

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

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Abstract

Background and Objectives

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, we included patients with MS with (1) an episode of acute ON, (2) available spectral domain OCT scans within 12 months before ON onset ($OCT_{baseline}$), within 1 week after ON onset (OCT_{acute}), and 3–6 months after ON ($OCT_{follow-up}$), and (3) at least 1 non-ON relapse after the ON episode. Subsequent non-ON relapses were classified as displaying either complete or incomplete remission based on change in the Expanded Disability Status Scale score assessed 6 months after relapse. Association of retinal thinning in the peripapillary retinal nerve fiber layer ($\Delta pRNFL$) and macular ganglion cell and inner plexiform layer ($\Delta GCIPL$) with incomplete remission was tested by multivariate logistic regression models adjusting for age, sex, disease duration, relapse severity, time to steroid treatment, and disease-modifying treatment status.

Results

We analyzed 167 patients with MS (mean age 36.5 years [SD 12.3], 71.3% women, 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 1 relapse showed incomplete remission. In the multivariable analyses, incomplete remission of non-ON relapse was associated with $\Delta GCIPL$ thinning both from $OCT_{baseline}$ to $OCT_{follow-up}$ and from OCT_{acute} to $OCT_{follow-up}$ (OR 2.4 per 5 μm , $p < 0.001$, respectively), independently explaining 29% and 27% of variance, respectively. $\Delta pRNFL$ was also associated with incomplete relapse remission when measured from $OCT_{baseline}$ to $OCT_{follow-up}$ (OR 1.9 per 10 μm , $p < 0.001$), independently accounting for 22% of variance, but not when measured from OCT_{acute} to $OCT_{follow-up}$.

Discussion

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

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Glossary

ART = automatic real-time tracking; **DMT** = disease-modifying treatment; **EDSS** = Expanded Disability Status Scale; **FS** = functional score; **GCIPL** = ganglion cell and inner plexiform layer; **H-DMT** = highly effective DMT; **M-DMT** = moderately effective DMT; **MS** = multiple sclerosis; **OCT** = optical coherence tomography; **ON** = optic neuritis; **pRNFL** = peripapillary retinal nerve fiber layer; **VIF** = variance inflation factor; **VMSD** = Vienna MS database.

Multiple sclerosis (MS) is characterized by a highly heterogeneous disease course on an individual level.¹ The currently pathophysiologic 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.³⁻⁷ 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.^{4,8} Although 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.⁸⁻¹³ Optical coherence tomography (OCT) enables noninvasive, inexpensive, well-tolerated high-resolution *in vivo* imaging of distinct layers of the retina with excellent reproducibility.¹⁴ 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.¹⁵⁻¹⁷

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.¹⁸ ON causes a reduction in both RNFL and GCIPL thickness corresponding to the degree of neuroaxonal damage.^{19,20} 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

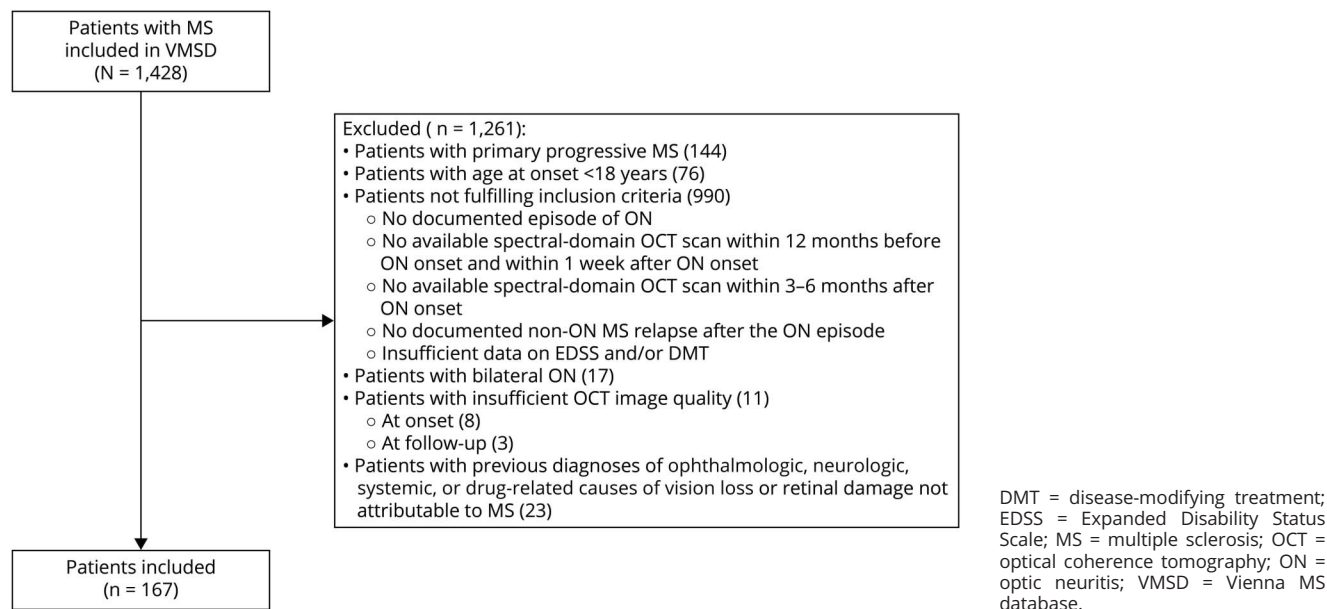
For this longitudinal observational study, we used the Vienna MS database (VMSD), which is established at the MS Clinic of the Department of Neurology, Medical University of Vienna, serving as both primary and reference center mainly for Vienna and its geographical catchment area. By July 2021, a cohort of

1,428 patients with MS diagnosed according to the respective McDonald criteria had been included.²¹⁻²³ VMSD case reports include demographic data, details of MS course (disease onset, time to diagnosis, relapses, Expanded Disability Status Scale [EDSS] score, and onset of secondary progression), diagnostic investigations (MRI, OCT, and CSF findings), and disease-modifying treatment (DMT) history (including initiation, interruption, changes, and adverse effects). Data are collected retrospectively at the first visit and prospectively whenever the patient returns for scheduled (every 3–6 months) follow-up or unscheduled visits.

We included patients with MS 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 1 non-ON MS relapse after the ON episode. Patients with bilateral ON were excluded from the study. The detailed inclusion/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.

The end point 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 the EDSS score assessed 6 months after relapse compared with the last documented EDSS score before relapse in the VMSD. Incomplete remission was defined as the EDSS score after relapse ≥ 0.5 points compared with the EDSS score before relapse.²⁴ Similarly, recovery from ON was classified based on the visual EDSS functional score (FS) with incomplete recovery defined as ≥ 1 -point increase in the visual FS after relapse compared with 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 before 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.²² Relapse severity was defined as mild (if the EDSS score increase at relapse was <2 points compared with the last documented EDSS score before relapse) or severe (EDSS score increase ≥ 2 points compared with the last documented EDSS score before relapse).⁸ Relapses were subclassified according to the EDSS FS involved as pyramidal, cerebellar, brainstem, sensory, or polysymptomatic. All relapses included (ON and non-ON) were treated with high-dose

Figure 1 Inclusion and Exclusion Flow Diagram



methylprednisolone (HDMP; 3,000–5,000 mg 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, anti-CD20 monoclonal antibodies (ocrelizumab, ofatumumab, and rituximab), cladribine, natalizumab, or sphingosine-1-phosphate receptor modulators (fingolimod, ozanimod, and 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 dilation in a dark room. For pRNFL measurement, a custom 3.4-mm ring scan (12°) centered on the optic nerve head was used (1,536 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 4 inner and outer quadrants of the circular grid centered around the foveola corresponding to the 3- and 6-mm rings as defined by the Early Treatment Diabetic Retinopathy Study.²⁵ 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.^{26,27} ON-associated thinning of the pRNFL (Δ pRNFL) and GCIPL (Δ GCIPL) 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 ophthalmologic (i.e., myopia greater than –4 diopters and optic disc drusen), neurologic, or drug-related causes of vision loss or retinal damage not attributable to MS.²⁶ 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

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

Statistics

Statistical analysis was performed using SPSS 26.0 (SPSS Inc, Chicago, IL) and R Statistical Software (Version 4.0.0). Univariate group comparisons were performed by the χ^2 test, Mann-Whitney *U* test, or independent *t* test (with Welch correction in case of unequal SDs between the groups) as appropriate. Univariate correlations were analyzed by the 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 Δ pRNFL/ Δ 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 stepwise removal from the regression models. A predefined subgroup analysis was conducted with the same model setup 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 the pRNFL and GCIPL at OCT_{baseline} as additional covariates into the regression models. We tested all variables for normal distribution by the 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 approach with pooling of estimates according to Rubin rules.²⁸ A 2-sided *p* value <0.05 was considered statistically significant.

Results

We analyzed 167 patients with MS 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.

Mean retinal thinning from OCT_{baseline} to OCT_{follow-up} was 25.3 μ m (SD 22.7) in the pRNFL and 13.2 μ m (SD 7.9) in the GCIPL, whereas from OCT_{acute} to OCT_{follow-up}, it was 43.1 μ m (SD 45.2) in the Δ pRNFL and 12.1 μ m (SD 8.2) in the Δ GCIPL.

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

Similarly, complete ON recovery (visual FS postrelapse \leq prerelapse) was associated with lower pRNFL and GCIPL

Table 1 Cohort Characteristics

	n = 167
Women ^a	119 (71.3)
Age at ON onset ^b (y)	36.5 (12.3)
Disease course	
RMS ^a	167 (100)
MS disease duration at ON ^c (mo)	9 (1–123)
No. relapses before baseline ^c	2 (1–6)
Relapse in year before baseline ^a	55 (32.9)
Incomplete relapse remission before ON	32 (19.2)
Visual FS at ON ^c	2 (1–5)
Time to HDMP (d)	4 (1–33)
DMT at ON	
No. previous DMTs ^c	0 (0–3)
Any DMT ^a	70 (41.9)
Interferon-beta ^a	15 (21.4)
Dimethyl fumarate ^a	23 (32.9)
Glatiramer acetate ^a	18 (25.7)
Teriflunomide ^a	6 (8.6)
S1PM ^a	5 (7.1)
Anti-CD20-MAbs ^a	3 (4.3)
Median time on DMT at ON ^c (mo)	6 (0–123)
EDSS score after ON ^c	1.0 (0–6.5)
Complete recovery from ON	87 (52.1)

Abbreviations: anti-CD20-MAbs = anti-CD20 monoclonal antibodies (ocrelizumab, rituximab, and ofatumumab); DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; FS = EDSS functional score; HDMP = high-dose methylprednisolone; MS = multiple sclerosis; RMS = relapsing MS; ON = optic neuritis; S1PM = sphingosine-1-phosphate receptor modulators (fingolimod, ozanimod, and siponimod).

^a Absolute number (percentage).

^b Mean and SD.

^c Median and range.

thinning from OCT_{baseline} to OCT_{follow-up} compared with incomplete ON recovery (Δ pRNFL: 19.9 μ m [SD 24.3] vs 31.1 μ m [SD 29.4], *p* = 0.008; Δ GCIPL: 10.2 μ m [SD 10.8] vs 16.5 μ m [SD 11.6], *p* < 0.001). Looking at thinning from OCT_{acute} to OCT_{follow-up}, only Δ GCIPL was associated with complete recovery (9.6 μ m [SD 11.3] vs 14.8 μ m [SD 12.2], *p* = 0.005) but not Δ pRNFL (37.6 μ m [SD 44.3] vs 49.1 μ m [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 1 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 the 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%). The median time on DMT at relapse was 20 months (interquartile range 7–31 months).

In univariate analyses, age at relapse was significantly higher in relapses with incomplete remission compared with 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%], and polysymptomatic 20/30 [66.6%], $p = 0.153$). Incomplete remission occurred in 81/215 (37.7%) of fully ambulatory patients (EDSS score at relapse < 4.0) compared with 18/35 (51.4%) with EDSS score ≥ 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 the pRNFL (30.4 μm [SD 22.8] vs 22.1 μm [SD 19.6], $p = 0.002$) and the GCIPL (16.3 μm [SD 9.5] vs 11.3 μm [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 (15.5 μm [SD 9.7] vs 9.7 μm [SD 9.8], $p < 0.001$) but not ΔpRNFL (44.6 μm [SD 29.9] vs 38.7 μm [SD 28.3], $p = 0.116$).

In the multivariable analyses, incomplete remission of non-ON relapse was associated with ΔGCIPL both from OCT_{baseline} to OCT_{follow-up} and from OCT_{acute} to OCT_{follow-up} (OR 2.4 per 5 μm , $p < 0.001$, respectively), independently explaining 29% and 27% of variance, respectively (Table 2, Figure 3). Thinning of the pRNFL was also associated with incomplete relapse remission when measured from OCT_{baseline} to OCT_{follow-up} (OR 1.9 per 10 μm , $p < 0.001$), independently accounting for 22% of variance but not when measured from OCT_{acute} to OCT_{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 ΔGCIPL from OCT_{baseline} to OCT_{follow-up} (OR 2.6 per 5 μm , 95% CI 1.4–4.5, $p < 0.001$) and from OCT_{acute} to OCT_{follow-up} (OR 2.5 per 5 μm , 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 ΔpRNFL , thinning from OCT_{baseline} to OCT_{follow-up} was also associated with incomplete relapse remission (OR 2.1 per 10 μm , 95% CI 1.1–5.8, $p = 0.032$), independently accounting for 18% of variance, but again ΔRNFL from OCT_{acute} to OCT_{follow-up} was not.

Sensitivity analyses including absolute values of the pRNFL and GCIPL at OCT_{baseline} as additional covariates into the regression models revealed that incomplete remission of non-ON relapse was still significantly associated with ΔGCIPL both from OCT_{baseline} to OCT_{follow-up} (OR 2.2 per 5 μm , $p < 0.001$, 23% variance explained) and from OCT_{acute} to OCT_{follow-up} (OR 2.1 per 5 μm , $p < 0.001$, 20% variance explained) and ΔpRNFL from OCT_{baseline} to OCT_{follow-up} (OR 1.6 per 10 μm , $p < 0.001$, 16% variance explained).

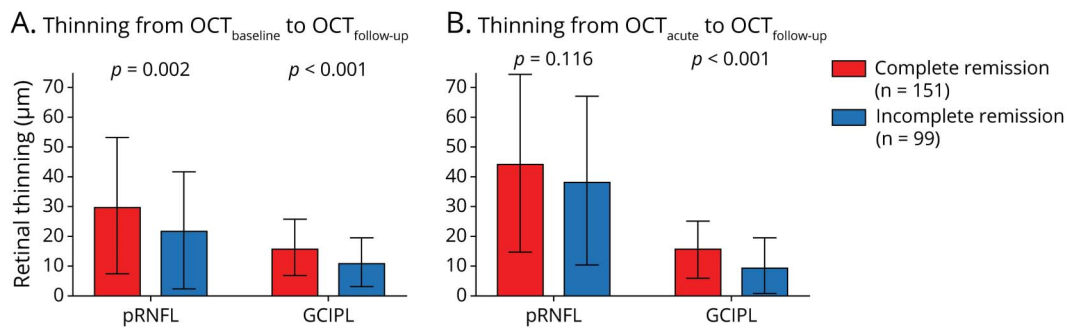
Discussion

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 ON 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 effect was higher when using GCIPL rather than pRNFL thinning as it explained more of the variance in relapse remission and ΔGCIPL —but not ΔpRNFL —remained robustly associated when determining retinal thinning at follow-up from an OCT scan obtained within 1 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, neurologic reserve function, cortical and connective remodeling, or

Figure 2 Retinal Thinning After Previous Optic Neuritis Is Associated With Relapse Remission



(A) Measuring from OCT at baseline to follow-up. (B) Measuring from OCT during acute optic neuritis to follow-up. OCT = optical coherence tomography; OCT_{baseline} = OCT scan within 12 months before optic neuritis onset; OCT_{acute} = OCT scan within 1 week after optic neuritis onset; OCT_{follow-up} = OCT scan 3–6 months after optic neuritis onset.

electrophysiologic 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}

Table 2 Multivariable Regression Models Regarding Incomplete Relapse Remission

GCIPL models	OCT _{baseline} to OCT _{follow-up}				OCT _{acute} to OCT _{follow-up}			
	OR ^a	95% CI	p Value	Change in R ²	OR ^a	95% CI	p Value	Change in R ²
Age at relapse (per 5-y increase)	1.42	1.16–1.83	0.025	0.103	1.40	1.13–1.87	0.015	0.100
Incomplete relapse remission before ON	1.57	1.09–2.13	0.024	0.094	1.56	1.04–2.23	0.031	0.094
Severe relapse ^b	1.71	1.35–2.40	0.002	0.113	1.74	1.37–2.39	0.002	0.115
Polysymptomatic relapse ^c	1.34	0.76–1.98	0.341	0.021	1.29	0.64–2.13	0.477	0.014
H-DMT at relapse ^d	0.60	0.31–0.77	<0.001	0.148	0.61	0.31–0.78	<0.001	0.138
GCIPL thinning (per 5 µm)	2.43	1.67–3.93	<0.001	0.290	2.40	1.65–3.96	<0.001	0.273
	R ² overall: 0.773; p < 0.001				R ² overall: 0.734; p < 0.001			
pRNFL models	OCT _{baseline} to OCT _{follow-up}				OCT _{acute} to OCT _{follow-up}			
	OR ^a	95% CI	p Value	Change in R ²	OR ^a	95% CI	p Value	Change in R ²
Age at relapse (per 5-y increase)	1.40	1.10–1.93	0.032	0.097	1.42	1.15–1.95	0.025	0.102
Incomplete relapse remission before ON	1.61	1.03–2.44	0.030	0.090	1.62	1.04–2.39	0.030	0.093
Severe relapse ^b	1.74	1.32–2.54	0.006	0.111	1.80	1.33–2.61	0.004	0.114
Polysymptomatic relapse ^c	1.30	0.71–1.83	0.366	0.018	1.26	0.69–1.93	0.552	0.010
H-DMT at relapse ^d	0.61	0.28–0.80	<0.001	0.131	0.58	0.26–0.78	<0.001	0.141
pRNFL thinning (per 10 µm)	1.91	1.13–3.26	<0.001	0.220	1.76	0.90–2.90	0.202	0.050
	R ² overall: 0.667; p < 0.001				R ² overall: 0.510; p < 0.001			

FS = functional system; GCIPL = ganglion cell and inner plexiform layer; OCT = optical coherence tomography; OCT_{acute} = OCT scan within 1 week after optic neuritis onset; OCT_{baseline} = OCT scan within 12 months before optic neuritis onset; OCT_{follow-up} = OCT scan 3–6 months after optic neuritis onset; ON = optic neuritis; pRNFL = peripapillary retinal nerve fiber layer.

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 R² through stepwise removal from the regression models.

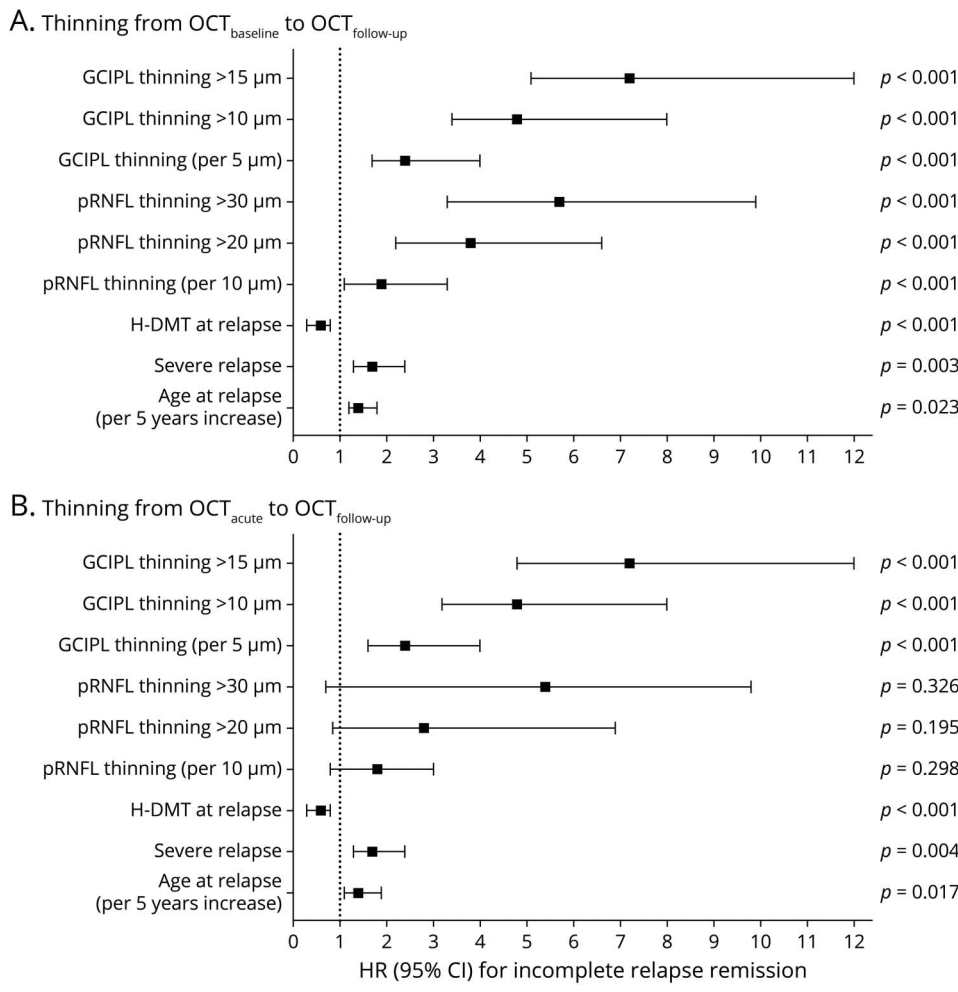
^a Values above/below 1 indicate higher/lower probability of incomplete relapse remission.

^b Defined as the Expanded Disability Status Scale (EDSS) score increase at relapse ≥2 points compared with the last documented EDSS score before relapse.

^c Defined as more than 1 EDSS FS involved with reference to monosymptomatic relapses (defined as only one FS involved).

^d Defined as patients receiving either alemtuzumab, anti-CD20 monoclonal antibodies (ocrelizumab, ofatumumab, and rituximab), cladribine, natalizumab, or sphingosine-1-phosphate receptor modulators (fingolimod, ozanimod, and siponimod) at relapse.

Figure 3 Retinal Thinning After Previous Optic Neuritis Is Independently Associated With Relapse Remission in Multivariable Analyses



(A) Measuring thinning from OCT at baseline to follow-up. (B) Measuring thinning from OCT during acute optic neuritis to follow-up. 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 stepwise removal from the regression models. Values above/below 1 indicate higher/lower probability of incomplete relapse remission. GCIPL = ganglion cell and inner plexiform layer; H-DMT = defined as patients receiving either alemtuzumab, anti-CD20 monoclonal antibodies (ocrelizumab, ofatumumab, and rituximab), cladribine, natalizumab, or sphingosine-1-phosphate receptor modulators (fingolimod, ozanimod, and siponimod) at relapse; OCT = optical coherence tomography; OCT_{acute} = OCT scan within 1 week after optic neuritis onset; OCT_{baseline} = OCT scan within 12 months before optic neuritis onset; OCT_{follow-up} = OCT scan 3–6 months after optic neuritis onset; pRNFL = peripapillary retinal nerve fiber layer.

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 with 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 GCIPL thicknesses is completed and therefore measurable 3–6 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 occurred 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 the likelihood of EDSS score progression and long-term disability.^{15,16,35,36} We

conducted sensitivity analyses with absolute values of the pRNFL and GCIPL at baseline as additional covariates into the regression models, where both Δ GCIPL and Δ pRNFL 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.^{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, Δ GCIPL was still robustly associated with relapse remission, whereas the CIs (i.e., range of variation) for Δ pRNFL widened to an extent

where statistical significance was lost. This can most likely be explained by the considerable amount of edematous 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 pseudoatrophy.^{17,19}

Consequently, we should strive to obtain a baseline OCT scan in every patient with MS 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.^{15,16,35} In patients with acute MS-associated ON, an OCT scan should be obtained immediately and then after 3–6 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 overestimated, whereas 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.^{37–39} 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, that is, “the size of the iceberg below the water level.” Armed with an increasing array of H-DMT options, reliable biomarkers detecting subclinical processes are paramount for both determining the necessary level of efficacy and enabling early adaption of treatment.²⁴

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.^{5,8,9,12} Although the effect 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 with patients on DMT.^{6,13} Our study adds to that evidence showing that H-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 create a variety of possible biases, although these are mitigated by the standardized data collection and thorough quality control applied within in the VMSSD. Still, the results of our study need to be validated in a prospective cohort.

The EDSS score, 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 VMSSD has begun to collect additional outcome data such as timed 25-foot walk test, 9-hole peg test, or symbol digit modalities test. Although we did not have sufficient data available to conduct valid analyses of other outcomes than the EDSS score in this study, this is an important future direction. The large majority of patients in our study were 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 nonrandomized 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 effect. 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 ophthalmologic, neurologic, 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 multi-center 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, is not available for this cohort.

In conclusion, retinal layer thinning after ON, that is, MS-associated neuroaxonal damage, may be useful as a marker of future relapse remission in RMS, potentially informing treatment strategy.

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Appendix 1 (continued)

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