DOI 10.5935/0034-7280.20170027



# Campimetry changes, optical coherence tomography and visual function changes in patients with multiple sclerosis

## *Alterações da campimetria, tomografia de coerência óptica e função visual em pacientes portadores de esclerose múltipla*

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## *ABSTRACT*

***Objectives:*** *To determine the frequency and characteristics of alterations in ophthalmologic examinations of optic nerve and macula coherence tomography (OCT), and Campimetry in multiple sclerosis (MS) patients.* ***Methods****: Sixty eyes were examined, 30 of which were diagnosed with MS and 30 of the control patients, all attended at the General Hospital of the Federal District of Brazil. The patients were evaluated regarding the parameters: characteristics and alterations of the ophthalmological examination, OCT of the nerve and macula and Campimetry.* ***Results:*** *Patients with MS presented worse results in all parameters evaluated. On visual field examination localized losses were found in 50% of the cases . In relation to OCT of the optic nerve it was observed a reduction of the nerve fiber layer in temporal quadrants (p = 0.0251) and lower (p = 0.0041). The macular OCT revealed a decrease in the CFN, mainly in the internal nasal quadrants (p = 0.0002) and external (p = 0.0016), internal inferior (p = 0.0007) and external superior (p = 0.0108) plus internal (p = 0.0046). Patients with lower values of macular thickness also had worse results in the visual field (p = 0.0001).* ***Conclusion:*** *This study demonstrated that MS is a disease capable of causing changes in OCT and visual field tests even in the absence of visual symptoms reported by patients. Examinations such as visual field and OCT of macula and nerve can be a useful tool to estimate the damage by the disease and to assist in the follow-up of these patients*


***Keywords:*** *Multiple sclerosis; Tomography, optic coherence; Campimetry*


## RESUMO

**Objetivos:** Determinar a freqüência e as características das alterações em exame oftalmológico, em exame de Tomografia de coerência óptica (OCT) do nervo e mácula e Campimetria em pacientes com Escrelose Multipla(EM). **Métodos:** Foram examinados 60 olhos sendo 30 de pacientes com o diagnóstico de EM e 30 de pacientes controles, atendidos no Hospital de Base do Distrito Federal. Os pacientes foram avaliados quanto aos parâmetros: características e alterações do exame oftalmológico, do OCT do nervo e da macula e Campimetria. **Resultados:** Os pacientes com EM apresentaram piores resultados em todos os parâmetros avaliados. No exame de campo visual Foram encontradas perdas localizadas em 50%. Em relação ao OCT de nervo óptico foi observado redução da camada de fibras nervosas em quadrantes temporal (p=0,0251) e inferior (p=0,0041), o OCT de mácula revelou diminuição da CFN principalmente nos quadrantes nasal interno (p=0,0002) e externo (p=0,0016),inferior interno (p=0,0007) e superior externo (p=0,0108) e interno (p=0,0046). Os pacientes com menores valores de espessura macular também tiveram piores resultados no campo visual (p=0,0001). **Conclusão:** Este estudo demonstrou que a EM é uma doença capaz de ocasionar alterações nos exames de OCT e Campo visual mesmo na ausência de sintomas visuais relatados pelos pacientes. A realização de exames como campo visual e de OCT de macula e nervo podem ser uma ferramenta útil para estimar o comprometimento pela doença e auxiliar no seguimento desses pacientes.


**Descritores:** Esclerose múltipla; Tomografia de coerência optica; Campimetria

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**The authors declare no conflicts of interest.**

Received for publication: 21/3/2017 - Accepted for publication: 3/7/2017.

## Introduction

Multiple sclerosis is a chronic, immune-mediated disease that demyelinates the central nervous system and affects mainly young women.[1] About 85% of individuals suffering from MS have their clinical onset in the form of an outbreak. The remainder begin the pathology with progressive neurological deficits, although occasional outbreaks may occur during the course of the disease. MS may involve any part of the CNS so that it can present an extensive list of signs and symptoms[2].

Ocular findings in Multiple Sclerosis include optic neuritis, retinitis, peripheral vasculitis, abnormalities in ocular motility that manifest with diplopia or nystagmus and pars planitis. The ophthalmologist should recognize them all, although optic neuritis is the most important ocular change in the follow-up of these patients due to its high frequency and established correlation with MS. Visual field defects are varied and not always present. The arched defect in one of the quadrants or peripheral can keep the visual acuity unchanged. Cecocentral scotoma is found in the minority of the patients[1].

Multiple sclerosis can lead to obvious clinical manifestations, such as optic neuritis, nystagmus, and diplopia, and subclinical manifestations, which occurs more frequently. In some cases, the patient reports blurred vision even with good visual acuity. In other cases, there is no eye symptoms reported, but specific exams can reveal sub-clinical abnormalities. In patients without symptoms and signs of impairment of the visual system, subjective and psychophysical tests such as the contrast sensitivity test, the visual field test, and the color vision test with the best corrected visual acuity have been useful for assessing changes[3].

In patients with Multiple Sclerosis, the decreased retinal nerve fiber layer (RNFL) can exist without evidence of pallor of optic disc, and this may precede visual field defects. The analysis of the RNFL is an important element of semiology because changes in the fibers are easier to observe and estimate than the pallor of the disc, especially in discrete injuries[4].

There are approximately 350,000 cases of Multiple Sclerosis in the United States, and 2,500,000 worldwide. The disease results in functional impairment and disability in people who are at their productivity peak1. Studies confirming the impairment of visual function in MS patients have the potential to contribute to the formulation of future therapeutic strategies capable of offering neuroprotection to the optic pathways not yet affected, as well as restoring functions already damaged by the disease.

## Materials And Methods

This is a descriptive cross-sectional case-control study. The normatives of the Declaration of Helsinki were observed, with approval by the FEPECS Ethics Committee under number 61100916.2.0000.5553. Patients with multiple sclerosis attended at the neurology ambulatory of Hospital de Base do Distrito Federal with or without visual complaints who accepted to participate in the study by signing the Informed Consent Term were included in the group of cases (GMS). For the group control (CG) the inclusion criteria were the absence of systemic comorbidities or past ophthalmological disease and belong to the age group found in the group with multiple sclerosis.

Patients with ocular motor disorders, tremors, or other movement disorders impairing the assessment of visual functions were excluded from the study. As well as those with previous or current history of ophthalmological diseases, presence of evidence of any other neuro-ophthalmological disease detected at clinical examination, previous or current history of other neurological diseases, and history of ON started less than 6 months ago.

Patients with MS were referred from the Neurology Department of Hospital de Base do Distrito Federal where they undergo follow-up to the ophthalmologic assessment at the Ophthalmology service of the hospital. The participants were taught on the purpose of the study, and invited to integrate the research after the signing of the informed consent term. A complete assessment was performed in a single day and by the same examiner for the parameters of corrected visual acuity, Cover test, biomicroscopy examinations, fundoscopy, and intraocular pressure. Then, the campimetry exams of the type SITA fast standard 30:2 white-white, OCT of optic nerve and macula were performed.

Sixty eyes were analyzed, with 30 being from MS patients and 30 of controls. Each visual field was assessed and classified as normal or altered according to criteria established by the Optic Neuritis Study Group in 1991.19 The exams classified as altered were subclassified as predominantly diffuse or localized changes. The loss of sensitivity was classified as minimal (mean deviation between -3.0 and -6.0 dB), moderate (mean deviation between -6.0 and -20.0 dB), or severe (mean deviation greater than -20,0 dB).

**Statistical analysis**

For the comparison of optic nerve thickness, macula and overall indexes between the two groups, namely GMS (n = 30) and GC (n = 30), descriptive and inferential statistical methods were applied. The quantitative variables were presented by measures of central tendency and variation. The qualitative variables were presented by absolute and relative frequency distributions. The Shapiro-Wilk test wapplied to evaluate the normality of the quantitative variables. Nonparametric methods were applied for the comparisons because the variables were not normal. The Mann-Whitney U test and the Kruskal-Wallis test with Dunn's Post-test (Ayres et al, 2007, p.65) were applied. The linear correspondence evaluation was performed by the Pearson's Linear Correlation. The level of significance alpha = 0.05 was previously set for rejection of the null hypothesis. Statistical processing was performed on the softwares GrafTable version 2.0 and BioEstat version 5.3.

## Results

The present study analyzed data from two groups: GMS (With Multiple Sclerosis) and GC (Control). The GMS comprised 66.7% female patients and 33.3% male patients, with an average age of 38,8±10,6 years. Seven patients with MS reported visual complaints during the anamnesis, with low visual acuity being the most reported one. Four patients had history of previous optic neuritis. Three had history of 1 past outbreak of ON, and one patient had history of 2 outbreaks of ON. All MS patients had normal biomicroscopic examination and aplanation tonometry, fulfilling the study criteria. The visual acuity with correction found was 20/20 in all patients.

Changes were found in the visual field of 20 eyes (66.6%) of patients with MS. Fifteen eyes with minimal change (MD between -3.0 and -6.0), 5 with moderate change (between -6.0 and -20.0). Among the control patients, 6 eyes had minimal changes in the visual field. Four had diffuse changes of character, and 2

**Table 1**

**Assessment of macula and nerve, and Global Indexes between the two groups: GMS (n=30) and GC (n=30). Hospital de Base do Distrito Federal, Brasília/DF, year 2016.**

| | GMS (n=30) | | | | | GC (n=30) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Average | SD | MD | P25 | P75 | Average | SD | MD | P25 | P75 | p-value |
| **Mácula (µm)** | | | | | | | | | | | |
| SupExt Q | 281.7 | 20.3 | 288.0 | 276.3 | 299 | 296.1 | 21.9 | 298.5 | 292.3 | 311.5 | 0.0108* |
| SupInt Q | 327.8 | 26.0 | 332.5 | 322.3 | 340.8 | 340.9 | 29.3 | 347 | 331 | 356.5 | 0.0046* |
| TempExt Qt | 288.0 | 26.2 | 280.0 | 272.3 | 292.5 | 290.2 | 24.8 | 286.5 | 275.3 | 299.3 | 0.3711(ns) |
| TempInt Q | 322.6 | 18.2 | 319.5 | 317 | 330.5 | 328.7 | 27.7 | 336.5 | 318.5 | 343.5 | 0.0451* |
| InfExt Q | 287.7 | 23.7 | 285.0 | 271.8 | 293.8 | 288.8 | 16 | 286.5 | 279.3 | 301.3 | 0.4688(ns) |
| InfInt Q | 320.8 | 21.2 | 325.5 | 317.3 | 334 | 339.3 | 21 | 343 | 330 | 355 | 0.0007* |
| Nasal Ext Q | 295.9 | 24.0 | 296.0 | 284 | 306.8 | 310.6 | 24.9 | 313 | 306 | 320 | 0.0016* |
| Nasal Int Q | 324.3 | 18.5 | 328.0 | 319 | 333.8 | 345.1 | 19.3 | 346.5 | 330.5 | 357.5 | 0.0002* |
| Cent Q | 267.1 | 20.9 | 256.0 | 252.3 | 283 | 271.9 | 23.6 | 275.5 | 259.3 | 282 | 0.2170(ns) |
| General macula | 317.0 | 59.6 | 302.3 | 293.9 | 312.9 | 312.4 | 16.1 | 311.6 | 301.2 | 321.5 | 0.2371(ns) |
| **Nerve(µm)** | | | | | | | | | | | |
| SupQuad | 124.2 | 22.5 | 117.0 | 108 | 140.8 | 119.3 | 13.8 | 120.5 | 110 | 128.5 | 0.6101(ns) |
| NasalQuad | 77.4 | 14.7 | 76.0 | 64 | 85 | 70.6 | 12.6 | 67.5 | 61 | 79.3 | 0.0773(ns) |
| InfQuad | 111.1 | 20.8 | 112.5 | 102.3 | 124.8 | 127 | 17.9 | 123 | 116.3 | 137.5 | 0.0041* |
| TempQuad | 69.4 | 31.7 | 59.5 | 49.5 | 70 | 69.2 | 8.9 | 68.5 | 62 | 74 | 0.0251* |
| General nerve | 95.5 | 13.7 | 96.8 | 86.1 | 101 | 96.6 | 8.6 | 95 | 92 | 104.2 | 0.7172(ns) |
| Global indexes | | | | | | | | | | | |
| MD (dB) | -4.5 | 3.8 | -4.0 | -5.4 | -2.1 | -1.6 | 2.1 | -2.1 | -2.8 | -1 | 0.0002* |
| PSD (dB) | 2.7 | 1.7 | 2.1 | 1.7 | 2.8 | 2.1 | 0.7 | 2 | 1.5 | 2.3 | 0.1602(ns) |

SD: Standard deviation MD: Median; P25 (25 percentile); P75 (75 percentile)
*Mann-Whitney U Test

**Table 2**

**Evaluation of Macular Thickness according to the presence of Visual Field Change in both groups: GMS (n=30) e GC (n=30). Hospital de Base do Distrito Federal, Brasília/DF, year 2016.**

| | GMS | | | GC | |
|---|---|---|---|---|---|
| | Visual Field Change | | | Visual Field Change | |
| Macula (µm) | Min | Mod | Sev | Min | Mod |
| Sample Size | 10 | 18 | 2 | 24 | 6 |
| Minimum | 291.3 | 268.1 | 319.1 | 298.9 | 283.2 |
| Maximum | 527.3 | 324.3 | 537.1 | 351.0 | 298.4 |
| Median | 297.8 | 303.0 | 428.1 | 315.5 | 293.2 |
| First Quartile | 294.4 | 293.7 | 373.6 | 306.4 | 287.7 |
| Third Quartile | 303.3 | 312.9 | 482.6 | 323.4 | 297.1 |
| Arithmetic mean | 320.8 | 302.6 | 428.1 | 317.5 | 292.0 |
| Standard Deviation | 72.7 | 13.8 | 154.1 | 13.5 | 6.3 |
| Coefficient of Variation | 22.7% | 4.6% | 36.0% | 4.3% | 2.2% |

*p-value < 0.0001 Kruskal-Wallis with Dunn post-test.

had change of central nature.

As observed in Table 1, the GMS had worse performance in the visual field exam because the MD of the patients with MS was on average -4.5 dB, whereas the average found in the group control was -1.6 dB. This difference was statistically significant (p=0.0002).

The comparison between the PSD from the GMS and the GC had no statistical significance.

None of the groups had changes in the macula OCT. The average macular thickness was 317 µm in the GMS, and 312.4 µm in the GC. This difference did not show statistical significance. However, when the internal and external nasal quadrants, the internal inferior quadrant, internal superior and external quadrants were analyzed, there were significant differences between the two groups, with lower values of macular thickness being in the GMS. (Table 1)

Changes in OCT of optic nerve were seen in 16 eyes of patients with MS (53.33%), with a predominance of temporal losses in the layer of nerve fibers. The average thickness of the nerve

fibers ranged from 82.5 µm to 118 µm. One patient showed change in OCT of the ON in the control group. The average thickness of the NFL ranged between 84.125 µm and 110.37 µm (Table1).

The average thickness of the optic nerve in the eyes of patients with MS was 95.5 µm. The value found for the optic nerve of the group control was 96.6 µm. When the temporal and inferior quadrants of the groups were analyzed they showed decreased thickness of the nerve fiber layer (p=0.0041 for the temporal quadrant and P=0.0251 for the inferior quadrant).

Patients with lower macula thickness also presented worse visual field results (Table 2).

When analyzing the thickness of the nerve fiber layer in the optic nerve of patients with neuriteoptic history and of patients without neuriteoptic history, no statistically significant values were found (p = 0.2728).

## Discussion

The sample of patients with multiple sclerosis found in this study comprised mainly of young, middle-aged women, which is in agreement with the profile usually reported in the literature[1].

MS patients had worse results in the visual field test when compared to the group control. The change in visual function exam even in patients with no prior history of optic neuritis demonstrates that vision decline can be found as the patient experiences episodes of demyelination. Balcer (2010) mentions that although optic neuritis is the most recognized ophthalmologic manifestations of multiple sclerosis, patients may experience decreased visual function in the absence of ON.[5]

The present study found changes in the visual field of 66.6% of GMS, and all patients with neurological disease achieved 20/20 visual acuity test. Similarly, Polizzi et al. [6] found asymptomatic visual field changes in 50% of patients, whereas Sisto et al. [3] found it in 63.6% of patients, and Chorqzy et al.[7] found campimetry changes in 73.1% of the sample. Lyckeet et al. 8 found asymptomatic visual field changes in 27% of patients when evaluating patients with clinically defined MS with the relapsing-remitting clinical form.[9]

The study revealed that although the average thickness of macula and optic nerve in patients with MS is lower than the values found in the control patients, said difference did not have statistical significance. However, there was a significant reduction in certain quadrants of the macula and optic nerve. Literature reveals that patients with MS show a reduction in RNFL both the optic nerve and in the macula when compared to the population without the disease. These findings may not depend on the presence or absence of optic neuritis, as mentioned by Kanamoriet et al., 2003, Costa et al., 2006, and Parisi et al., 1999, who demonstrated a significant reduction in the average RNFL in the optic nerve of these patients.[10,11,12] Fisher et al. (2006) also demonstrated a small but significant reduction in RNFL in eyes not affected by optic neuritis in patients with MS.[13,14]

In the present study, when the internal and external nasal quadrants, the internal inferior quadrant, internal superior and external quadrants of the macula were analyzed, there were significant differences between the two groups, with lower values of macular thickness being in the GMS. Similarly, the study by Khanifar (2010) found macular thickness reduction in the internal and external nasal quadrants of MS patients when compared to the group control. In addition, the author observed that patients with history of optic neuritis had lower values of macular thickness 24. The observation of reduction of total macular volume in patients with MS was further reported by the studies of Henderson (2008), Pulicken (2007) and Burkholder (2009). [14,15,16]

It was also observed that patients with lower values of macular volume had worse results in the visual function evaluated by visual field examination. Burkholder (2009) demonstrated that in the eyes of MS patients thinning of peripapillary RNFL was associated to reductions in the total macular volume and mainly in the internal quadrants of the macula. Patients with macular thinning also showed worse results in contrast sensitivity tests[16].

All patients in the group MS had no apparent visual acuity impairment. However, in addition to the visual field changes observed in 66.6% of the patients, quadrants were found with thinning of the RNFL in the macula and optic nerve. From this, we can infer that the isolated evaluation of visual acuity may be insufficient to follow the visual function of these patients. Balcer (2010) in his study demonstrated that traditional tests for visual acuity measurement such as the Snellen chart may not identify all patients with MS having visual disorders. In patients with MS with apparently normal visual acuity on high contrast tests undergoing contrast sensitivity tests and evoked potentials may reveal visual impairment.[5]

The study revealed that OCT may be an important tool to verify the degree of impairment of RNFL in patients with MS, since patients presented a reduction in the thickness of RNFL in certain quadrants when compared to the group control. Huang et al. (1991) reported that the optical coherence tomography (OCT) is a noninvasive technique allowing the quantification of NFL through a cross-section. Its use has been predominantly to investigate axonal retinal loss in glaucoma. However, several studies have used the exam in patients with MS17. Balcer (2010) considers that decreases in RNFL thickness can predict visual dysfunction after ON. In addition, the use of OCT in clinical trials of MS could be useful to evaluate the creation of future therapies for the disease[5].

Saidha (2015) reinforces the importance of developing new techniques such as the OCT to quantify neurodegeneration in MS. The author reveals that although magnetic resonance imaging (MRI) is considered as the standard gold imaging modality for the monitoring of MS, the techniques used in the exam may not have the sensitivity to evaluate progression individually or in a small number of patients. However, the idea that the atrophy found within specific layers of the retina observed in OCT is a reflection of global neurodegeneration in MS is still controversial. [18]

In contrast to what is reported in the literature, it was observed that patients with multiple sclerosis with a history of optic neuritis did not have worse results in the tests performed when compared to the patients with MS without past history of ON. Araujo (2009) found in his study worse performances of patients with ON history in the visual field and contrast sensitivity tests.[9] The Optic Neuritis Study Group (2008) states that after recovery from an acute episode of ON, most patients have stable visual acuity. However, particularly those with significant disability due to MS perceive their vision as more limited than a population free from disease. The result found in the comparison of the exams between patients with and without history of ON can be justified by the small sample of patients with history of ON within the GMS[19].

The assessment of patients with multiple sclerosis allowed to find changes in nerve and macula OCT exams, as well as in the visual field, demonstrating that structural and functional losses of vision can often be silent. Araujo (2009), in one of the few Brazilian studies on visual changes in MS, points out that the asymptomatic and progressive loss of visual functions suggests

the early, progressive, and silent degenerative character of axonal damage in MS19. Better knowledge of visual changes in MS may allow the future development of neuroprotection techniques not only of the optic pathways, but also of other functional systems involved in the disease.

## Conclusion

The present study demonstrated that Multiple Sclerosis is a disease capable of causing changes in OCT and visual field tests, even in the absence of symptoms reported by patients and in the presence of visual acuity 20/20.

The observation of worse results in OCT and visual field exams of MS patients demonstrates that patient assessment should involve not only visual acuity but also all other exams that are important for a more complete assessment of the outbreak effects of demyelination. The OCT test can be used as a way to check the severity of the disease and allow patient follow-up. In addition, the technique may also serve as an aid in the diagnosis of disease activity and monitoring the response to treatment.

The scarce presence of Brazilian studies on the visual changes in patients with Multiple Sclerosis reveals the importance of investigations in this population. Further studies with bigger samples are needed to verify the possibility of estimating the neurological impairment due to loss in the RNFL.

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