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Correlations Between Disability Score, Optical Coherence Tomography and Microperimetry in Patients with Multiple Sclerosis

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Purpose: To characterize ocular motility disturbances through Microperimetry (MP) in patients with Multiple Sclerosis (MS) trying to detect those capable of influencing the disability to improve the accuracy of assessing visual impact in EDSS scale. MP results were compare with some structural parameters obtained by OCT.

Patients and Methods: Cross-sectional analytical and correlational case-control study approved by Ethical Committee. A total of 82 eyes (41 patients) and 30 healthy eyes (15 subjects) were enrolled after informed consent. All participants underwent ophthalmological evaluation with MP and OCT. Variables included MS disease duration, Expanded Disability Status Scale (EDSS) score; in OCT: central macular thickness (CMT), ganglion cell-inner plexiform layer thickness (GCIPL), and peripapillary retinal nerve fiber layer thickness (pRNFL); and in MP: test duration, reaction time, average macular threshold (AT), and 4 fixation stability indexes (P1, P2, BCEA63, BCEA95).

Results: MS group showed a significant decrease in GCIPL ($p < 0.001$) and pRNFL thickness ($p < 0.001$) compared to the control group. Furthermore, patients demonstrated a longer examination ($p < 0.001$) and reaction ($p < 0.001$) times, reduced AT ($p < 0.001$), more unstable fixation indexes (P1 $p < 0.004$, P2 $p = 0.018$, BCEA63 $p = 0.005$ and BCEA95 $p = 0.007$), measured by MP. In addition, patients with a history of ON (n=16) demonstrated longer examination times in MP ($p = 0.049$) compared to MS patients without ON, but they were not correlations with OCT measurements, EDSS score correlated with the CMT ($p = 0.023$, $r = -0.25$), MP duration ($p = 0.043$, $r = 0.22$), and fixation indexes (P1 $p = 0.049$, $r = -0.22$, BCEA63 $p = 0.041$, $r = 0.23$, BCEA95 $p = 0.049$, $r = 0.22$).

Conclusion: Our study emphasizes the complementary utility of MP and OCT in assessing MS patients. Additionally, it highlights that using MP for objective measurements of oculomotor dysfunction could improves accuracy in disability assessment on the EDSS scale.

Keywords: ocular movement anomalies, expanded disability status scale, neurodegenerative diseases, fixation instability, retinal sensitivity

Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) with inflammatory and neurodegenerative characteristics. In our environment, it represents the main cause of nontraumatic disability in young adults being more frequent in women.[1]

Epidemiological studies confirm that Spain is a medium-high-risk country for MS although its prevalence has increased significantly in recent years, especially in women. Currently, it is estimated that there are between 80 and

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180 cases per 100,000 inhabitants.[1] Thus means, according to data from the Spanish Society of Neurology, every 5 h, a new case of MS is diagnosed in the country.

Neuro-ophthalmological manifestations are a consequence of relapses and/or the chronic disease phase. Optic neuritis (ON) as a classic example of afferent visual system involvement, being the most frequent and most studied manifestation of relapsing forms. In addition, these patients may also develop ocular motor disorders manifested by diplopia or oscillopsia. Thus, chronic ocular motor dysfunction can affect visual function, leading to poor visual outcomes and reduced quality of life.[2]

The extended disability scale status known as the "Expanded Disability Status Scale" (EDSS) is a widely used tool for assessing disability in people with MS. The score ranges from 0 to 10, where 0 indicates a normal neurological examination and 10 indicates death by MS. This scale is based on the functional abilities of the patient in different aspects of their daily life, including mobility, coordination, strength, vision, speech, and the ability to perform daily activities.[3,4]

The EDSS, developed in 1983, assesses, among other aspects, visual optic functions.[3] However, its primary focus is on high-contrast visual acuity, measured using the Snellen chart as a gold standard for disability quantification.[5] Additionally, it assesses the presence of visual field scotomas, particularly central ones, and the status of the optic disc. These evaluations provide a limited perspective of overall visual function because it does not consider other important parameters such as full visual field, contrast sensitivity, or color vision.[5,6] Moreover, the evaluation of brain stem functions should include the evaluation of the alteration of extraocular movements and nystagmus.[6]

In addition, it does not incorporate data from more recent diagnostic tools, such as fixational microsaccades analysis, which have proven to provide objective measurements of MS disability level and disease worsening and this limitation hinders a precise quantification of the disease's impact on the patients.[7] The same has been attempted by analyzing the pursuit movements using an eye tracker, or with low contrast optotypes.[8,9]

Imaging studies focusing on retinal structures to evaluate neurodegenerative diseases are increasingly used because the retina shares embryological, histological, biochemical, microvascular, and neurotransmitter similarities with the cerebral cortex, making it a potential source for biomarkers in neurodegenerative diseases (diagnosis, evolution, classification, response to treatments and others).[10]

The clinical impact of these explorations based in OCT and OCT angiography (OCT-A) has triggered an enormous interest in recent years because there is clear evidence that these pathologies decrease the thickness of the layer of nerve fibers and also induce vascular changes in the retina and choroidal vascular patterns that can be demonstrated by a non-invasive tool such as OCT-A.[10]

In patients with MS, OCT has shown that there is a significant thinning of the inner layers of the retina, even in those without a history of clinical ON.[11] Between different OCT retinal and optic nerve measurements, retinal peripapillary nerve fiber layer (pRNFL) thickness and ganglion cell and inner plexiform layer (GCIPL) complex thickness are more sensitive and robust to reflect neurodegeneration.[11]

Other researchers have shown that ganglion cell layer (GCL) thickness is significantly reduced in patients with and without previous ON compared with healthy controls and that such thinning was associated with visual function and EDSS scores.[3] There are even studies indicating that OCT findings can help identify different patterns in different clinical phenotypes of MS.[11] Even more OCT could be a predictive biomarker of disease duration and the clinical evolution of neurodegeneration and disability and could even be useful for evaluating the efficacy of drugs.[12,13] Therefore, OCT scans of two different regions (optic disc and macular area) should be routinely included in clinical practice, research, and MS trials, following a standardized protocol.[13,14]

Furthermore, the changes in ocular motility described in patients with MS are diverse and include among the most frequent inaccurate fixations, alterations in saccadic movements such as square wavelets and dysmetrics such as hypermetry.[2,15] Thus the objective identification and measurement of these anomalies is relevant in the study of the difficulties experienced by these patients in daily tasks such as reading, a complex activity where ocular movements and their control are implicated because our perception is guided by the alternation of sequences of fixations and saccades.[15]

For the oculomotor function study, several recording systems have been implemented, such as electrooculography (EOG) and videooculography (VOG), but they have not yet been incorporated into routine clinical practice.[16]

Microperimetry (MP) is another tool that could be used for specific evaluation of fixations. It combines the anatomical and functional study of the central retina, allowing for a simultaneously visual field examination or perimetry using an eye tracking system.[17] Previously, MP has shown that macular sensitivity is altered, especially in eyes with previous ON, affecting the patient's fixation pattern.[17]

Despite this valuable information, clinical units, neither neurology nor ophthalmology usually do not include these objective assessments in their clinical exploration protocols, although, as mentioned, they could be critical in determining the degree of visual disability of these patients and in the design of personalized visual neuro-rehabilitation programs.

Therefore, the objective of this study has been to characterize by objectives measures some of ocular motility disorders in terms of stability of fixation through MP in patients with MS and to analyze if they correlate with the disability score provided by the EDSS scale. This would allow a better evaluation of the impact of vision on the disability caused by visual alterations and would stimulate to improve the neuro-ophthalmological examination of these patients.

Materials and Methods

A cross-sectional analytical and correlational clinical study of patients and controls was designed.

The study was approved by the local clinical research ethics committee (CEIm) of the Hospital Universitario Río Hortega (HURH) (Code: 22-PI045) and CEIm of the Hospital Clínico Universitario de Valladolid (HCUV) (Code: CASVE-NM-21-514) and was registered in ClinicalTrials.gov (ID NCT05706220).

All procedures were performed in accordance with the standards of Good Clinical Practice, the Declaration of Helsinki, and the Organic Law 3/2018, of 5 December, on Protection of Personal Data and guarantee of digital rights.

Patients were recruited from the Department of Neurology (HURH) and controls from the Instituto Universitario de Oftalmobiología Aplicada (IOBA Eye Institute) from January to June 2023. All subjects signed an informed consent before participating in the study.

Inclusion criteria for both groups were age between 18 and 80 years, with best corrected visual acuity (BCVA) of 0.7 or better (decimal scale) or 20/30 (Snellen scale) or greater.

Patients had to comply with the diagnosis of MS according to McDonald's criteria[18] without ON history or non-active ON (> 6 months after discharge).

The existence of an ON episode was verified through a report provided by neurologists/ophthalmologist and anamnesis. Typical cases of ON were defined by a history of: acute or subacute decrease in BCVA, associated with periocular pain that worsened with eye movements, decreased contrast sensitivity, dyscromatopsia, relative afferent pupillary defect, visual field defect (diffuse depression, central or centro-cecal scotomas, quadrantanopsias, altitudinal defects and contracted field) and/or optic disc pallor.[19]

The typical findings on OCT, when the intraorbital portion is involved, is acute optic disc swelling. On the other hand, signs indicating optic nerve damage due to ON, include interocular thickness asymmetry of ≥5 µm for the pRNFL and/or ≥4 µm for the GCIPL.[19,20]

Cases with MS were referred to IOBA with a report including the following data: disease phenotype and activity, score according to the EDSS scale, time of evolution since the onset of symptoms (months), history of ON, and history of supratentorial and infratentorial lesions. The classification according to the phenotype was made according to the clinical presentation: clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), and progressive multiple sclerosis (PMS).[18] Patients with RRMS had a clear history of relapse (new or recurrent), whereas those in the PMS group had a progression of neurological disability measured using the EDSS scale.[21]

Progression was considered as an increase of at least 1 point if the patient had an initial EDSS of 5.5 or less in the previous year. If the initial score was higher than 5.5, half a point was needed to define progression. Progression needed to be sustained and confirmed by a follow-up neurological examination 6 months later. PMS group included patients with primary progressive MS (PPMS) and secondary progressive MS (SPMS) forms. Disease activity status was also considered based on the presence of symptoms or clinical signs of activity in the form of relapse or the presence of new lesions on MRI, enlargement of preexisting lesions, or gadolinium-enhancing lesions in the last year.[18]

The ophthalmological examination included evaluation of eye alignment and motility, observation in the primary gaze, cover tests for far and near distances, evaluation of extrinsic ocular motility (versions and vergences), BCVA evaluation, anterior segment, and fundoscopy.

Patients with CIS, other diseases of the retina and optic nerve, advanced cataracts according to the international classification LOCS III (opacities greater than C2N2), other ophthalmological diseases that could affect central visual acuity, and subjects with high refractive error (± 6 diopters) were excluded. Subjects with a history of other demyelinating neurological disorders (optic neuromyelitis or acute disseminated encephalomyelitis) were also excluded. Patients with a history of acute ON and/or who experienced an episode of ON <6 months prior to the study were excluded to avoid possible interference with optic disc edema with measurements of pRNFL thickness.

Controls were selected so that they could be comparable in age and sex, and their ophthalmologic examination was strictly normal.

Microperimetry

Measurements were performed using the Macular Integrity Assessment system (MAIA, Centervue, Padova, Italy); its technical specifications have been previously detailed.[17,22,23] Before the examination, the patient was adapted in a dark room for 3 minutes. Both eyes were examined separately. Right was first examined while left eye was occluded and viceversa. Both measurements were performed consecutively with a break of at least 10 minutes between them.

The projected light stimulus was 26 arc minutes in size and was small enough to obtain detailed field of view information and large enough to be easily identified by the subject. Patients were instructed to mark the stimulus each time they perceived it.

Throughout the exam, the participant had to set a central stimulus, which consisted of a red circle with a diameter of 1° allowing the projection of a stimulus in its center. While the individual kept his eye on this fixation stimulus, the luminous points began to be projected in different positions and eccentricities. This let the evaluation of the different areas of the central retina.[17,22,23]

Moreover, the projection pattern was predetermined by the instrument in a standard grid formed by 37 points distributed in three concentric circles of 12 points each plus the central one. The projection strategy used was the "expert exam" in the form of a ladder or 4–2.[17,22,23]

If a point was not detected, the instrument increased the intensity of the light stimulus. In contrast, when the individual indicated that the point was detected, the instrument reduced the intensity. As the answers were obtained, the instrument decreased the range of intensities by steps of 4 dB and then 2 dB until the stimulus was not detected.

Fixation Indexes

The study variables in the MP were: duration of the test (seconds), average reaction time (milliseconds), average macular threshold (AT, decibels) and analysis of the stability of fixation. Fixation was characterized by calculating the area of an ellipse containing all fixation points (Bivariate contour ellipse area, BCEA). The BCEA was calculated by the system considering two standard deviations (vertical and horizontal) containing 63% (BCEA63) and 95% (BCEA95) of the fixing points. Also, P1 (%) and P2 (%) indexes were considered, indicating the percentage of fixation points that were within a circle of 1° and 2° radius, respectively.

Optical Coherence Tomography

Subjects were studied using the HD-Cirrus OCT 5000 (Carl Zeiss Meditec, Dublin, CA, USA) with the default 512×128 A-scan protocol for acquiring macular cube equipment. In addition, both groups had a default 200×200 cubic scan of the optical disk.

The scans were manually checked for segmentation and positioning errors, and the scans were performed by the same operator, who determined if the images were of good quality and have a high signal strength (above 6). Scans of poor quality and low signal strength (less than 6) were excluded. Pupillary dilation was performed in patients with small pupils (< 4 mm), and when a poor signal was obtained after examination.

Variables in the OCT that were taken into account in this work were: central macular thickness (CMT) (microns, µm), average GCIPL thickness (microns, µm) and average pRNFL thickness (microns, µm).

Statistical Analysis

For the calculation of the minimum sample size, the variability observed for RNFL and GCIPL in Behbehani et al[24] was considered. According to the results, including 30 patients per group allowed for the detection of differences of 5.1 units in pRNFL and 6.4 units in GCIPL with a probability of 80% (0.8), while maintaining the type I error probability at 0.05. Additionally, a loss of around 10% of individuals was assumed. Therefore, the statistical power of this study indicated that with a sample size of 30 patients per group, there was an 80% probability of detecting significant differences in the variables of interest, pRNFL and GCIPL, while maintaining a significance level of 5%.

A database based on clinical data provided by neurologists and the results of ophthalmological examinations was designed. Subsequently, the statistical programs IBM® SPSS® Statistics (version 26.0.0.1) and R studio (2023.09.1 Build 494) were used.

The univariate analysis of the variables was initially performed using descriptive statistics, employing frequency distribution tables for categorical variables and measures of central tendency (such as the mean or median) for quantitative variables, depending on the data distribution. Additionally, measures of variability, including standard deviation and 95% confidence intervals (95% CI), were calculated for these variables.

To determine whether these variables follow a normal distribution, the Kolmogorov–Smirnov test was first applied. For variables following a normal distribution, the mean and its corresponding 95% CI was presented. However, for variables that did not follow a normal distribution, the median and its associated 95% CI were reported.

Then a bivariate analysis was then performed using the independent *t*-test for the continuous quantitative variables that met the criterion of normal distribution, while the chi-squared test was used to compare categorical variables.

To compare the medians of the quantitative variables of two independent groups when they were not normally distributed, the Mann–Whitney test was used.

Finally, correlation analysis was employed to examine the relationship between variables. Pearson correlation coefficient was used for variables that followed a normal distribution, while Spearman's rank correlation coefficient was used for those that did not. A value of $p < 0.05$ was considered significant for the interpretation of the p-values in the results of the contrasts.

Results

Demographic and Clinical Characteristics

41 patients and 15 controls were recruited. There were 63% (n=26) of women in the case group and 67% (n=10) in the control group (p=0.9). The average age of the group of patients was 49±10 years old and that of healthy individuals was 47±10 years old (p= 0.52).

88% (n=36) of patients had the RRMS phenotype, 7% (n=3) were diagnosed with PPMS, and the remaining 5% (n=2) had the SPMS type. Regarding activity, 88% (n=36) did not meet the neurological criteria for activity, while 12% (n=5) exhibited it.

According to the location of the demyelinating lesions, all cases have of supratentorial lesions and 68% (n=28) also infratentorial.

In the patient's group, the RRMS phenotype was predominant, with inactive disease and regarding the degree of disability patients had a median disability score of 1.0 (minimum= 0.0, maximum =6.5) on the EDSS scale.

The evolution time of the disease since the onset of symptoms varied, with a median of 180 months (minimum=25, maximum =509).

Ocular Examination

A total of 30 eyes were counted from 15 healthy individuals and 82 eyes from 41 patients with MS.

According to the history of inflammation of the optic nerve, 80% (n=66) had no history of ON and 20% (n=16) had a history of ON.

All eyes in the control group had a BCVA of about 20/20 and in the case group BCVA was 20/20 in 93% (n=76) of the eyes and 20/30 in 7% (n=6) of the eyes.

There was neither history of paralysis nor paresis of the ocular muscles, and no evidence of nystagmus in the primary position of the gaze. No history of ocular hypertension or glaucoma was detected.

The results of the OCT and MP variables in cases and controls are summarized in Table 1. Furthermore, Table 2 shows the correlation values between MP and OCT variables for whole individuals. In addition, a subgroup analysis was performed, considering the history of ON (Table 3). Moreover, in the subgroup of individuals with a history of ON (n=16), no correlations were observed between MP duration and OCT variables: CMT [p=0.52 (r=0.17)], GCIPL [p=0.43

Table 1 Results of the OCT and MP Variables in Cases and Controls

	Control Group CI – Median	Patient Group CI – Median	*p*
OCT			
CMT (µm)	(258.5, 271.5)	(253, 261.5)	0.0682
GCIPL average (µm)	(81.5, 84.5)	(71.9, 76)	<0.001
pRNFL average (µm)	(90.5, 96.5)	(80, 85.9)	<0.001
MP			
Duration of the test (s)	(275.5, 288.5)	(296.5, 306)	<0.001
Average reaction time (ms)	(481.5, 511.5)	(523.5, 552.9)	<0.001
AT (dB)	(28.9, 29.9)	(27.2, 28)	<0.001
P1 (%)	(97.5, 100)	(95, 98.5)	<0.004
P2 (%)	(99.3, 99.5)	(99.56, 100)	0.018
BCEA63 ($^{\circ 2}$)	(0.14, 0.348)	(0.35, 0.8)	0.005
BCEA95 ($^{\circ 2}$)	(0.45, 0.97)	(1.05, 2.2)	0.007

Notes: Confidence intervals for the median and p-values obtained when comparing the results of OCT and MP in the control group and in the group of patients with MS.
Abbreviations: OCT, optical coherence tomography; MP, microperimetry; SD, standard deviation; CMT, central macular thickness; µm, microns; GCIPL, ganglion cell and inner plexiform layer; pRNFL, peripapillary retinal nerve fiber layer; s, seconds; ms, milliseconds; dB, decibel; CI, confidence interval.

Table 2 Correlation Values Between MP and OCT Variables in Whole Individuals, Including Both MS Patients and Controls

	CMT (µm)	GCIPL Average (µm)	pRNFL Average (µm)
Duration of the test (s)	*p*= 0.08 (r= −0.17)	*p*<0.001 (r=−0.36)	*p*=0.0093 (r=−0.24)
Average reaction time (ms)	*p*=0.034 (r=−0.2)	*p*=0.046 (r=−0.19)	*p*=0.07(r=−0.068)
AT (dB)	*p*=0.4 (r=0.081)	*p*<0.001 (r=0.37)	*p*<0.001 (r=0.36)
P1 (%)	*p*=0.82 (r=0.02)	*p*=0.046(r=0.19)	*p*=0.018(r=0.22)
P2 (%)	*p*=0.29 (r=0.1)	*p*=0.031 (r=0.2)	*p*=0.01(r=0.24)
BCEA63 ($^{\circ 2}$)	*p*=0.79 (r=−0.025)	*p*=0.038 (r=−0.2)	*p*=0.01 (r=−0.24)
BCEA95 ($^{\circ 2}$)	*p*=0.68 (r=−0.039)	*p*= 0.066 (r=−0.17)	*p*=0.019 (r=−0.22)

Notes: Representation of the correlation index (r) with the Spearman correlation test *p-value (p)* obtained by correlating the MP and OCT in the individuals in the sample, both MS patients and controls.
Abbreviations: MP, microperimetry; OCT, optical coherence tomography; CMT, central macular thickness; GCIPL, ganglion cell and inner plexiform layer; pRNFL, peripapillary retinal nerve fiber layer; µm, microns; s, seconds; ms, milliseconds; AT, average macular threshold; dB, decibel; BCEA, bivariate contour ellipse area.

Table 3 Results of OCT and MP in the Group of Patients w/w ON

	Patients with a History of ON CI Median	Patients without History of ON CI Median	*P*
OCT			
CMT (µm)	(250, 267)	(252, 262)	0.9115
GCIPL average (µm)	(63.9, 72.4)	(73, 77.9)	0.003
pRNFL average (µm)	(67, 81.5)	(82, 88)	0.007
MP			
Duration of the test (s)	(299, 335)	(294, 304)	0.049
Average reaction time (ms)	(523.5, 586.5)	(518, 551)	0.228
AT (dB)	(25.3, 28.2)	(27.4, 28.2)	0.167
P1 (%)	(93.9, 99.5)	(94, 98.5)	0.431
P2 (%)	(99.5, 100)	(99, 99.9)	0.274
BCEA63 ($^{\circ 2}$)	(0.20, 0.85)	(0.35, 0.9)	0.354
BCEA95 ($^{\circ 2}$)	(0.60, 2.49)	(0.95, 2.5)	0.405

Notes: Confidence intervals for the median and p-values obtained when comparing the results of OCT and MP in the group of patients with and without ON applying the Mann–Whitney.

Abbreviations: OCT, optical coherence tomography; MP, microperimetry; SD, standard deviation; CMT, central macular thickness; µm, microns; GCIPL, ganglion cell and inner plexiform layer; pRNFL, peripapillary retinal nerve fiber layer; s, seconds; ms, milliseconds; dB, decibel; ON, optic neuritis; CI, confidence interval.

(r=−0.21)] and pRNFL [p=0.84 (r=−0.055)]. Neither in the subgroup without a history of ON (n=66) were there correlations between MP duration and OCT [p=0.12 (r= −0.19)], GCIPL [p=0.38 (r=−0.11)] and pRNFL [p=0.23 (r=−0.15)].

Correlations between OCT and MP with the EDSS disability scale and the time of evolution of the disease were analyzed in Tables 4 and 5.

Discussion

The main finding of this study was the presence of significant changes by MP, as MS patients have decreased retinal sensitivity, increased fixation instability, and both extended reaction and test duration times. As described by other

Table 4 Correlations Between OCT and MP with the EDSS Disability Scale

	EDSS
OCT	
CMT (µm)	*p*= 0.023 (r= −0.25)
GCIPL average (µm)	*p*=0.08 (r=−0.19)
pRNFL average (µm)	*p*=0.33 (r=−0.11)
MP	
Duration of the test (s)	*p*=0.043 (r=0.22)

(*Continued*)

Table 4 (Continued).

	EDSS
Average reaction time (ms)	*p*= 0.54 (r= 0.07)
AT (dB)	*p*=0.15 (r=−0.16)
P1 (%)	*p*= 0.049 (r= −0.22)
P2 (%)	*p*= 0.53 (r= −0.07)
BCEA63 ($^{\circ 2}$)	*p*= 0.041 (r= 0.23)
BCEA95 ($^{\circ 2}$)	*p*= 0.049 (r= 0.22)

Notes: Representation of the correlation index (r) together with the *p-value* of the Spearman correlation test (p) obtained by correlating the MP and OCT variables with the EDSS variable in the patients of the collected sample (n=82).
Abbreviations: EDSS, expanded disability status scale; MP, microperimetry; OCT, optical coherence tomography; CMT, central macular thickness; GCIPL, ganglion cell and inner plexiform layer; pRNFL, peripapillary retinal nerve fiber layer; µm, microns; s, seconds; ms, milliseconds; AT, average macular threshold; dB, decibel; BCEA, bivariate contour ellipse area.

Table 5 Correlations Between OCT and MP with the Time of Disease Evolution

	Time of Evolution (Months)
OCT	
CMT (µm)	*p*= 0.16 (r= −0.16)
GCIPL average (µm)	*p*=0.021 (r=−0.25)
pRNFL average (µm)	*p*=0.078 (r=−0.2)
MP	
Duration of the test (s)	*p*=0.13 (r=0.17)
Average reaction time (ms)	*p*= 0.045 (r= 0.22)
AT (dB)	*p*=0.12 (r=−0.17)
P1 (%)	*p*= 0.62 (r= −0.056)
P2 (%)	*p*= 0.54 (r= −0.07)
BCEA63 ($^{\circ 2}$)	*p*= 0.12 (r= 0.27)
BCEA95 ($^{\circ 2}$)	*p*= 0.19 (r= 0.15)

Notes: Representation of the correlation index (r) together with the *p-value* of the Spearman correlation test *(p)* obtained by correlating the MP and OCT variables with the time of evolution of the disease (months) in the patients of the collected sample.
Abbreviations: MP, microperimetry; OCT, optical coherence tomography; CMT, central macular thickness; GCIPL, ganglion cell and inner plexiform layer; pRNFL, peripapillary retinal nerve fiber layer; µm, microns; s, seconds; ms, milliseconds; AT, average macular threshold; dB, decibel; BCEA, bivariate contour ellipse area.

authors, MP registries allowed a functional assessment of the central retina and an analysis of fixation stability.[17] Additionally, patients with higher EDSS scores spend more time to complete the test and exhibited greater fixation instability. As the duration of the disease progresses, patients had slower reaction times. These findings suggest that a longitudinal study examining long-term oculomotor dysfunction in MS patients would be valuable.

It is already known that MS may cause various oculomotor alterations, but these are often considered to be late-stage manifestations of the disease.[25] However, recent studies suggest that functional lesions in MS can precede anatomical ones.[26] Even more, there are patients who do not show clear oculomotor alterations, but they complain of reading difficulties outside of alexia and agraphia and having a normal ocular routine examination.

MP has been shown to be useful in characterizing sensory and oculomotor conditions such as amblyopia or nystagmus.[23] This technique has also been proposed for the evaluation of early stages of MS, demonstrating that macular sensitivity was decreased in patients with normal visual acuity and no history of ON, and correlated positively with macular thickness as measured by OCT. As such, MP may represent a non-invasive and efficient method to identify signs of subclinical visual dysfunction that correspond with early macular architectural changes characteristic of MS.[27]

Currently, OCT is the primary method for visualizing and quantifying morphological retinal changes associated with MS. As mentioned, structural alterations in the retina of patients with MS, detected by OCT and OCT-A are considered biomarkers both to support the diagnosis, to establish the progression and even to assess the effect of the treatments and differentiate the different phenotypes[28]

But the aim of this study was to investigate the changes of MP and OCT in a group of MS patients compared to a control group and to correlate the results with their EDSS score.

Other authors used the same MAIA MP system and analyzed three groups: eyes without ON, with previous ON, and with previous ON in the fellow eye. All groups showed a significant reduction in AT compared to the control group, although the reduction was more important in the eyes with previous ON.[17]

These results are consistent with the findings of our study, as the eyes of people with MS showed a significant decrease in AT.[17] However, there were no significant differences in AT between those patient's w/w history of ON.

This discrepancy could be attributed to the sample size, given that the proportion of patients with ON was lower in our group. Furthermore, it is important to consider that some cases of ON may go unnoticed that they have suffered this complication, as some authors have documented cases of asymptomatic ON.[29,30] Therefore, cases of asymptomatic ON could influence the interpretation of our results.

In addition, fixation indexes indicated a lack of fixation stability in MS patients compared to healthy individuals. As reported in previous studies, this may be explained by neurodegeneration affecting efferent pathways.[15,17,31–33]

A significant decrease in some OCT variables has been observed, such as GCIPL and pRNFL layers, in the group of patients with MS, despite the majority of cases have not a history of ON. This finding reflects neurodegeneration and is consistent with previously reported findings by other authors.[34–36] Although, no significant differences were found in CMT, as observed in other studies.[36]

Furthermore, the analysis demonstrated significant correlations between the MP and OCT variables. Individuals with lower GCIPL and pRNFL thickness showed lower AT, a more unstable fixation and required more time to complete MP. Moreover, slower reaction to the light stimulus was correlated with the decrease in CMT and GCIPL.

In the current study, results show the possible relation of both MP and OCT with the degree of disability. As other authors have described, visual dysfunction is common in patients with MS and most common conditions include acute optic neuritis, internuclear ophthalmoplegia, nystagmus, and saccadic dysmetria.[37] While these visual impairments may often go unnoticed by patients, they can significantly impact quality of life.[37]

On the other hand, OCT measures are associated with brain and spinal cord atrophy, and appear to be more closely related to disability than volumetric MRI measures.[38] According to a recent meta-analysis, OCT measurements correlate with disability in MS, and can complement comprehensive neurological routine examinations.[39]

Even more, there are some papers showing that total macular volume measured by OCT significantly predicts higher disability at 10 years, even after accounting for baseline disability status.[40] Some others found that reduction of average pRNFL, inferior pRNFL and temporal pRNFL thickness is associated with physical and cognitive disability in MS, and

they suggested the use of temporal pRNFL as a more sensitive outcome as it showed the strongest association to both EDSS and cognitive function with the Symbol Digit Modalities Test (SDMT).[41]

In a meta-analysis conducted by Mirmosayyeb et al, it was found that macular ganglion cells and the inner plexiform layer complex (mGCIPL) in patients with RRMS, as well as pRNFL in patients with progressive MS, had strong correlations with EDSS scores.[39] In the current study, an association was observed between the decrease in CMT and an increase in disability scores in patients. However, similar correlations were not found with other thicknesses such as pRNFL or GCIPL, unlike those investigated by other authors.[38,42]

Additionally, as the duration of the disease increased, a decrease in GCIPL thickness was observed, consistent with findings by Vidal-Jordana et al.[38]

Regarding limitations of the current work, during patient recruitment, there were difficulties in including PMS patients, given that, in general, these patients had a greater degree of disability and had more mobility difficulties, which led to many of them not to participate in observational studies. Furthermore, some of them suffered partial or total paralysis in their upper limbs, which prevented them from performing MP. Patients with MS commonly experience fatigue, particularly during tasks that require concentration.[43] Therefore, taking this factor into account when analyzing test results could provide a better understanding of patient's performances and possible limitations in these types of assessments.

Future research should focus on conducting follow-up studies, considering more homogeneous patient samples according to phenotype, degree of activity, degree of disability and implemented treatments, among other aspects. More prospective longitudinal studies are needed, since this would provide more high-quality data on the association of MS/ON with OCT/MP.

Our findings suggest that functional oculomotor alterations measured with MP and structural damage to the retina measured by OCT may correlate with the degree of disability in these patients and some of the parameters (duration of the MP, P1, BCEA63, BCEA95 indexes and CMT) provided by these two explorations should be included to improve discrimination in disability assessment.

Conclusions

Assessing visual function on the EDSS scale requires consideration of various factors, including optic nerve damage and oculomotor coordination. According to our results, we propose using MP and OCT to obtain objective and precise measurements of fixation instability and structural retinal damage. This approach can provide a more comprehensive and accurate assessment of visual dysfunction, facilitating a better understanding of their disability of visual cause generated in the patient.

Our findings highlight the complementary utility of MP and OCT in the clinical assessment of MS patients. We consider it important to conduct longitudinal prospective studies that complement the study of the afferent and efferent visual pathway, considering phenotypes, treatments, and the impact on visual disability.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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