and 12.1µm (SD 8.2) in \Delta GCIPL.

Visual impairment at ON (visual FS) was weakly to moderately correlated with retinal thinning from OCT\textsubscript{baseline} to OCT\textsubscript{follow-up} in both pRNFL (Spearman rho = 0.219, p=0.046) and GCIPL (Spearman rho = 0.326, p=0.002), whereas from OCT\textsubscript{acute} to OCT\textsubscript{follow-up} only \Delta GCIPL (Spearman rho = 0.302, p=0.008) but not \Delta pRNFL (Spearman rho = 0.103, p=0.374) correlated with visual impairment.

Similarly, complete ON recovery (visual FS post-relapse ≤ pre-relapse) was associated with lower pRNFL and GCIPL thinning from OCT\textsubscript{baseline} to OCT\textsubscript{follow-up} compared to incomplete ON recovery (\Delta pRNFL: 19.9µm [SD 24.3] vs. 31.1µm [SD 29.4], p=0.008; \Delta GCIPL: 10.2µm [SD 10.8] vs. 16.5µm [SD 11.6], p<0.001). Looking at thinning from OCT\textsubscript{acute} to OCT\textsubscript{follow-up}, only \Delta GCIPL was associated with complete recovery (9.6µm [SD 11.3] vs. 14.8µm [SD 12.2], p=0.005), but not \Delta pRNFL (37.6µm [SD 44.3] vs. 49.1µm [SD 53.9], p=0.133). The amount of retinal thinning was not significantly associated with sex, age, disease duration, number of relapses before baseline or time to HDMP.

Of 250 non-ON relapses recorded occurring after a mean 1.8 years (SD 3.1) after the ON episode, 99/250 (39.6%) showed incomplete remission and 61 (36.5%) of the 167 patients included had at least one relapse with incomplete remission. Relapse severity was mild in 202/250 (80.8%) but severe in 48/250 (19.2%) relapses. Relapses were distributed according
to EDSS FS involved as follows: 55 (22.2%) pyramidal, 24 (9.6%) cerebellar, 28 (11.2%) brainstem, 113 (45.2%) sensory and 30 (12%) polysymptomatic. DMT status at the respective relapse was N-DMT in 41 relapses (16.4%), M-DMT for 118 (47.2%) and H-DMT for 91 (36.4%). Median time on DMT at relapse was 20 months (IQR 7 – 31).

In univariate analyses, age at relapse was significantly higher in relapses with incomplete remission compared to relapses with complete remission (37.2 years, SD 10.3 vs. 32.0 years, SD 11.5; p<0.001) and the proportion of severe relapses was significantly higher (32/99 [32.3%] vs. 16/151 [10.6%], p<0.001) as was the proportion of incomplete relapse remission before ON (36/99 [36.4%] vs. 21/151 [13.9%], p<0.001). Type of FS involved was not significantly associated with incomplete remission (pyramidal: 21/55 [38.2%], cerebellar: 11/24 [45.8%], brainstem: 9/28 [32.1%], sensory: 38/113 [33.6%], polysymptomatic 20/30 [66.6%], p=0.153). Incomplete remission occurred in 81/215 (37.7%) of fully ambulatory patients (EDSS at relapse <4.0) compared to 18/35 (51.4%) with EDSS ≥4.0, but this was not statistically significant (p=0.123). There was no difference in the median number of relapses between patients with incomplete and complete relapse recovery (2 vs. 2; p=0.823). Incomplete relapse recovery was significantly less frequent in patients on H-DMT (22/91 [24.2%], p<0.001) than on M-DMT (57/118 [48.3%] or without DMT (22/91 [48.8%]). Neither time on DMT at baseline nor time on DMT at relapse was associated with relapse recovery. Patients with incomplete relapse remission displayed significantly more thinning of both pRNFL (30.4µm [SD 22.8] vs. 22.1µm [SD 19.6], p=0.002) and GCIPL (16.3µm [SD 9.5] vs. 11.3µm [SD 8.2], p<0.001) from OCT_{baseline} to OCT_{follow-up} (Figure 2A). When comparing thinning from OCT_{acute} to OCT_{follow-up}, only ΔGCIPL was associated with incomplete remission (15.5µm [SD 9.7] vs. 9.7µm [SD 9.8], p<0.001), but not ΔpRNFL (44.6µm [SD 29.9] vs. 38.7µm [SD 28.3], p=0.116).
Placeholder Figure 2. Retinal thinning after previous optic neuritis is associated with relapse remission.

In the multivariable analyses, incomplete remission of non-ON relapse was associated with $\Delta\text{GCIPL}$ both from $\text{OCT}_{\text{baseline}}$ to $\text{OCT}_{\text{follow-up}}$ and from $\text{OCT}_{\text{acute}}$ to $\text{OCT}_{\text{follow-up}}$ (odds ratio [OR] 2.4 per 5µm, $p<0.001$, respectively), independently explaining 29% and 27% of variance respectively (Table 2, Figure 3). Thinning of pRNFL was also associated with incomplete relapse remission when measured from $\text{OCT}_{\text{baseline}}$ to $\text{OCT}_{\text{follow-up}}$ (OR 1.9 per 10µm, $p<0.001$) independently accounting for 22% of variance, but not when measured from $\text{OCT}_{\text{acute}}$ to $\text{OCT}_{\text{follow-up}}$ (Table 2, Figure 3).

In all regression models, age at relapse (OR 1.4 per 5 years increase), incomplete remission before ON (OR 1.6) and severe relapse (OR 1.7-1.8) remained significantly associated with incomplete remission, whereas H-DMT at relapse was associated with lower likelihood of incomplete recovery (OR 0.6) (Table 2, Figure 3).

In the predefined subgroup analysis including only patients with complete recovery from ON (n=87), incomplete remission of non-ON relapse was still associated with $\Delta\text{GCIPL}$ from $\text{OCT}_{\text{baseline}}$ to $\text{OCT}_{\text{follow-up}}$ (OR 2.6 per 5µm, 95% CI 1.4 – 4.5, $p<0.001$) and from $\text{OCT}_{\text{acute}}$ to $\text{OCT}_{\text{follow-up}}$ (OR 2.5 per 5µm, 95% CI 1.4 – 4.8, $p<0.001$), independently explaining 38% and 30% of variance, respectively, after adjusting for age, relapse severity, and DMT status. In the model regarding $\Delta\text{pRNFL}$, thinning from $\text{OCT}_{\text{baseline}}$ to $\text{OCT}_{\text{follow-up}}$ was also associated with incomplete relapse remission (OR 2.1 per 10µm, 95% CI 1.1 – 5.8, $p=0.032$) independently accounting for 18% of variance, but again $\Delta\text{RNFL}$ from $\text{OCT}_{\text{acute}}$ to $\text{OCT}_{\text{follow-up}}$ was not.

Sensitivity analyses including absolute values of pRNFL and GCIPL at $\text{OCT}_{\text{baseline}}$ as additional covariates into the regression models revealed that incomplete remission of non-ON relapse was still significantly associated with $\Delta\text{GCIPL}$ both from $\text{OCT}_{\text{baseline}}$ to $\text{OCT}_{\text{follow-up}}$ (OR 2.2 per 5µm, $p<0.001$, 23% variance explained) and from $\text{OCT}_{\text{acute}}$ to $\text{OCT}_{\text{follow-up}}$ (OR...
2.1 per 5µm, p<0.001, 20% variance explained) and ΔpRNFL from OCT\textsubscript{baseline} to OCT\textsubscript{follow-up}

(OR 1.6 per 10µm, p<0.001, 16% variance explained).

**Placeholder Figure 3. Retinal thinning after previous optic neuritis as an independent marker of relapse remission in multivariable analyses.**

**Placeholder Table 2. Multivariable regression models regarding incomplete relapse remission.**

**Discussion**

In this study, extending the concept of similar trajectory of recovery of demyelinating events in individual patients, we aimed to investigate whether OCT based assessment of retinal thinning after optic neuritis was associated with relapse remission after subsequent non-ON relapses.

We found that retinal thinning following previous ON is associated with incomplete remission of non-ON relapses, independently adding to the known predictors age, previous incomplete relapse remission, relapse severity and disease-modifying treatment. The impact was higher when using GCIPL rather than pRNFL thinning as it explained more of the variance in relapse remission and ∆GCIPL – but not ∆pRNFL – remained robustly associated when determining retinal thinning at follow-up from an OCT scan obtained within one week of ON onset instead of a baseline scan obtained before ON onset.

On a group level, the degree of relapse remission, particularly in early disease phases, is a predictor of long-term disability and therefore used as one of several factors for determining prognosis and, thus, timing and aggressiveness of treatment strategy in clinical practice. 3–7
At the individual level, the trajectory of recovery seems to stay similar over subsequent demyelinating events within patients, and thus, there may be predetermined individually specific disease features responsible for the degree of recovery with pathologic homogeneity within, but not between, individuals. ⁸

Clinical recovery may be the result of a variety of heterogenic pathophysiological processes such as remyelination, neurological reserve function, cortical and connective remodeling, or electrophysiological reorganization. ²⁹–³¹ Incomplete recovery, the clinical correlate of neuroaxonal damage, may result from a more severe initial injury or from limited repair and/or functional compensation processes. ³² Thus, complete clinical recovery from MS relapse may mask the accumulation of neuroaxonal damage below the clinical threshold, particularly in younger patients with less severe relapses, where both repair and compensation capacities are generally better. ³²,³³

In this context, the anterior visual pathway provides an ideal opportunity to study the degree of neuroaxonal damage: Acute ON represents the prototype of MS relapse as it is common comprising about 15-25% of relapses and displays both similar rates and predictors of recovery compared to other relapse types. ¹⁸,³⁴ Unlike in other MS relapses, the amount of neuroaxonal damage caused can be easily and reliably measured by means of OCT based measurement of retinal layer thicknesses. ¹⁷ ON-associated reduction of both pRNFL and GCIP thicknesses is completed and therefore measurable three to six months after the ON episode and its degree corresponds to the degree of structural neuroaxonal damage as well as functional visual recovery. ¹⁹,²⁰

Our results show that the degree of retinal neuroaxonal damage suffered after an episode of ON provides prognostic value for determining the likelihood of incomplete recovery from future relapses outside the visual system. This extends previous studies, which have shown that cross-sectionally measured retinal thickness predicts likelihood of EDSS progression and
long-term disability.\textsuperscript{15,16,35,36} We conducted sensitivity analyses with absolute values of pRNFL and GCIPL at baseline as additional covariates into the regression models, where both ΔGCIPL and ΔpRNFL remained significant predictors of incomplete relapse remission, showing the independent additional value of ON-associated retinal thinning over baseline thickness.

Of note, retinal thinning was still associated with future incomplete relapse remission in the subgroup of patients with complete recovery from the respective ON episode, clearly underlining the additional value retinal thinning provides over the degree of clinical relapse recovery.

In line with results from previous studies in MS regarding the prognostic value of pRNFL and GCIPL measurement, GCIPL performed better both regarding effect size and range of variation.\textsuperscript{16,17} This was particularly apparent when determining retinal thinning comparing the follow-up OCT scan with an OCT obtained at the time of the acute ON onset instead of a scan before ON onset. In the latter setting, ΔGCIPL was still robustly associated with relapse remission, while the confidence intervals (i.e., range of variation) for ΔpRNFL widened to an extent where statistical significance was lost. This can most likely be explained by the considerable amount of oedematous swelling often observed during acute ON in the axon-containing pRNFL (but not in the neuron-containing GCIPL), which may cause overestimation of axonal damage, a phenomenon known as pseudo-atrophy.\textsuperscript{17,19}

Consequently, we should strive to obtain a baseline OCT scan in every MS patient at the earliest possible time, ideally at initial diagnosis or first consultation, providing not only the opportunity for stratification of future risk of disease progression but also a reliable baseline scan in case of a future ON episode.\textsuperscript{15,16,35} In patients with acute MS-associated ON, an OCT scan should be obtained immediately and then after three to six months to allow assessment of the amount of neuroaxonal damage accumulated. If there is no pre-ON OCT scan available in
a patient with acute ON, pRNFL thinning should be interpreted very cautiously as the degree of thinning is likely over-estimated, while GCIPL thinning is still reliable. Another option in case of a missing pre-ON OCT scan might be using the clinically unaffected fellow eye as a substitute for a baseline scan. In our study, this was unfortunately not possible because the fellow eye was not routinely investigated in all patients. However, clinically unaffected eyes are frequently affected by subclinical ON, which needs to be considered as a potential confounder when using the fellow eye as baseline substitute. Therefore, we believe that comparison of the affected eye to a previous baseline scan of the same eye is preferable.

Going forward, retinal layer thinning seems as one of the most promising biomarkers of MS-associated neurodegeneration, particularly suitable to measure subclinical neuroaxonal damage below the clinical threshold, i.e. “the size of the iceberg below the water level”. Armed with an increasing array of highly effective DMT options, reliable biomarkers detecting subclinical processes are paramount for both determining the necessary level of efficacy and enabling early adaption of treatment.

This study confirms previous reports that incomplete relapse recovery is associated with higher age at relapse, previous incomplete relapse remission, severity of relapse and polysymptomatic relapse. While the impact of DMT status on relapse recovery is not extensively studied, it has been shown that the likelihood of incomplete relapse recovery is higher in untreated patients compared to patients on DMT. Our study adds to that evidence showing that highly effective DMT is independently associated with a decreased risk of incomplete relapse remission. However, due to the sample size available in our cohort, further analyses of single DMT substance groups were not feasible, but this an important future direction in the field.

There are several limitations to this study. The retrospective analyses of data collected in clinical routine creates a variety of possible biases, although these are mitigated by the...
standardized data collection and thorough quality control applied within in the VMSD. Still, the results of our study need to be validated in a prospective cohort.

The EDSS, which we used as outcome measure in this study, has some well-known limitations as it is strongly driven by walking impairment at the cost of insensitivity to reflecting changes in other functional systems such as vision, upper-extremity function or neuropsychological disability \(^{24}\). Much like other MS databases, the VMSD has begun to collect additional outcome data such as timed 25-foot walk test, 9-hole peg test or symbol digit modalities test. While we did not have sufficient data available to conduct valid analyses of other outcomes than EDSS in this study, this is an important future direction. The large majority of patients in our study was still fully ambulatory. The sample was insufficient to conduct a valid subgroup analysis of patients with restricted ambulation, thus limiting the applicability of our results to patients with more advanced disease. Inherent to the study design, patients in our cohort received a variety of DMT in a non-randomized fashion. While that could influence both degree of relapse recovery as well as of retinal thinning, we adjusted for different levels of DMT efficacy in the multivariable models, limiting the potential confounding impact. Although acquired in a real-world cohort, OCT scans were meticulously controlled for quality and confounding factors were ruled out rigorously, e.g. severe myopia, optic disc drusen or previous diagnoses of ophthalmological, neurological, systemic or drug-related causes of vision loss or retinal damage not attributable to MS. Biological variability and measurement errors are also minimized by a homogeneous single-center data set. These sources of errors might be increased when OCT protocols and devices vary, and multicenter data sets are used. Also, CNS imaging with quantitative measures of injury and repair, which could add to our understanding of the pathophysiologic processes involved, are not available for this cohort.
In conclusion, retinal layer thinning after optic neuritis, i.e. MS-associated neuroaxonal damage, may be useful as a marker of future relapse remission in RMS, potentially informing treatment strategy.

**Figure legends**

**Figure 1. Inclusion and exclusion flow diagram.**
DMT: Disease-modifying treatment. EDSS: Expanded Disability status scale. MS: multiple sclerosis. OCT: optical coherence tomography. ON: optic neuritis. VMSD: Vienna MS Database.

**Patients with MS included in VMSD (N = 1,428)**

Excluded (n = 1,261):
- Patients with primary progressive MS (144)
- Patients with age at onset <18 years (76)
- Patients not fulfilling inclusion criteria (990)
  - No documented episode of ON
  - No available spectral-domain OCT scan within 12 months before ON onset and within 1 week after ON onset
  - No available spectral-domain OCT scan within 3-6 months after ON onset
  - No documented non-ON MS relapse after the ON episode
  - Insufficient data on EDSS and/or DMT
- Patients with bilateral ON (17)
- Patients with insufficient OCT image quality (11)
  - At onset (8)
  - At follow-up (3)
- Patients with previous diagnoses of ophthalmological, neurologic, systemic or drug-related causes of vision loss or retinal damage not attributable to MS (23)

**Patients included (n = 167)**

**Figure 2. Retinal thinning after previous optic neuritis is associated with relapse remission.**
OCT: optical coherence tomography. OCT\textsubscript{baseline}: OCT scan within 12 months before optic neuritis onset. OCT\textsubscript{acute}: OCT scan within 1 week after optic neuritis onset. OCT\textsubscript{follow-up}: OCT scan 3-6 months after optic neuritis onset.
Figure 3. Retinal thinning after previous optic neuritis is independently associated with relapse remission in multivariable analyses.

Calculated by multivariate logistic regression models with incomplete relapse remission as the dependent variable and pRNFL/GCIPL thickness as the independent variable adjusted for sex, disease duration, time to HDMP, and DMT status at ON. Contribution of variables of interest to explanation of variance was assessed by change in $R^2$ through step-wise removal from the regression models.

Values above/below 1 indicate higher/lower probability of incomplete relapse remission.

H-DMT: defined as patients receiving either alemtuzumab, antiCD20 monoclonal antibodies (ocrelizumab, ofatumumab, rituximab), cladribine, natalizumab, or sphingosine-1-phosphate receptor modulators (fingolimod, ozanimod, siponimod) at relapse.

OCT: optical coherence tomography. OCT$_{\text{baseline}}$: OCT scan within 12 months before optic neuritis onset. OCT$_{\text{acute}}$: OCT scan within 1 week after optic neuritis onset. OCT$_{\text{follow-up}}$: OCT scan 3-6 months after optic neuritis onset. GCIPL: ganglion cell and inner plexiform layer.

OR: odds ratio. pRNFL: peripapillary retinal nerve fiber layer. 95% CI: 95% confidence interval
References


Table 1. Cohort characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>119 (71.3)</td>
</tr>
<tr>
<td>Age at ON onset (years)</td>
<td>36.5 (12.3)</td>
</tr>
<tr>
<td>Disease course</td>
<td>167 (100)</td>
</tr>
<tr>
<td>MS disease duration at ON (months)</td>
<td>9 (1 – 123)</td>
</tr>
<tr>
<td>Number of relapses before baseline</td>
<td>2 (1 – 6)</td>
</tr>
<tr>
<td>Relapse in year before baseline</td>
<td>55 (32.9)</td>
</tr>
<tr>
<td>Incomplete relapse remission before ON</td>
<td>32 (19.2)</td>
</tr>
<tr>
<td>Visual FS at ON (months)</td>
<td>2 (1 – 5)</td>
</tr>
<tr>
<td>Time to HDMP (days)</td>
<td>4 (1 – 33)</td>
</tr>
<tr>
<td>Number of previous DMTs</td>
<td>0 (0 - 3)</td>
</tr>
<tr>
<td>Any DMT</td>
<td>70 (41.9)</td>
</tr>
<tr>
<td>Interferon beta</td>
<td>15 (21.4)</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>23 (32.9)</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>18 (25.7)</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>6 (8.6)</td>
</tr>
<tr>
<td>S1PM</td>
<td>5 (7.1)</td>
</tr>
<tr>
<td>antiCD20-MAbs</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Median time on DMT at ON (months)</td>
<td>6 (0 – 123)</td>
</tr>
<tr>
<td>EDSS after ON (months)</td>
<td>1.0 (0 - 6.5)</td>
</tr>
<tr>
<td>Complete recovery from ON</td>
<td>87 (52.1)</td>
</tr>
</tbody>
</table>

Notes: ¹absolute number (percentage). ²mean and standard deviation. ³median and range. 
Table 2. Multivariable regression models regarding incomplete relapse remission.

<table>
<thead>
<tr>
<th>GCIPL models</th>
<th>OCT&lt;sub&gt;baseline&lt;/sub&gt; to OCT&lt;sub&gt;follow-up&lt;/sub&gt;</th>
<th>OCT&lt;sub&gt;acute&lt;/sub&gt; to OCT&lt;sub&gt;follow-up&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age at relapse (per 5 years increase)</td>
<td>1.42</td>
<td>1.16 – 1.83</td>
</tr>
<tr>
<td>Incomplete relapse remission before ON</td>
<td>1.57</td>
<td>1.09 – 2.13</td>
</tr>
<tr>
<td>Severe relapse&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.71</td>
<td>1.35 – 2.40</td>
</tr>
<tr>
<td>Polysymptomatic relapse&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.34</td>
<td>0.76 – 1.98</td>
</tr>
<tr>
<td>H-DMT at relapse&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.60</td>
<td>0.31 – 0.77</td>
</tr>
<tr>
<td>GCIPL thinning (per 5 µm)</td>
<td>2.43</td>
<td>1.67 – 3.93</td>
</tr>
</tbody>
</table>

R<sup>2</sup> overall: 0.773; p<0.001

<table>
<thead>
<tr>
<th>pRNFL models</th>
<th>OCT&lt;sub&gt;baseline&lt;/sub&gt; to OCT&lt;sub&gt;follow-up&lt;/sub&gt;</th>
<th>OCT&lt;sub&gt;acute&lt;/sub&gt; to OCT&lt;sub&gt;follow-up&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age at relapse (per 5 years increase)</td>
<td>1.40</td>
<td>1.10 – 1.93</td>
</tr>
<tr>
<td>Incomplete relapse remission before ON</td>
<td>1.61</td>
<td>1.03 – 2.44</td>
</tr>
<tr>
<td>Severe relapse&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.74</td>
<td>1.32 – 2.54</td>
</tr>
<tr>
<td>Polysymptomatic relapse&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.30</td>
<td>0.71 – 1.83</td>
</tr>
<tr>
<td>H-DMT at relapse&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.61</td>
<td>0.28 – 0.80</td>
</tr>
<tr>
<td>pRNFL thinning (per 10 µm)</td>
<td>1.91</td>
<td>1.13 – 3.26</td>
</tr>
</tbody>
</table>

R<sup>2</sup> overall: 0.667; p<0.001

FS: functional system, OCT: optical coherence tomography, OCT<sub>baseline</sub>: OCT scan within 12 months before optic neuritis onset. OCT<sub>acute</sub>: OCT scan within 1 week after optic neuritis onset. OCT<sub>follow-up</sub>: OCT scan 3-6 months after optic neuritis onset. ON: optic neuritis. GCIPL: ganglion cell and inner plexiform layer. OR<sup>a</sup>: odds ratio. pRNFL: peripapillary retinal nerve fiber layer. 95% CI: 95% confidence interval. Calculated by multivariate logistic regression models with incomplete relapse remission as the dependent variable and pRNFL/GCIPL thickness as the independent variable adjusted for sex, disease duration, time to HDMP, and DMT status at ON.

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Contribution of variables of interest to explanation of variance was assessed by change in $R^2$ through step-wise removal from the regression models.

aValues above/below 1 indicate higher/lower probability of incomplete relapse remission.

bdefined as Expanded Disability Status Scale (EDSS) increase at relapse $\geq 2$ points compared to the last documented EDSS before relapse.

cdefined as more than one EDSS FS involved with reference to monosymptomatic relapses (defined as only one FS involved).

ddefined as patients receiving either alemtuzumab, antiCD20 monoclonal antibodies (ocrelizumab, ofatumumab, rituximab), cladribine, natalizumab, or sphingosine-1-phosphate receptor modulators (fingolimod, ozanimod, siponimod) at relapse.
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