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Peripapillary retinal nerve fibre layer as measured by optical coherence tomography is a prognostic biomarker not only for physical but also for cognitive disability progression in multiple sclerosis

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Abstract

Background: Peripapillary retinal nerve fibre layer (pRNFL) thickness is emerging as a marker of axonal degeneration in multiple sclerosis (MS).

Objective: We aimed to prospectively assess the predictive value of pRNFL for progression of physical and cognitive disability in relapsing-remitting MS (RRMS).

Methods: In this 3-year longitudinal study on 151 RRMS patients, pRNFL was measured by spectral-domain optical coherence tomography (OCT). We used proportional hazard models, correcting for age, sex, disease duration, Expanded Disability Status Scale (EDSS) and Symbol Digit Modalities Test (SDMT) at baseline, to test a pRNFL thickness ≤88 µm at baseline for prediction of EDSS progression and cognitive decline. We also evaluated the decrease in pRNFL thickness from baseline to year 3 in a multivariate linear regression model.

Results: pRNFL thickness ≤88 µm was independently associated with a threefold increased risk of EDSS progression ($p < 0.001$) and a 2.7-fold increased risk of cognitive decline within the subsequent 3 years ($p < 0.001$). Mean pRNFL delta was −5.3 µm (SD, 4.2). It was significantly negatively impacted by EDSS progression, cognitive decline, higher age and disease duration, while positively impacted by disease-modifying therapy (DMT).

Conclusion: Cross-sectional and longitudinal monitoring of pRNFL is useful as a biomarker for prediction of physical and cognitive disability progression in patients with RRMS in everyday clinical practice.

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Introduction

Multiple sclerosis (MS) disease course is highly variable among individuals and highly unpredictable, especially in terms of future risk of disability.[1] Thus, there is a strong need for reliable biomarkers in this regard. Retinal neurodegenerative signs occur in the majority of MS patients, more frequently and more pronounced in patients with progressive disease course, longer disease duration and with marked disability and brain atrophy.[2] Optical coherence tomography (OCT) is a non-invasive, inexpensive, well-tolerated high-resolution imaging technique used for the assessment of retinal structures. Retrograde degeneration of optic nerve axons is captured by OCT and reflected by thinning of the peripapillary retinal nerve fibre layer (pRNFL), which consists of unmyelinated axons only.[2] pRNFL thickness is associated with physical disability and brain

atrophy in MS.[3–5] However, there are only cross-sectional studies showing an association between pRNFL thickness and cognitive impairment.[6,7] Recently, pRNFL thickness ≤88 µm was reported to indicate a twofold increased risk of physical disability worsening within subsequent years.[8] In this study, we aimed to assess the usefulness of cross-sectional monitoring of pRNFL in prediction of not only physical, but also cognitive disability progression in relapsing-remitting MS (RRMS) using this cut-off point. In addition, we also investigated the value of longitudinal pRNFL monitoring in this regard.

Methods

We prospectively included 151 consecutive RRMS patients aged between 18 and 65 years from the MS Clinic of the Clinical Department of Neurology at the Medical University Innsbruck. RRMS was diagnosed according to the 2010 McDonald criteria.[9]

Retinal atrophy is more pronounced in eyes with acute optic neuritis (ON) than in unaffected eyes.[10,11] Therefore, we only included patients with at least one eye without a clinical history of previous ON and excluded eyes with previous clinical history of ON from the analysis to avoid a confounding effect of ON.[8] Other exclusion criteria were previous diagnoses of ophthalmological (e.g. severe hyperopia/myopia), neurological, or drug-related causes of vision loss or retinal damage not attributable to MS.[5,12]

pRNFL thickness was measured by two experienced technicians at baseline and after 3 years by use of the same spectral-domain OCT with Spectralis (Heidelberg Engineering, Heidelberg, Germany; software Heidelberg eye explorer software version 5.4.8.0) without pupil dilatation in a dark room on both eyes of each patient. For evaluation of pRNFL, a custom 3.4-mm ring scan (12°) centred on the optic nerve head was used (automatic real-time ART 100). Image processing was conducted semi-automated with manual correction of obvious errors. All examinations were checked for sufficient quality using OSCAR-IB criteria.[13]

For patients without a history of ON, pRNFL thickness was calculated as the mean of the values for both eyes. For patients with a history of unilateral ON, only the values of eyes without ON were used in the analyses.[8] Patients suffering ON in an eye initially included in the analysis were excluded from the longitudinal part of the study.

Clinical study visits were conducted at baseline and after 1 (Y1), 2 (Y2) and 3 years (Y3) of follow-up. A structured questionnaire regarding demographic data, neurological and treatment history including disease-modifying therapy (DMT) and occurrence and date of relapses was obtained from each participant at every visit. A relapse was defined as patient-reported symptoms or objectively observed neurological signs typical of an acute central nervous system (CNS) inflammatory demyelinating event with duration of at least 24 hours in the absence of fever or infection and separated from the last relapse by at least 30 days.[14] Relapse activity was defined as occurrence of one or more confirmed relapses during the observation period.

Expanded Disability Status Scale (EDSS) was obtained at every visit.[15] If a relapse had occurred within 6 months before the scheduled visit, EDSS was only considered when confirmed after 6 months. EDSS progression was defined as a confirmed EDSS increase of ≥1.0 point in patients with a baseline score of ≤5.5, or an increase of ≥0.5 points in patients with a baseline score of >5.5 sustained for at least 12 months as compared to baseline.

For assessment of cognitive function, we chose the Symbol Digit Modalities Test (SDMT) as a well-established, easy obtainable and sensitive screening test for cognitive dysfunction in MS, particularly suitable for longitudinal assessment of MS-related cognitive changes as it does not have significant practice effects.[16–18] The SDMT was performed at each visit. Based on previous observations of longitudinal changes in the SDMT score in MS patients and in concordance with the suggestion of the Multiple Sclerosis Outcome Assessments Consortium (MSOAC), we defined cognitive decline as a loss of ≥4 points or a ≥10% decrease in SDMT score as compared to baseline. Any decrease was only considered when the SDMT deterioration was sustained for at least 12 months.[18]

The investigators performing the OCT were blinded to clinical parameters and the investigators assessing relapses, EDSS and SDMT were blinded to OCT results.

The study was approved by the ethics committee of the Medical University Innsbruck (ethical approval number: AM3743-281/4.3) and all participants gave written informed consent before inclusion.

Statistics

Statistical analysis was performed using SPSS 24.0 (SPSS Inc, Chicago, IL, USA). Categorical variables

were expressed in frequencies and percentages, continuous variables as mean and standard deviation or 95% confidence interval (CI). Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. Univariate 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.

We used Cox proportional hazard models correcting for age, disease duration and EDSS at baseline to test the value of pRNFL thickness ≤88 µm for prediction of EDSS progression.[8] We tested all variables for normal distribution by Kolmogorov–Smirnov 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. As our cohort was not large enough to generate and validate different cut-off values, we used the previously reported cut-off value of ≤88 µm which represents the lowest tertile of normative values of Spectralis. We used the same cut-off value in a Cox proportional hazard model correcting for age, disease duration and SDMT at baseline for prediction of cognitive decline.

We also calculated the difference in pRNFL thickness from baseline to year 3 (labelled as pRNFL delta). We performed univariate correlation analyses between pRNFL delta and age, sex, disease duration, relapse activity, EDSS progression, cognitive decline and DMT (no DMT vs DMT exposure during the whole observation period). We also performed pRNFL delta comparisons regarding different DMTs (no DMT vs one single DMT during observation period vs DMT switch during observation period). Subsequently, we included all variables, which showed statistically significant correlations to pRNFL delta on a univariate basis, in a multivariate linear regression model. We could only include DMT versus no DMT in the multivariate model since inclusion of more grades of freedom would have resulted in overmatching compromising the validity of our model.

Results

Demographics and characteristics of the study cohort are given in Table 1. In all, 141 of 151 (93.4%) recruited patients completed the study. In all, 10 patients were lost to follow-up (8 before the first follow-up visit and 2 before the second follow-up) and therefore had to be censored for statistical analysis.

Overall, EDSS progression occurred in 46 (32.6%) and cognitive decline in 36 (25.5%) patients. In total, 46 (32.6%) patients had a pRNFL thickness equal to or smaller than 88 µm at baseline. This group was significantly older (38.6 vs 33.5 years; $p<0.001$), had a longer disease duration (6.5 vs 4.4 years; $p<0.001$), a higher median EDSS (2.5 vs 1.0; $p<0.001$) and a lower SDMT (49.3 vs 56.6; $p<0.001$) at baseline. There were no significant group differences regarding sex or DMT status at baseline. Using a multivariate Cox proportional hazard model (correcting for age, disease duration and EDSS at baseline), a pRNFL thickness ≤88 µm was associated with a threefold increased hazard ratio (HR: 2.96; 95% CI: 1.56–5.65; $p<0.001$) of EDSS progression within the subsequent 3 years (Figure 1). Using a similar model (correcting for age, disease duration and SDMT at baseline), a pRNFL thickness ≤88 µm was associated with a 2.7-fold increased risk (HR: 2.69; 95% CI: 1.31–5.53; $p=0.0047$) of cognitive decline within the subsequent 3 years (Figure 2). In both models, higher age at baseline (per 5 years: HR for EDSS progression 1.34; 95% CI: 1.12–1.57; $p=0.023$; HR for cognitive decline 1.23; 95% CI: 1.02–1.43; $p=0.042$), longer disease duration (per 5 years: HR for EDSS progression 1.67; 95% CI: 1.54–1.81; $p=0.003$; HR for cognitive decline 1.59; 95% CI: 1.43–1.75; $p=0.010$) and higher EDSS at baseline (per 1 EDSS point: HR for EDSS progression 1.73; 95% CI: 1.61–1.86; $p=0.001$; HR for cognitive decline 1.62; 95% CI: 1.45–1.79; $p=0.006$) were associated with increased risk of EDSS progression and cognitive decline within the subsequent 3 years. Overall, 78.3% of patients with EDSS progression and 71.1% of patients with cognitive decline were correctly classified by pRNFL thickness ≤88 µm.

Overall, mean pRNFL delta was −5.3 µm (SD, 4.2) within 3 years. pRNFL decrease was significantly higher in patients with EDSS progression and cognitive decline during the observation period (Figure 3(a) and (b)). There was also a stronger decrease in pRNFL in patients with relapse activity although this did not reach statistical significance (Figure 3(c)). pRNFL decrease was significantly lower in patients receiving only natalizumab or only alemtuzumab compared to patients receiving either no DMT, or only interferon beta, glatiramer acetate, dimethyl fumarate, fingolimod or patients who switched DMTs during the observation period (Figure 3(d)). Decrease in pRNFL was also stronger in patients with a pRNFL ≤88 µm at baseline as compared to patients with a pRNFL >88 µm at baseline (−7.5 vs −4.2; $p<0.001$).

A multivariate linear regression model regarding pRNFL delta showed that EDSS progression and cognitive decline had the strongest negative impact on

Table 1. Demographics and clinical characteristics.

	n = 151	*n* = 143	*n* = 141	*n* = 141
Females[a]	119 (78.8)			
Age[b] (years)	35.1 (9.4)			
MS disease duration[b] (years)	5.8 (2.7)			
Number of DMTs prior to baseline[c]	1 (0–3)			
Relapse[a]	53 (35.1)			
Previous optic neuritis[a]	30 (19.9)			
	Baseline	Year 1	Year 2	Year 3
EDSS[c]	1.5 (0–6.5)	2.0 (0–7)	2.0 (0–7)	2.5 (0–8.5)
SDMT[b]	54.0 (10.1)	53.3 (9.8)	52.1 (10.4)	50.9 (11.3)
pRNFL thickness[b]	91.7 (13.2)			86.4 (12.9)
Current DMT[a]				
Interferon beta	42 (27.8)	40 (27.9)	30 (21.3)	26 (18.4)
Glatiramer acetate	20 (13.2)	19 (13.5)	11 (7.8)	8 (5.7)
Dimethyl fumarate	1 (0.7)	8 (5.7)	18 (12.8)	16 (11.3)
Fingolimod	10 (6.6)	13 (9.2)	16 (11.3)	22 (15.6)
Natalizumab	14 (9.2)	19 (13.3)	23 (16.3)	29 (20.6)
Alemtuzumab	2 (1.4)	2 (1.4)	2 (1.4)	2 (1.4)
All DMTs	90 (59.6)	99 (70.2)	100 (70.9)	103 (73.0)

DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; SDMT: Symbol Digit Modalities Test; pRNFL: peripapillary nerve fibre layer.
[a]Number (percentage).
[b]Mean and standard deviation.
[c]Median and range.

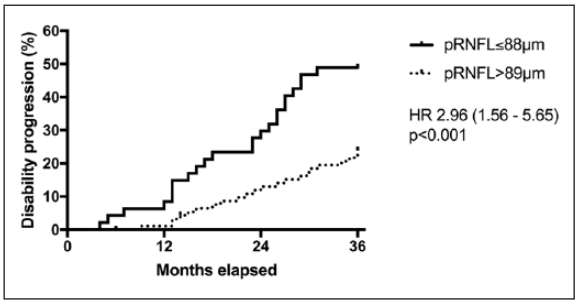

Figure 1. Risk of EDSS progression according to pRNFL at baseline.
pRNFL: peripapillary retinal nerve fibre layer; HR: hazard ratio (95% confidence interval).

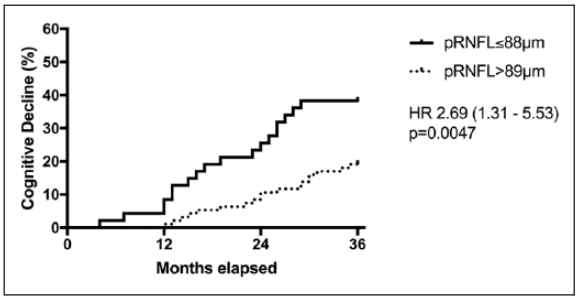

Figure 2. Risk of cognitive decline according to pRNFL at baseline.
pRNFL: peripapillary retinal nerve fibre layer; HR: hazard ratio (95% confidence interval).

pRNFL decrease during the observation period. Higher age and longer disease duration were also significantly associated with stronger decrease in pRNFL although to a lesser extent. Exposure to DMT did have a small but significant positive impact on pRNFL delta (Table 2).

Discussion

In this 3-year, prospective longitudinal study on 151 RRMS patients, we aimed to assess the predictive value of cross-sectional (using a previously reported cut-off value of pRNFL ≤88 µm) and longitudinal monitoring (using decrease in pRNFL over 3 years) of pRNFL thickness for physical and cognitive disability progression.

There are two key findings resulting from our study: (1) a pRNFL ≤88 µm at baseline is associated with a threefold increased risk of EDSS progression and a 2.7-fold increased risk of cognitive decline within the subsequent 3 years and (2) the decrease in pRNFL

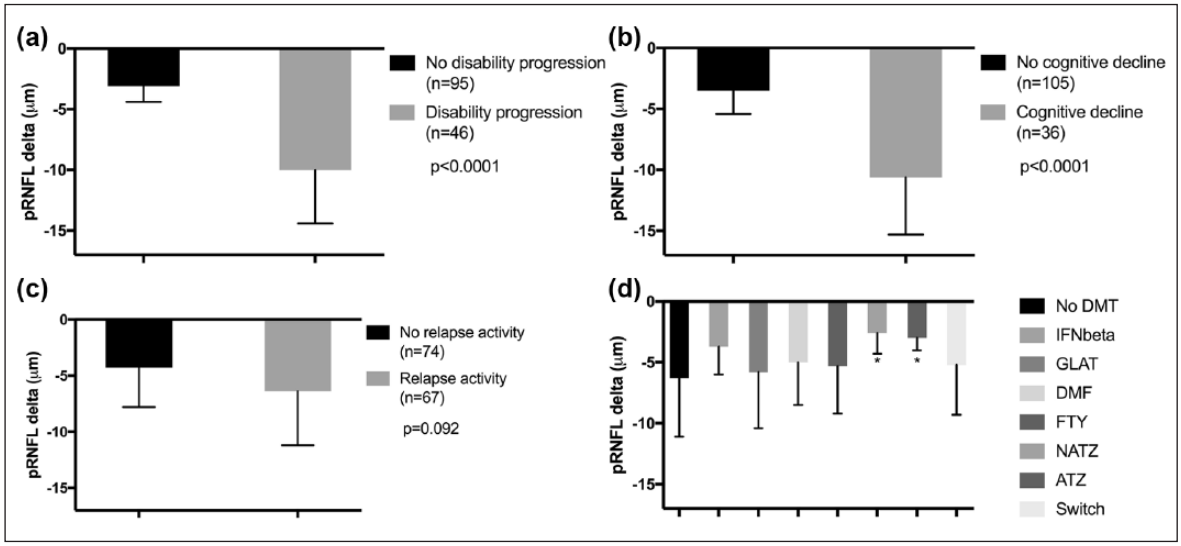

Figure 3. Univariate differences in pRNFL delta according to EDSS progression (Panel a), cognitive decline (b), relapse activity (c) and different disease-modifying agents (d).
pRNFL: peripapillary retinal nerve fibre layer; DMT: disease-modifying therapy; IFN-beta: interferon beta preparations; GLAT: glatiramer acetate; DMF: dimethyl fumarate; FTY: fingolimod; NATZ: natalizumab; ATZ: alemtuzumab; switch: change of DMT during observation period.
pRNFL delta values are shown as means with standard deviation. *p value < 0.05 compared to no DMT, IFN-beta, GLAT, DMF, FTY, NATZ, ATZ and switch after correction for multiple comparison (Bonferroni).

Table 2. Linear regression model regarding pRNFL delta.

	Mean pRNFL change	95% confidence interval	p value
Age at baseline (per year)	−0.7	−1.3 to −0.1	0.039
Disease duration (per year)	−0.5	−1.2 to 0.2	0.217
Male sex	−0.2	−1.3 to 0.8	0.694
EDSS progression	−5.6	−6.7 to −4.4	<0.001
Relapse activity	−1.1	−2.0 to 0.1	0.223
Cognitive decline	−2.4	−3.6 to −1.2	0.034
DMT exposure	0.2	0.1 to 0.5	0.026

DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; pRNFL: peripapillary retinal nerve fibre layer.
R^2: 0.735; p < 0.001.

thickness over 3 years is strongly negatively impacted by EDSS progression and cognitive decline and to a lesser degree by higher age and disease duration, while it is positively impacted by DMT exposure.

These results are a further step towards validation of pRNFL measurement as a biomarker to monitor physical and cognitive disability progression in RRMS.

The association of pRNFL thinning and neurodegenerative changes such as axonal loss with physical and cognitive disability and brain atrophy is well established in MS.[3–6,12,19] However, it is unclear whether these changes occur slowly progressive or relapsing (meaning an acute to subacute loss of axons followed by stable phases without loss of axons) and whether they are attributable to retrograde axonal degeneration or microscopic optic nerve inflammation, trans-synaptic degeneration, primary retinal neurodegeneration or systemic effects of inflammation.[3–6,12,19] The currently prevailing concept of clinically apparent disease progression suggests a threshold of CNS damage after which further damage translates to increasing clinical disability.[8,20] This threshold might transfer to a level of axonal damage which is reflected by pRNFL thickness. We found that EDSS progression and cognitive decline did have a significant impact on pRNFL thinning – while relapse activity did not

– which lends support to the notion that pRNFL thinning is more a steadily progressive rather than a relapsing process.

Mean rates of pRNFL thinning are mostly reported to range from 1 to 2 µm/year with faster thinning occurring in active MS and it was suggested that repeated pRNFL measurements should be performed at intervals of at least 2–3 years to avoid bias due to SD-OCT resolution issues.[4,10,21] There is only one report which did not find pRNFL thinning over 2 years, but these results are limited by a low sample size and inconsistent follow-up intervals.[22] We found a mean pRNFL thickness decrease of 5.3 µm over 3 years translating to 1.8 µm/year, strongly exceeding the mean rate of age-related average RNFL thinning in healthy individuals which ranges from 0.52 to 0.54 µm per year.[23,24]

Retinal layer thinning has been reported to be slowed in patients treated with natalizumab compared to patients with interferon beta or glatiramer acetate indicating the potential utility of OCT measures for monitoring neurodegenerative (by potentially less inflammatory triggers) treatment effects in RRMS.[25] We found slower rates of pRNFL thinning in patients treated with natalizumab or alemtuzumab as compared to patients receiving any other DMT or no DMT, which clearly supports this concept. Still, this does raise the paramount question whether most of DMTs – especially those classified as basic immunomodulatory drugs – are truly able to impact disease progression over time. Still, our study was neither designed nor powered to investigate the impact of different DMTs on pRNFL thinning in a multivariate model but urgently warranting further prospective studies on this matter with larger sample sizes.

Magnetic resonance imaging (MRI)-based measurement of brain volume is the most commonly used method for assessment of neurodegeneration in MS. Since our study did not include MRI measures, we were unable to investigate any associations to MRI measures such as brain atrophy. However, OCT has significant advantages as it is non-invasive, relatively inexpensive, easy to perform and accessible, fast, and produces reliable quantitative measures.[26] OCT measures are also easier to standardize with no confounding inter-rater variability enabling intra-individual longitudinal monitoring. In addition, in the absence of acute ON, pRNFL thickness is not directly affected by inflammation as compared to MRI – probably because MRI is reflecting both unmyelinated and myelinated axons – which makes it a useful biomarker to complement MRI in routine monitoring of MS. In this light, we suggest that pRNFL thickness should be included in the concept of 'no evidence of disease activity' (NEDA).

Our study has several limitations. We did not include ganglion cell layer (GCL) or ganglion cell layer and inner plexiform layer (GCIPL) thickness which was also reported to reflect the global MS disease process.[4,27,28] We concentrated on pRNFL since it is the most widely used OCT measure in MS making it the most likely candidate for usage as a biomarker in MS. However, GCL or GCIPL might be of additional value in the future warranting further studies in this context. In case of unilateral ON, only the pRNFL thickness of the eye without ON was used in the analyses. Occurrence of previous unilateral ON might have a confounding effect on pRNFL of the unaffected eye by retrograde axonal degeneration through the connection of both optic nerves via the optic chiasm.[10] Moreover, our results cannot be applied to patients with progressive courses of MS or patients who had bilateral ON or ON affecting both eyes at different time since they were excluded from our study. While the SDMT is a sensitive screening test for cognitive dysfunction in MS recommended for longitudinal assessment of MS-related cognitive changes, it does not provide a complete evaluation of cognitive status of MS patients.

In conclusion, both cross-sectional and longitudinal monitoring of pRNFL is a useful biomarker for prediction of physical and cognitive disability progression in patients with RRMS. Based on the existing body of evidence, pRNFL should be included in routine disease monitoring in everyday clinical practice.

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Declaration of Conflicting Interests

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