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Associations of optical coherence tomography with disability and brain MRI volumetry in patients with multiple sclerosis

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ABSTRACT

Aim of the study. To investigate in a cross-sectional study the correlations of optical coherence tomography (OCT) with clinical and magnetic resonance imaging (MRI) parameters in multiple sclerosis (MS) patients.

Material and methods. OCT parameters include the peripapillary retinal nerve fibre layer (pRNFL) and ganglion cell complex (GCC). Brain magnetic resonance volumetry (T2- and T1- lesions volume, whole brain volume and grey matter volume) was evaluated using the Icobrain program. Clinical data was compared according to the history of optic neuritis (HON). Correlations were determined between OCT parameters and demographic (age, gender), clinical (disease duration, Expanded Disability Status Scale score [EDSS]), and MRI data.

Results. Out of 83 recruited people with MS, 27 had HON. The mean age of 75 patients with non-ON eyes was 42.08 ± 10.36 years, and 70.67% of the sample were females. Significant correlations were found between pRNFL and disability, along with several brain MRI-volumetry variables (Fluid-attenuated Inversion Recovery lesions volume [FLAIR]; T1-hypointense lesions volume; T1-lesions volume change; T1-volume lesions enlarging; whole brain volume; whole brain volume normative percentile; and volume of periventricular lesions). Multivariable linear regression analysis showed that age, pRNFL and GCC were significantly associated with T1-hypointense lesions volume change (the model explained 24% of the overall variance of the dependent variable).

Conclusions. The pRFNL value correlates with disability and brain MRI-volumetric parameters in MS patients, serving as a useful neurodegeneration and inflammation surrogate marker.

Key words: neuro-ophthalmology, brain magnetic resonance volumetry, multiple sclerosis, optical coherence tomography

Introduction

Multiple sclerosis (MS) is an autoimmune chronic inflammatory central nervous system disease with an unpredictable course. Irreversible neuro-axonal loss is a substrate of chronic neurodegeneration, the principal cause of patient disability. Neurodegeneration is considered a diffuse, silent and ongoing process that spreads all over the CNS, including the optic

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nerves. Current research is focused on the identification of sensitive and accessible imaging biomarkers related to disease activity in order to optimise treatment in daily practice.

Optical coherence tomography (OCT) is an easily accessible, non-invasive and rapid imaging evaluation of the retina and optic nerve fibres. OCT has proven to be very useful with regards to research, monitoring and predicting disability in multiple sclerosis [1–4]. Several studies have identified OCT as a useful biomarker of neuro-axonal damage in MS with the potential to be a tool complementary to magnetic resonance imaging (MRI) in MS practice. A few studies have found an association between OCT parameters and MRI volumetric parameters using different methods of brain and spinal cord MRI volumetry [1, 5–7].

We postulated that OCT parameters could be used as a substitute marker for brain volume change in MS patients. Therefore, we investigated in an MS cohort the OCT correlations with demographic, clinical and brain MRI-volumetric parameters, using the Icobrain program. To the best of our knowledge, these variables have not been previously studied in such a context.

Material and methods

Study design

This was an observational cross-sectional study carried out by the Neurology and Ophthalmology Departments of Pavol Jozef Šafárik University and University Hospital L. Pasteur in Košice, Slovakia from May 2020 to September 2021 after approval by the research ethics committee of our institution (protocol 2016/EK/120021).

Study sample and clinical assessment

Eighty-three consecutive patients with MS were eligible to participate in the study and enrolled in a cohort study (see Fig. 1 for study design). The study was performed in accordance with the Good Clinical Practice standard and the Declaration of Helsinki.

The inclusion criteria were: 1) a diagnosis of MS based on the revised 2017 McDonald criteria; 2) age 18 years or older; and 3) the ability to give written informed consent. The exclusion criteria were: 1) the presence of a comorbidity and treatments that could influence OCT parameters (pathology of the retina considered by the OSCAR-IB criteria) [8]; 2) optic neuritis or MS relapse in the last six months and the use of corticosteroids in the last six months; and 3) diseases and conditions affecting the CNS that might influence brain MRI-volumetric results, such as neurological CNS disorders (neurodegenerative CNS disorders other than MS, vascular brain disorders, history of brain injury), autoimmune disorders, and pregnancy.

Disease duration was considered from the time of the first symptoms of MS to the date of the OCT examination. MS disease course, and whether it was relapsing-remitting (RRMS), secondary progressive (SPMS), or primary progressive (PPMS) [9], as well as disability assessed using the Expanded Disability Status Scale (EDSS), were determined [10].

Optic neuritis (ON) was determined according to the symptoms defined in the Optic Neuritis Treatment Trial: pain with eye movement, loss of visual acuity, visual field defect, colour vision impairment, and relative afferent pupillary defect [11]. All cases were carefully confirmed by optic nerve MRI, OCT and visual evoked potentials. All patients during diagnostic work-up underwent a VEP examination. VEP results were considered negative in the case of normal P100 wave latency (or insignificant interocular difference of P100 wave latency) or abnormal morphology or amplitude of NPN complex. Optic neuritis was excluded based on the absence of a history and clinical symptoms related to optic neuritis, along with a negative ophthalmological examination (absence of relative afferent pupillary defect, visual field defect, visual acuity) and negative results of ancillary tests (OCT, VEP). Only OCT-derived measures from eyes not previously affected by ON were included in the analysis (Fig. 1), and any ophthalmological disease that could affect an OCT finding (see also exclusion criteria). For patients with no previous history of ON, the mean estimate of the OCT-derived measures for the two eyes was calculated so that only one value per patient was included in the analysis.

Disease activity was established using NEDA-3 status [12]. Data was obtained from the history of the last 12 months. NEDA-3 status was defined as the absence of relapse, EDSS worsening, and MRI activity in the last 12 months. EDSS worsening or CDP (confirmed disability progression) was defined as an increase in the EDSS score of 1.5 points, if the previous EDSS score (12 months ago) was 0; an increase of ≥ 1.0 point, if EDSS ≤ 5.0; or an increase of ≥ 0.5 points, if EDSS ≥ 5.5, confirmed at 6 months [13]. The EDSS score 12 months before was used to determine the CDP at the OCT evaluation visit. MRI activity was defined as having at least two or more new or enlarging T2 hyperintense lesions or the presence of a gadolinium (Gd)-enhancing T1 lesion in the brain MRI compared to the previous scan 12 months before. Patient characteristics are set out in Table 1.

All patients were treated with disease modifying treatment (DMT) according to the Slovak MS treatment criteria. The pharmacological treatment history of the patients was used to classify them as 1st line treatment (interferon ß-1a, interferon ß-1b, peg-interferon ß-1a, teriflunomide, glatiramer acetate and dimethylfumarate) or 2nd line treatment (fingolimod, natalizumab, alemtuzumab, cladribine and ocrelizumab).

The study period was May 2020 to September 2021. Patients underwent clinical ophthalmological evaluation with OCT, clinical neurological examination, including the Expanded Disability Status Scale (EDSS), and brain MRI. Data for the study was collected in a prospective fashion from the medical, OCT and MRI records with less than a three month interval between examinations. EDSS assessment, radiological

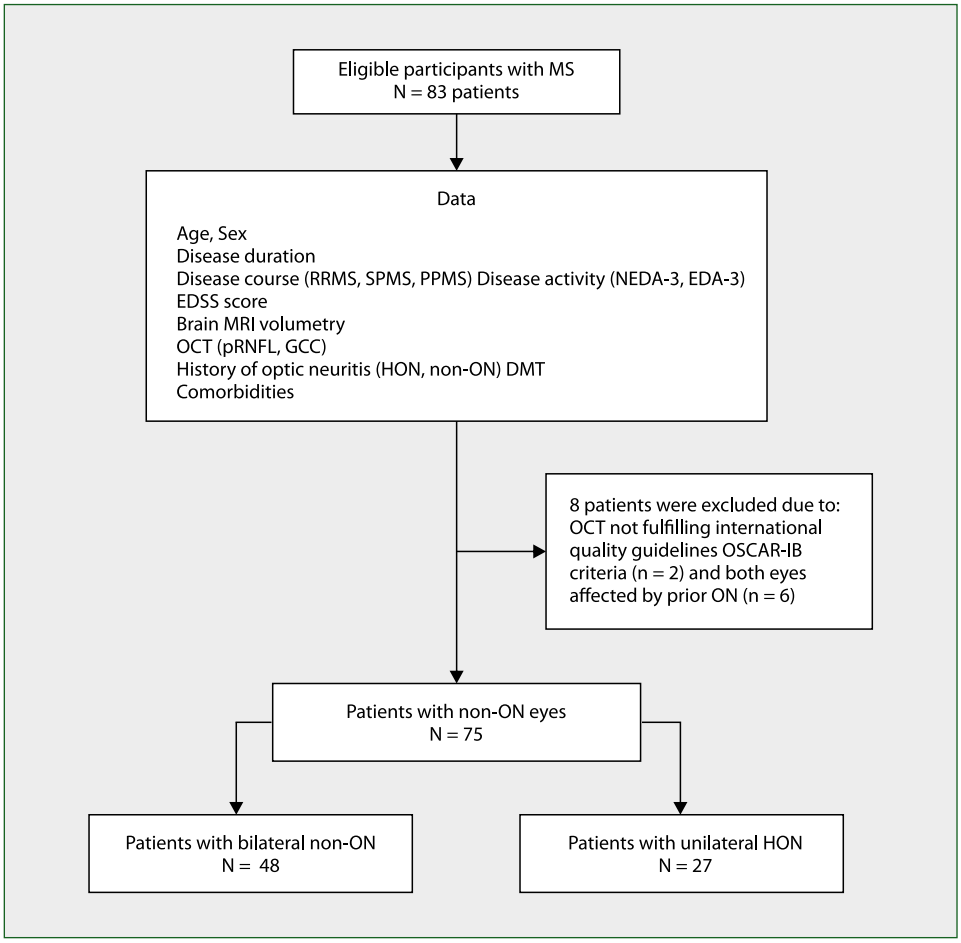

Figure 1. Schematic flowchart showing procedure by which data tested in MS patients. DMT — disease-modifying treatment; EDA-3 — evident disease activity; EDSS — Expanded Disability Status Scale; GCC — ganglion cell complex; HON — history of optic neuritis; MRI — magnetic resonance imaging; MS — multiple sclerosis; NEDA-3 — no evident disease activity; ON — optic neuritis; OCT — optical coherence tomography; PPMS — primary-progressive MS; pRNFL — peripapillary retinal fibre layer; RRMS — relapsing-remitting MS; SPMS — secondary-progressive MS

MRI analysis and OCT performance were made by different researchers. Each of these was blind to each other.

Optical coherence tomography

The OCT images were acquired using RTVue-100 version 5.1 (Fourier-domain optical coherence tomography; Optovue Inc., Fremont, CA, USA) on both eyes and without pupil dilatation. The pRNFL thickness was obtained from a 3.45 mm diameter circle scan centred on the optic disc, and GCC was obtained with a 7.0 mm^2 diameter circle around the fovea. In order to be included in the study, all OCT images needed to fulfil OSCAR-IB and APOSTEL recommendations [8, 14, 15].

Magnetic resonance imaging measurements

Brain MRI was performed using a standardised three-dimensional (3D) T1-weighted magnetisation-prepared rapid gradient-echo sequence, and a 3D T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence with MS protocol in all MS patients. Lesion maps were initially drawn on T2-weighted 3D FLAIR images using a PHILIPS Ingenia 3.0T Omega HP (Philips North America Corporation, dStream, direct digital technology). Longitudinal coregistration fusion was used for the identification of T2 lesions, FLAIR lesions, T1 lesions, T1 gadolinium-enhancing lesions and their occurrence as well as new or enlarged lesions; their volume was also measured. Whole brain (WB) volume and grey matter (GM) volume were measured using the Icobrain program (ICOMETRIX). Volumetric parameters were calculated by automatic brain volume quantification using FLAIR and T1-weighted scans by means of longitudinal, transsectional and segmentational techniques [16].

The Icobrain program compares the measured values of brain volumes in patients to those of healthy controls, and calculates the deviation from the standard values evaluated in the healthy controls (the database is mainly from Europe and North America), to the average expected annual change in volume for controls matched for age and gender. Whole brain volume and grey matter volume parameters were adjusted for skull size using Icobrain, and the normal range and normative volume percentile change in healthy controls was used

Table 1. Demographic, clinical, OCT and MRI characteristics of study cohort

Demographic characteristics	
Sample size, n	75
Female, n (%)	53 (70.67%)
Age (years), mean (SD)	42.08 (± 10.36)
Clinical characteristics	
Disease duration (years), median, IQR	9.0 (5.0–17.0)
EDSS, median, IQR, Min. — Max.	3.5 (2.5–4.0), 1.5–6.5
Clinical course	
Relapsing-remitting MS, n (%)	62 (82.67)
Secondary-progressive MS, n (%)	12 (16)
Primary-progressive MS, n (%)	1 (1.33)
Disease activity	
NEDA-3 status / last 12 months, n (%)	62 (82.67)
EDA-3 status / last 12 months, n (%)	13 (17.33)
1st line DMTs, n (%)	53 (70.67)
2nd line DMTs, n (%)	22 (29.33)
OCT measures	
pRNFL [µm], median, IQR	97.21 (86.74–106.08)
GCC [µm], median, IQR	88.14 (80.09–93.46)
MRI measures	
FLAIR lesions volume [mL], median, IQR	7.17 (3.58–14.54)
FLAIR lesions volume change [mL], median, IQR	0.04 (–0.07–0.37)
FLAIR lesions enlarging, median (mL), IQR	0.27 (0.09–0.72)
T1 hypointense lesions volume [mL], median, IQR	4.43 (2.25–10.87)
T1 hypointense lesions volume change [mL], median, IQR	0.09 (–0.09–0.29)
T1 hypointense lesions new [mL], median, IQR	0.02 (0.00–0.05)
T1 hypointense lesions enlarging [mL], median, IQR	0.29 (0.09–0.53)
WB volume [mL], median, IQR	1,509.00 (1,443.00–1,560.00)
WB volume normative percentile, median, IQR	8.80 (1.10–35.43)
WB annualised volume change [mL], median, IQR	–0.20 (–0.48–0.02)
GM volume [mL], median, IQR	904.00 (846.50–934.00)
GM volume normative percentile, median, IQR	19.75 (6.40–47.20)
GM annual volume change [mL], median, IQR	–0.30 (-0.77–0.25)
Periventricular lesions volume [mL], median, IQR	6.09 (2.16–13.90)
Juxtacortical lesions volume [mL], median, IQR	0.25 (0.10–0.47)
Infratentorial lesions volume [mL], median, IQR	0.02 (0–0.08)
Deep white matter lesions volume [mL], median, IQR	0.53 (0.29–0.89)

DMTs — disease-modifying treatments; EDA-3 — evident disease activity; EDSS — Expanded Disability Status Scale; FLAIR — fluid-attenuated inversion recovery; GCC — ganglion cell complex, GM — grey matter; IQR — interquartile range; MRI — magnetic resonance imaging; MS — multiple sclerosis; NEDA-3 — no evident disease activity; OCT — optical coherence tomography; pRNFL — peripapillary retinal fibre layer; SD — standard deviation; WB – whole brain

Table 2. Correlation analyses of variables under study

Variables	OCT measures	
	pRNFL (µm)	GCC (µm)
EDSS	–0.331**	–0.115
FLAIR lesions volume [mL]	–0.293*	–0.212
T1-hypointense lesions volume [mL]	–0.306*	–0.176
T1-hypointense lesions volume change [mL]	–0.325*	–0.152
T1-hypointense lesions volume enlarging [mL]	–0.370**	–0.184
WB volume [mL]	0.261*	0.108
WB volume normative percentile	0.277*	0.144
Periventricular lesions volume [mL]	–0.330**	–0.221

EDSS — Expanded Disability Status Scale; FLAIR — fluid-attenuated inversion recovery; GCC — ganglion cell complex; OCT — optical coherence tomography; pRNFL — peripapillary retinal nerve fibre layer; WB — whole brain; * — correlation is significant at 0.05 level (2-tailed); ** — correlation is significant at 0.01 level (2-tailed)

as a reference. The annual rate brain volume loss (AR-BVL) threshold was based on the annual percentage brain volume change (PBVC) as a value below the normal range of reference values in healthy controls (database), in accordance with gender and age. Abnormal BVL was defined as a threshold annual BVL rate of 0.4% according to the study by De Stefano et al. [17]. MRI data was analysed by blinded radiologists and Icobrain raters who had no information about OCT or disability parameters.

Statistical analysis

First, descriptive statistical analyses were performed to provide basic information about the study cohort. Next, the Pearson coefficient was used to analyse the correlations between variables, as appropriate. The Mann-Whitney U-test and Pearson T-test were used for comparing the subgroup of patients with RRMS and PMS (Progressive MS, SPMS and PPMS) in demographic, clinical, MRI-volumetric, and OCT (pRNFL and GCC) parameters. OCT and MRI-volumetric values were compared between subgroups of patients with NEDA-3 status and EDA-3 status. Finally, multivariable linear regression analyses were performed. The model included demographic (age, gender), OCT (pRFNL, GCC), clinical (disease duration, EDSS) and radiological (MRI-volumetry) variables as independent variables.

Statistical analyses were performed using the IBM SPSS (Statistical Package for the Social Sciences) software version 26.0.

Results

A total of 83 patients with MS were initially assessed; eight patients were excluded due to both eyes being affected by prior ON or to OCT not fulfilling international quality guidelines i.e. the OSCAR-IB criteria [8]. The final cohort included 75 patients with eyes without ON (non-ON), of whom 48 were patients with no prior ON, and 27 were patients with unilateral

HON (Fig. 1). The demographic, clinical, OCT and MRI characteristics of the sample with MS are set out in Table 1.

The mean age of patients was 42.08 ± 10.36 years (21–63), and the median disease duration was nine years (IQR: 5.0–17.0). Fifty-three (70.67%) patients were female. The median EDSS was 3.5 (IQR: 2.5–4.0) and the median pRNFL was 97.21 (IQR: 86.74–106.08). From a total of 75 patients, 62 (82.67%) showed NEDA-3 status, while the other 13 (17.33%) patients showed EDA-3 status. Patients were treated with DMTs in the following proportions: 53 patients (70.67%) were on first line DMTs, and 22 (29.33%) on second line DMTs (Tab. 1).

T-test analyses showed that the pRNFL was significantly thinner in the HON subgroup (n = 27) compared to the non-ON subgroup (n = 75) (89.70 ± 13.45 vs. 96.84 ± 15.0, $p < 0.01$), and the GCC was significantly thinner in the HON subgroup (n = 27) compared to the non-ON subgroup (n = 75) (81.34 ± 8.52 vs. 87.10 ± 9.02, $p < 0.01$).

Lower pRNFL thickness was associated with higher EDSS score ($r = –0.331$, $p < 0.01$), a higher volume of FLAIR lesions ($r = –0.293$, $p < 0.05$), a higher volume of T1-hypointense lesions ($r = –0.306$, $p < 0.05$), higher T1-hypointense lesions volume change ($r = –0.325$, $p < 0.05$), T1-hypointense lesions volume enlarging ($r = –0.370$, $p < 0.01$), a higher volume of periventricular lesions ($r = –0.330$; $p < 0.01$), a lower whole brain volume ($r = 0.261$; $p < 0.05$), and lower whole brain normative percentile ($r = 0.277$; $p < 0.05$) (Tab. 2). In our analyses, we did not find any significant correlations between GCC and clinical and MRI variables.

Compared to the relapsing-remitting (RRMS) subgroup, the progressive PMS (SPMS and PPMS) subgroup showed higher age ($p < 0.01$), longer disease duration ($p < 0.001$), higher EDSS score ($p < 0.001$), higher volume of FLAIR lesions ($p < 0.05$), higher volume of T1 hypointense lesions ($p < 0.05$), lower whole-brain volume ($p < 0,01$), higher value of whole brain annualised volume change ($p < 0.05$), lower value of GM volume ($p < 0.01$), and a higher value of periventricular lesions volume ($p < 0.01$). No significant differences between variables were found in subgroups of patients achieving the status NEDA-3 or EDA-3 (Tab. 3, Supplemental data).

Multivariable linear regression analysis, a model consisting of age, gender, disease duration, EDSS, RFNL and GCC as independent variables and T1-hypointense lesions volume change as the dependent variable, showed that age ($Adj.R^2 = 0.24$, Exp(B) 0.30; $p < 0.05$), pRNFL value ($Adj.R^2 = 0.24$, Exp(B) –0.38; $p < 0.01$), and GCC ($Adj.R^2 = 0.24$, Exp(B) –0.31; $p < 0.05$) were significant predictors of T1-hypointense lesions volume change. Lower pRFNL values indicated a bigger change in the T1-hypointense lesions volume. The variables pRNFL, GCC and age were significant predictors of T1-hypointense lesions volume change, with the model explaining 24.1% of the overall variance in the dependent variable (Tab. 4, Supplemental data). Other models were not significant.

Discussion

Many studies have presented associations between OCT parameters and MS pathology, mainly attributed to irreversible axonal and neuronal degeneration and brain tissue atrophy [1, 5–7, 8–20]. As reported by Klistorner et al., RNFL thinning may reflect progressive retinal nerve fibre layer loss by the mechanism of retrograde degeneration caused by the inflammatory process in MS [20].

In our study, we wanted to determine whether the OCT is, in addition to a disability (EDSS) rate indicator, also a marker of brain lesion volume and brain atrophy, using the Icobrain program.

In accordance with the findings of previous studies, our results showed differences in pRNFL and GCC thickness between eyes with and without a history of ON in MS patients [2, 7]. Eyes with a history of ON (HON) had thinner pRNFL and GCC compared to non-ON eyes.

In line with previous studies, we found inverse relationships between the pRNFL value in non-ON eyes and patients' disability (EDSS score) [1, 2, 21]. Thinner pRNFL was associated with a higher disability score (EDSS).

This finding leads us to the conclusion that as the degree of disability reflects irreversible loss of CNS neurons, the pRNFL value can be considered as a sensitive biomarker of neurodegeneration in MS patient.

As expected, in our study retinal thickness values correlated with brain MRI-volumetric parameters. The most important finding of our work was the significant relationship between pRFNL value and brain MRI-volumetric parameters. The pRFNL value inversely correlated with the volume of FLAIR lesions and T1-hypointense lesions, their current scope as well as the annual change — enlargement. A positive correlation was found between pRNFL value and whole brain volume, along with whole brain normative percentile. Along with patient age, the RNFL value and GCC were significant predictors of T1-hypointense lesions volume change, corresponding to the progression of neurodegeneration. Lower pRFNL values indicate a bigger change in the T1-hypointense lesions volume.

While the EDSS scale has known shortcomings in the subjective assessment of a patient's status by a neurologist, the relationship of pRFNL and brain lesions volume, together with whole brain volume, can be considered from the point of view of objective methods of measurement as providing even stronger evidence that pRNFL reflects the current rate of brain neurodegeneration. Other authors have come to similar conclusions; however, they used different methods of brain MRI-volumetry, such as brain parenchymal fraction (BPF) or the corpus callosum index (CCI) [6, 7]. This makes it impossible to directly compare our findings with others.

Over the past few years, only two studies have shown an association between pRNFL, GCC and brain atrophy as measured by MRI-volumetry. In the study by Barreiro-Gonzales et al. conducted in 2020, BPF correlated with the pRNFL of eyes

without HON in relapsing-remitting MS patients. They concluded that OCT data correlates with different CNS compartments, even with no anatomical or functional linkage, serving as a useful neurodegeneration and inflammation surrogate marker [7]. The study by Vidal-Jordana et al. showed that pRNFL thickness and ganglion cell/inner plexiform layer (GCIPL) volume outperformed MRI in predicting disability. In their conclusions, they pointed out that OCT measures correlate with brain and spinal cord atrophy; however, they appear to be more closely associated with disability than MRI volumetric measures [1].

A comparison between patients with relapsing (RRMS) and progressive (SPMS and PPMS) disease course showed that patients with a progressive disease course had a significantly higher age and longer disease duration, and a higher EDSS score, compared to those with a relapsing disease course. MRI-volumetric data showed in the subgroup with progressive MS greater atrophy of the whole brain and grey matter. We did not find any significant differences in parameters when comparing subgroups based on disease activity over the past 12 months (NEDA-3 vs. EDA-3 status). After comparing the subgroups of patients with RRMS and progressive MS (PMS) as well as patients with (EDA-3) and without disease activity (NEDA-3) in the last 12 months, we did not find any significant differences in OCT parameters (pRNFL, GCC), so we consider OCT parameters as independent of disease phase and disease activity. These results could be explained by the known shortcomings of the NEDA-3 concept and the fact that MS is one continuous disease with a porous boundary between the relapsing and the progressive phases of the disease. In this context, it should be noted that the NEDA-3 status shortcomings are given by subjective evaluation of both relapse and EDSS score, and that therefore NEDA-3 status proportions may be inaccurate and include both false positive and false negative cases of NEDA-3 status. OCT values probably reflect the current overall state of brain neurodegeneration and brain atrophy resulting from previous and ongoing inflammatory processes.

It is clear to us that due to the small number of patients in our cohort, our conclusions must be postulated with caution, and it is necessary to confirm our findings in large cohorts. We found significant associations between OCT values and whole brain atrophy and the volume of T1 hypointense lesions which correspond to irreversible brain neuronal loss. Thus we suggest that OCT appears to be a better biomarker of neurodegeneration rates compared to EDSS or the NEDA-3 concept, which are the two most widely used in clinical practice.

One of the important indicators of responsiveness to DMT is a reduction in the rate of brain atrophy, which is also the subject of clinical trials of new drugs, although the significant change in the brain atrophy process occurs with some latency. Newer DMTs have the potential to slow accelerated brain atrophy. All our patients were on some DMT treatment at the time of the OCT evaluation, and therefore we assume that the effect of the treatment was also reflected in the volumetric results, which showed significant correlations with OCT parameters. However, the small number of patients in our cohort did not allow us to further assess and compare the effect of individual drugs on OCT and MRI-volumetric results.

The goal of current MS therapy with DMTs is to stop inflammation and slow pathologically accelerated brain atrophy caused by neurodegeneration; therefore, pRNFL in this context appears to be an important and useful biomarker reflecting the current extent of both lesion volume and total brain atrophy.

Current research is focused on identifying reliable, sensitive and easily available laboratory and neuroimaging biomarkers of disease activity in treated MS patients that would reflect the effect of a given long-term treatment [22, 23]. Given that OCT is an easily accessible, non-invasive and objective method, regular OCT examination could be an alternative to annual brain MRI in multiple sclerosis patients monitored in routine practice, especially in clinically stable patients. Considering that disability worsens in patients with a progressive disease course, where relapse-independent progression of the disease is due to chronic inflammation in the brain, accelerated brain atrophy persists. In these patients, OCT could be a useful monitoring tool of 'hidden activity' of the disease.

Our work has some limitations. The first is the small sample of patients. Unfortunately, the COVID-19 pandemic affected our healthcare system and required a rapid reorganisation of the practice of care. A small number of patients did not allow us to draw broader conclusions and compare the results in the RRMS, SPMS and PPMS disease phenotypes. We did not include a healthy control group for comparisons of our data with the MS group. Due to the cross-sectional study design, we consider our results to be preliminary; further longitudinal studies with a larger homogenous cohort of patients are needed.

Conclusions

Our study results support OCT measures as a sensitive imaging biomarker of the inflammatory and neurodegenerative process in MS patients, closely associated with disability and brain MRI volumetric measures. The OCT (pRNFL) measure appears to be a useful tool for assessing the current neurodegenerative component of disease activity in MS patients treated with DMT.

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