Optic neuritis in Asian type opticospinal multiple sclerosis (OSMS-ON) in a non-Asian population: a functional-structural paradox

Nathalie Stéphanie Meneguette, Email nathi_meneguette@hotmail.com
Department of Neurology and Ophthalmology, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil

Kelly Mayane Figueiredo Ramos Almeida, Email kel.ramos19@hotmail.com
Department of Neurology and Ophthalmology, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil

Marco Túlio José de Oliveira Figueiredo, Email oliveira.tulio1@gmail.com
Department of Neurology and Ophthalmology, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil

Ana Carolina Ribeiro de Araújo e Araújo, Email anacarolinaraa@hotmail.com
Department of Neurology, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil
Multiple Sclerosis Center, Federal Hospital of Lagoa,Rio de Janeiro, Brazil

Marcos Papais Alvarenga, Email marcos_alvarenga@hotmail.com
Department of Neurology, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil
Multiple Sclerosis Center, Federal Hospital of Lagoa,Rio de Janeiro, Brazil

Claudia Cristina Ferreira Vasconcelos, Email cfvas@hotmail.com
Department of Neurology, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil

Anna Christiany Brandão Nascimento, Email annachrisbrandao@outlook.com
Department of Neurology, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil

Giovanni Nicola Umberto Italiano Colombini, Email colombini@infolink.com.br
Department of Neurology and Ophthalmology, Federal University of the State of Rio de Janeiro, Rio de Janeiro Federal Hospital of Lagoa, Brazil

Axel Petzold, Email a.petzold@ucl.ac.uk
Department of Neuro-ophthalmology, Moorfields Eye Hospital; The National Hospital for Neurology and Neurosurgery, Queen Square UCL Institute of Neurology, London, United Kingdom; Expert Centre Neuro-ophthalmology, Amsterdam UMC, The Netherlands.

Regina Maria Papais Alvarenga, Email regina_alvarenga@hotmail.com
Department of Neurology, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil
Multiple Sclerosis Center, Federal Hospital of Lagoa,Rio de Janeiro, Brazil

Correspondence to: Regina Maria Papais Alvarenga, Department of Neurology, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Street Mariz e Barros 775, Postcode 20.270-004, Brazil Tel (Fax): 55 21 226742123. Email: regina_alvarenga@hotmail.com

Abstract

Background: The discovery of biomarkers improved the diagnosis of autoimmune inflammatory disorders. Optic neuritis (ON) is the hallmark of multiple sclerosis, neuromyelitis spectrum disorders, MOG antibody-related disease (MOGAD), and Asian type multiple sclerosis (OSMS). There is a need for a more detailed understanding of the ophthalmic features of OSMS outside the original Asian literature.

Objective: We investigated the clinical features and prognosis of OSMS–ON in a Non-Asian population.

Methods: A single-center cohort study of patients from Rio de Janeiro (Brazil) with OSMS, defined by acute events of optic neuritis (ON) and transverse myelitis (TM), with small inflammatory spinal cord lesions (no-LESL), and negativity for AQP4 and MOG. Subjects and healthy controls (HC) were assessed for visual acuity (logMAR VA), automated perimetry mean deviation (MD), intraocular pressures, spectral-domain optical coherence tomography (OCT), followed by automated retinal layer segmentation of the peripapillary retinal nerve fiber layer (pRNFL) and macular ganglion cell and inner plexiform layer (mGCIPL). Receiver Operator Characteristics Curves were plotted and the area under the curve (AUC) was calculated for group comparisons of the IEPD and IEAD of the pRNFL and mGCIPL.

Results: The thirty patients with OSMS were predominantly female and white. The mean age was 48 years [range 20-70]. Unilateral ON was the visual index event in 83.3%. Over the average of 18 years follow-up period, 89 relapses of optic neuritis were observed. In OSMS patients, the average VA was RE 0.07±0.14 and LE 0.13±0.30. The MD was RE -5.37±5.88 dB and LE -5.23±3.34 dB. There was significant cumulative damage to the VA (p=0.0003) and MD (p = 0.0001) with recurrent episodes. Atrophy of the peripapillary RFNL thickness was significant in OSMS (RE 78.62 ± 16.01 µm, LE 79.86 ± 13.79 µm) if compared to HC (RE 98.87 ±10.68µm, LE 97.87 ± 10.85 µm, p=0.0001). Likewise, there was significant macular GCIPL atrophy in OSMS (RE 74.96 ± 14.46 µm, LE 73.88 ± 13.79 µm) if compared to HC (RE 90.50 ± 6.74 µm, LE 90.41± 6.89 µm, p=0.0001). The inter-eye percentage (AUC=0.89) and absolute (AUC=0.85) difference accurately separated unilateral ON from HC.

Conclusion: A structural-functional paradox was found in OSMS with a high diagnostic value of a novel metric based on retinal asymmetry. The functional visual outcome is excellent despite significant structural damage to the inner retinal layers with high ON relapse rate and long-term bilateral sequential involvement.

1.Introduction

Optico spinal multiple sclerosis or MS Asian type (OSMS) is a subtype of Multiple Sclerosis recognized in the Japanese population characterized by acute events of optic neuritis (ON) and transverse myelitis (TM) with a relapsing-remitting clinical course[1]. A similar disease called recurrent neuromyelitis optica or Devic's syndrome was recognized in Western countries in the same decade.[2,3,4,5]

The similarity of those syndromes was confirmed by Lennon et al. (2004),[6] discovering a biological marker, the NMO-IgG, in American patients with NMO or High-risk syndromes (HR-NMO) and Japanese patients with Asian type MS. The NMO-IgG binds selectively to the aquaporin-4 water channel, located in astrocytic foot processes at the blood-brain barrier. This biological marker also distinguished NMO from disseminated Multiple Sclerosis (MS).

The term Spectrum of Neuromyelitis Disorders (NMOSD) was coined to include NMO, HR-NMO, OSMS, and other rare syndromes where the NMO-IgG was identified [7,8].

Further evidence brought by clinical and laboratories studies identified, in Japan, two subtypes of OSMS, one like NMO with longitudinally extensive (longer than three vertebral segments) spinal cord lesions (LESL) positivity for AQP4-AB in 50% of the cases and severe clinical course and the other related to MS, with small spinal cord lesions (no-LESL), negativity for AQP4-Ab and milder disease [9,10]

A second biomarker for optic spinal diseases, the complement activating antibody to myelin oligodendrocyte glycoprotein (MOG-IgG), was found in a subset of patients with NMO or HR-NMO syndromes negative for the AQP4-IgG.[11,12] However, OSMS Japanese patients with small spinal cord syndrome (no-LESL) and negativity for AQP4-Ab showed negativity for this second biomarker.[13]

The main features of optic neuritis in Multiple Sclerosis (MS-ON), neuromyelitis optica spectrum disorders (NMOSD-ON), MOG-Ab syndrome (MOG-ON) are already described.[14,15,16] However, little data has been published about long-term visual dysfunction in optic spinal Asian type MS (OSMS-ON). There is a need for a more detailed understanding of the ophthalmic features of this MS phenotype outside the original Asian literature.

This study aimed to describe the clinical course of the OSMS-ON in a non-Asian population.

2.Materials and Methods

2.1. Participants and inclusion criteria

The Institutional Review Board Ethics Committee of the Hospital Universitário Gaffrée Guinle (HUGG) approved this cross-sectional observational study [CAAE: 07682712.8.0000.5258]. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist were used to assess study quality.[17]

The neurologists made the OSMS patients' selection (RMPA, ACAA, MPA) in the Hospital da Lagoa, the principal reference center for demyelinating diseases in Rio de Janeiro (Brazil)[18]. OSMS patients consecutively attended in 2017 and 2018 were invited to perform the ophthalmologic examination in HUGG.

The definition of OSMS[1,9,10,13] requires at least two index events: optic neuritis (ON) and transverse myelitis (TM). A relapsing clinical course needs further events of ON or TM. All cases are negative for AQP4-IgG and MOG-IgG tested by fixed cell-based assay (CBA) and had small spinal cord lesions (no-LESL) at MRI. Also, none of the patients had clinical evidence for the involvement of other CNS structures.

From the medical register were recorded demographic data, number, and characteristics of the acute index events: ON (unilateral, right or feft) or Bilateral (simultaneous binocular visual loss in 24 hours was distinguished from sequential bilateral visual loss), TM (partial or complete).

The visual dysfunction system (FS) and disability were scored by the FS/EDDS Kurtzke scale.[19]

A control group of healthy participants (HC) also performed the ophthalmological evaluation.

2.2. Ophthalmologic examination in HUGG (NSM, KMFRA, MTJOF)

2.2.1.Visual acuity, Visual Field, and Visual Function System

High contrast Snellen visual acuity (VA) was converted to logMAR.[14]

Visual Fields were realized with 30-2 SITA-Standard strategy (Humphrey Field Analyzer; Carl-Zeiss Meditec, Dublin, CA) following the Optic Neuritis Treatment Trial (ONTT) consensus and recommendations. The VF was classified as normal or abnormal. Abnormal VF was either diffuse or isolated. Loss of sensitivity was graded as normal (Median deviation (MD) above -3.0 dB), minimal (MD from -3.0 to -6.0 dB), moderate (MD from -6.1 to -20.0 dB), or severe (MD worse than -20dB). Most of the VF lost appearing on the overall deviation probability plot had to be absent on the pattern deviation probability plot to quality as diffuse sensitivity loss. Localized VF loss was defined as a defect on the overall deviation probability plot persisting on the pattern deviation plot. VF was excluded if they had unreliable test results, defined by quality as fixation losses >20%, false positives > 33%, or false negatives >33%.[20]

VA and VF data were used to calculate the FS visual score [19]:

- 0 – Normal
- 1 – Scotoma with visual acuity (corrected) better than 20/30
- 2 – Worse eye with scotoma with maximal visual acuity (corrected) of 20/30-20/59
- 3 – Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60-20/99
- 4 – Worse eye with marked decrease of fields and maximal visual acuity (corrected) of 20/100 – 20/200; grade 3 plus maximal acuity of better eye of 20/60 or less
- 5 – Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less
- 6 – Grade 5 plus maximal visual acuity of better eye of 20/60 or less
- 9 – (Unknown)

All patients underwent full investigation of the retina by indirect ophthalmoscopy (Volk 90®, Zeiss® retinography).

2.2.2. *Optical Coherence Tomography*

The OCT scanning used was commercial equipment (Cirrus HD-OCT® - Carl Zeiss Meditec, Inc) with pupillary dilation. The scanning protocol involved acquiring a set of 3 OCT images of the optic nerve head (ONH) and macula in a raster pattern covering a 6 mm area with a scan density of 512 x128 pixels in ~ 3.5 seconds (27,000 A-scans/sec). Scans were which failed the OSCAR-IB quality control criteria on consensus (NSM, AP) were excluded.[21] The proprietary Zeiss software was used for the quantitative pRNFL data. According to Costello et al., we used a pRNFL thickness threshold of 75μm as the expected "point of no return" for visual recovery after optic neuritis.

Macular retinal layers were segmentation using the free, downloadable *Orion software* (Voxeleron, USA, www.voxeleron.com).[22] The thicknesses of the macular retinal nerve fiber layer (mRNFL), ganglion cell layer/inner plexiform layer (mGCIPL), inner nuclear layer (mINL), outer plexiform layer (mOPL), outer nuclear layer (mONL) and the photoreceptor layer (mPR) were quantified. These layers were studied in all segments of the macular ETDRS grid and follow the APOSTEL recommendations.[23]

According to Costello and colleagues apud Balk et al[24], in contrast to the pRNFL, there is no validated cutoff for the mGCIPL. For this reason, we decided to use the same percentile corresponding to a pRNFL of fewer than 75 μm, which corresponded to the 25th percentile for the GCIPL. The 25th percentile for the GCIPL thickness resulted in a cutoff of $\leqslant$68μm.

We used Receiver Operator Characteristics (ROC) curve analyses for comparing patients with multiple sclerosis to control subjects and different combinations of disease groups. The ROC were used to calculate the Area Under the Curve (AUC) to describe the level of diagnostic accuracy. The diagnostic value was rated as good for an AUC > 0.7.[25,26,27]

2.3. Statistical analyses

All statistical analyses were performed using SPSS (Version 23.0) and SAS software Cary, United States of America (version 9.4M6). Normality was tested graphically and using Shapiro–Wilk statistics. Correlation analyses were performed using Pearson's R for normally distributed and Spearman's R for non–Gaussian data. Group comparisons were made with non-parametric or parametric tests according to distribution. The proportion of patients/eyes were compared using the Chi-square test. To correct for the inter-eye difference with used general estimating equations (GEE).[23] The Bonferroni method was used to correct for multiple correlations. An alpha of 0.05 was accepted as statistically significant.

3. Results

3.1. *Demographic and clinical*

The baseline characteristic of the 30 OSMS patients included in the study is summarized in Table 1. The majority were female (83.3%) and white (70%), with a mean age of 48 years.

The healthy control cohort was composed of 30 participants (23 female and 7 male).

3.2. *Visual acuity, Visual Field, and Visual Function System*

The Visual Index Event was unilateral ON in 25 cases (17 right ON, eight in left ON) and bilateral ON in five. The number of events ranged from one to nine. ON recurrences occurred in 20 of the 30 patients (66%). The longitudinal profile and distribution of visual events are presented in Figure 1.

Patients were followed on average for 18.6±9.7 years (3 to 37).

The high contrast visual acuity (HCVA) tested in the 44 affected ON-eyes (74%) had logMAR in 0.0/29; 0.1/5; 0.2/3;0.3/1;0.4/1;0.5/3;0.9/1;1.3/1; therefore 0.2 or better in 37 eyes (84%). Among the 16 non-affected ON eyes, 14 had logMAR 0.0 and two, logMAR 0.1 or 0.2. The mean intraocular pressure was 14 mmHg in both eyes. A mild pale optic disc in the temporal sector was observed in 28/30 cases (93.3%).

The visual field was analyzed in 40 eyes (27 affected and 13 non-affected eyes). The visual field was abnormal in 70.3 % (n=19) of affected eyes and 46.1 % (n=6) of non-affected eyes. Loss of sensitivity was graded as normal in eight affected eyes and seven non-affected eyes, minimum in eight affected eyes and four non-affected eyes, moderate in ten affected eyes and two non-affected eyes, and severe in one affected eye and none of the non-affected eyes. The pattern of the VF defect was predominantly a diffuse sensitivity loss.

The cumulative damage of repeated events to visual function was significant compared to healthy controls or single visual events (HCVA, p=0.0003, MD, p=0.0001, Figure 2; Figure 3).

Recovery on the Functional System[19] was excellent (FS=0) in 26.6%, (FS 1) in 56.6%, (FS 2) in 10%, (FS 3) in 3.3% and (FS 5) in 3.3%.

3.3. *Optical Coherence Tomography*

Atrophy of the pRFNL was significant in patients with OSMS (RE 78.62 ± 16.01µm, LE 79.86 ± 13.79 µm) were compared to healthy controls (RE 98.87 ± 10.68µm, LE 97.87 ± 10.85 µm). The same was the case for mGCIPL atrophy OSMS (RE 74.96 ± 14.46 µm, LE 73.88 ± 13.79 µm) if compared to HC (RE 90.50 ± 6.74 µm, LE 90.41± 6.89 µm).

The mean of pRNFL was 78 µm in the right eye and 80 µm in the left eye, and the mean of GCIPL was 75 µm in the right eye and 73 µm in the left eye. A higher proportion of patients with OSMS had a pRNFL below the Costello cutoff compared to controls (Chi2=29.47, p<0.0001). Likewise, a significant proportion of patients with OSMS had an mGCIPL below 68 µm compared to controls (Chi2=32.26, p<0.0001, see table 2).

The mean of pRNFL, mRNFL, mGCIPL, mGCC, and mINL in cases and controls were presented in Table 3, indicating a significant difference (p=0.0001). The results of OCT were not correlated with age, ethnicity, number of relapses, EDSS, and with affected ON-eyes and non-affected-ON eyes (data not shown).

There was a significant correlation between the pRNFL and the VA(R=-0.409, p=0.0013, figure 4). No such correlations were found for the number of relapses and VA (p=0.37) or the MD of the visual field (p=0.37).

Metrics for retinal asymmetry, the IEPD and IEAD, were all of good diagnostic value (ROCAUC >0.7). For the pooled cohort, the highest discriminatory power was obtained for the mGCIPL IEPD (AUC 0.8268) which was significantly better than for the mGCIPL IEAD (AUC 0.7845,p=0.189). The diagnostic value increased further if only patients with unilateral optic neuritis were compared to healthy controls. Again the mGCIPL IEPD (AUC 0.8986) performed significantly better than the mGCIPL IEAD (AUC 0.8528, p=0.199).[25,26,27]

The natural and neurophthalmological history of the OSMS-ON group was analyzed with a multimodal image, as illustrated in figure 5.

4. Discussion

The main finding of our study in a non-Asian population with OSMS is that recovery of visual function is excellent despite substantial structural damage to the inner retinal layers. This "functional-structural paradox" requires discussion.

The discovery of AQP4 and MOG antibodies improved the differential diagnosis of optic spinal diseases. ON is the hallmark of NMO, MOG, MS and OSMS. NMO-ON is characterized by bilateral and severe visual disfunction with poor recovery. In MOG-ON, a predominant bilateral visual involvement occurred at the onset, with good recovery, but exception cases with acuity reduction. In both entities, recurrences are likely.[12,14,16,28,29]

Asian type MS shares demographic, MRI, and laboratory features with Multiple Sclerosis (MS) (09,10,18]. Similarities between the ophthalmological evaluation of optic neuritis in Multiple Sclerosis (MS-ON) and OSMS-ON are expected.

The characteristics of MS-ON is well known. Optic Neuritis is defined by unilateral, subacute, and painful visual loss occurring as a clinically isolated syndrome (CIS) in almost one-third of the MS patients at the onset, with an excellent recovery to the acuity of 20/30 or better over one to three months in 85%-95% of the cases. After recovery from an acute ON attack, visual complaints and abnormal visual functions frequently remain even in the presence of apparently normal visual acuities. Recurrence of optic neuritis in either eye occurs in 20-36% of patients.[30]

In the long term, our results showed that OSMS-ON presents similar clinical features in the MS-ON literature. The differences were found as more recurrences, successive clinical involvement of both eyes in half of the cases, and remarkable good visual prognosis. The visual field and OCT were often abnormal even in the eyes non affected.[14,24-27,31-33] However, the distribution of RNFL loss not involved preferentially

the temporal quadrant[14], the visual fields abnormalities were predominantly diffuse in both affected and non affected eyes, and OCT results did not correlate with the number of relapses.

The inter-eye percentage difference (IEPD) and the pRNFL inter-eye absolute difference (IEAD) were consistent with recent studies of MSON.[25-27]A previous study by Coric et al of 296 patients showed that an intereye difference percentage of 5% in pRNFL, and even more so GCIPL thickness, is of diagnostic value for MS-associated ON.[25] In a study of Nolan et. al, the mean GCIPL thickness value for our MS cohort was 70.0 ± 10.7μm. An intereye difference of 4μm in GCIPL translates into a 5.7% intereye difference, which is similar to the previous study. The mean pRNFL thickness value for our MS cohort was 87.2±15.3μm, making the intereye difference of 5um, also 5.7%.[26]

The visual field after recurrent attacks of ON-MS has not been studied systematically. According to the ONTT study, after a follow-up of 15 years, 74.7% of the visual fields were classified as abnormal, 65.6% of them with localized loss. 6.2% of the abnormalities in the fellow eye at baseline consisted of diffuse and central loss.[31] Crazy et al. also demonstrated that asymptomatic visual field disturbances occur in MS patients without optic neuritis.[32] One of the principal findings of OCT in MS to date is that the RNFL and GCIPL thinning reflects MS-related optic nerve neurodegeneration in eyes with and without optic neuritis.

Afferent visual pathway damage in MS results from acute focal damage, i.e., by optic neuritis (ON) or chronic diffuse damage, which leads to visual dysfunction.[34]The MD visual field worsening was observed when correlated with the number of acute visual events in each eye that presented optic neuritis but not correlated to the OCT.

Many factors can contribute to a disagreement between tests. An apparent reason for disagreements between standard automated perimetry and OCT is the uncertainty of either one or both tests detecting abnormalities near the threshold, which is related to each test's sensitivity and specificity. In other words, the strength of agreement between the two tests depends on the severity of the deficits in the data sampled. A weaker agreement in our non-ON group is expected because of the mild deficits involved. Similarly, Costello and colleagues apud Cheng et al, found a significant correlation between MD and RNFL thickness only among ON eyes with more severe damage.[33]

Another hypothesis for the mechanism of structural visual system damage is related to higher cortical processing rather than focal optic nerve or even asymptomatic lesions.[34,35]

5. Conclusion

A structural-functional paradox was found in OSMS with a high diagnostic value of a novel metric based on retinal asymmetry. The functional visual outcome is excellent despite significant structural damage to the inner retinal layers with high ON relapse rate and long-term bilateral sequential involvement.

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Declaration of Competing Interest

The authors have any conflict of interest with the subject of the study.

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Nathalie Stéphanie Meneguette: Conceptualization, Investigation, Data curation, Software, Methodology, Formal analysis, Writing - original draft, Writing - review & editing; **Kelly Mayane Figueiredo Ramos Almeida:** Investigation, Data curation, Software;**Marco Túlio José de Oliveira Figueiredo:** Investigation, Data curation, Software;**Ana Carolina Ribeiro de Araújo e Araújo:** Investigation, Data curation, Software**;Marcos Papais Alvarenga:** Investigation, Data curation, Software; **Claudia Cristina Ferreira Vasconcelos:** Investigation, Data curation, Software;**Anna Christiany Brandão Nascimento:** Investigation, Data curation, Software; **Giovanni Nicola Umberto Italiano Colombini:** Investigation, Data curation, Software**; Axel Petzold:** Methodology, Software, Formal analysis, Writing - original draft, Writing - review & editing **Regina Maria Papais Alvarenga:** Conceptualization, Investigation, Data curation, Software, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Supervision, Project administration;

Table legends

CHARACTERISTICS		ASIAN TYPE MS N=30
Gender n (%)	Female:Male	25 (83.3): 5 (16.7)
Race/ethnicity n (%)	White: Afro Brazilian	21 (70): 9 (30)
Year of the first acute event mean (±SD), (minimum, maximum)		1998.8 (sd 9.852) (1981-2015)
Age of onset n (%)	0 < 20 years	7 (23.3)
	20-40 years	19 (70.0)
	40 - 60 years	4 (6.7)
First acute event n (%)	Optic Neuritis (ON)	17 (56.7)
	Transverse Myelitis (TM)	13 (43.3)
Index events (EI), n (%)	Unilateral ON	25 (83.3)
	Bilateral ON	5 (16.7)
	Partial TM	22 (73.3)
	Complete TM	8 (26.7)
Interval between the 1° and 2° EI (months) median (minimum, maximum)		42 (1-312)
Morbidity at last follow up		
Time of disease (Years) mean (±SD) (minimum, maximum)		18.63 ± 9.697 (3-37)
Total number of acute events		232
Type of acute events n (%)	ON: TM	89 (38):143(62)
Last EDSS Median (minimum, maximum)		1.5 (0-7)
	No disability (0-1.5)	16 (53.3)
	Mild disability (2.0 - 2.5)	6 (20)
	Moderate disability (3.0 - 5.5)	7 (23.3)
	Severe disability (6.0 - 9.5)	1 (3.3)

Table 1: Baseline description of the Rio De Janeiro OSMS-ON cohort.

Abbreviations - MS: multiple sclerosis; ON: optic neuritis; EI: index event; TM: transverse myelitis;

(A)	**pRNFL<75**	**pRNFL>75**
HC	n = 1 (1.7%)	n = 59 (98.3%)
OSMS-ON	NAONE(n=4) = 25% AONE (n=21) = 50%	NAONE (n=12) = 75% AONE (n=21) = 50%

(B)	**mGCIPL<68**	**mGCIPL>68**
HC	n = 17 (28,3%)	n = 43 (71.7%)
OSMS-ON	NAONE (n=13) = 81,25% AONE (n=33) = 80, 49%	NAONE (n=3) = 18,75% AONE (n=8) = 19,51%

Table 2: The proportion of patients with a (A) pRNFL and (B) mGCIPL below and above the predefined cutoff levels are shown.

Abbreviations - HC: healthty control; OSMS-ON: opticalspinal multiple sclerosis optic neuritis; pRNFL: peripapillary retinal nerve fiber layer; mGCIPL: ganglion cell-inner plexiform layer; n: number of patients; AONE: affected ON-eyes; NAONE: non-affected-ON eyes;

Mean	**RE HC**	**LE HC**	**RE OSMS – ON**	**LE OSMS-ON**	p-value
pRNFL	99 (90-105)	98 (91-106)	78 (67-90)	80 (70-90)	0.0001
mRNFL	33 (31-35)	33 (30-34)	28 (25-30)	28 (25-31)	0.0001
mGCIPL	90 (86-95)	90 (85-95)	75 (63-84)	74 (64-84)	0.0001
mGCC	123 (118-128)	123 (116-129)	103 (88-117)	102 (90-116)	0.0001
mINL	46 (45-49)	46 (45-48)	43 (40-45)	44 (43-46)	NS

Table 3: Retinal Segmentation in Healthy control subjects and patients with OSMS-ON.

Abbreviation - RE : right eye; LE: left eye; HC; healthty control; OSMS-ON:opticalspinal multiple sclerosis optic neuritis; pRNFL: peripapillary retinal nerve fiber layer; mRNFL: macular retinal nerve fiber layer; GCIPL: ganglion cell-inner plexiform layer,; GCC: ganglion cell complex; INL: inner nuclear layer; NS: not significant;

Figure legends

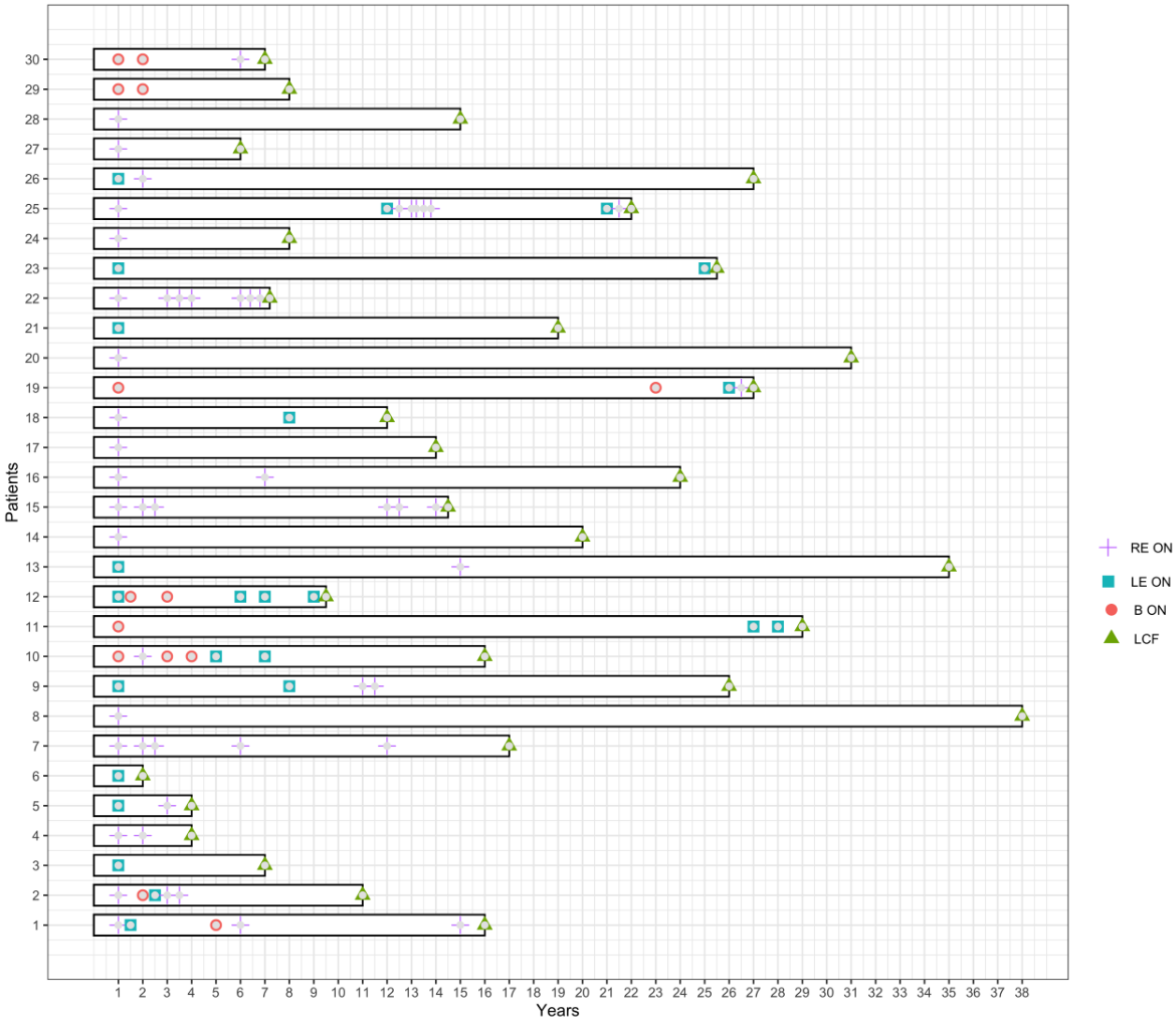

Figure 1: Laterality and recurrence in acute events of OSMS-ON. There are a single event of ON in ten patients (7 RE, 3 LE), recurrent ipsilateral ON in six patients (5 RE, 1 LE), recurrent contralateral ON in six patients (2 RE, 4 LE), recurrent unilateral ON associated with bilateral ON in seven patients (4 ONB, RE, LE; 2 ONB, LE; 1ONB, RE).
Abbreviations - RE: right eye; LE: Left eye; B: Bilateral; ON: optic neuritis; LCF: Last clinical follow-up;

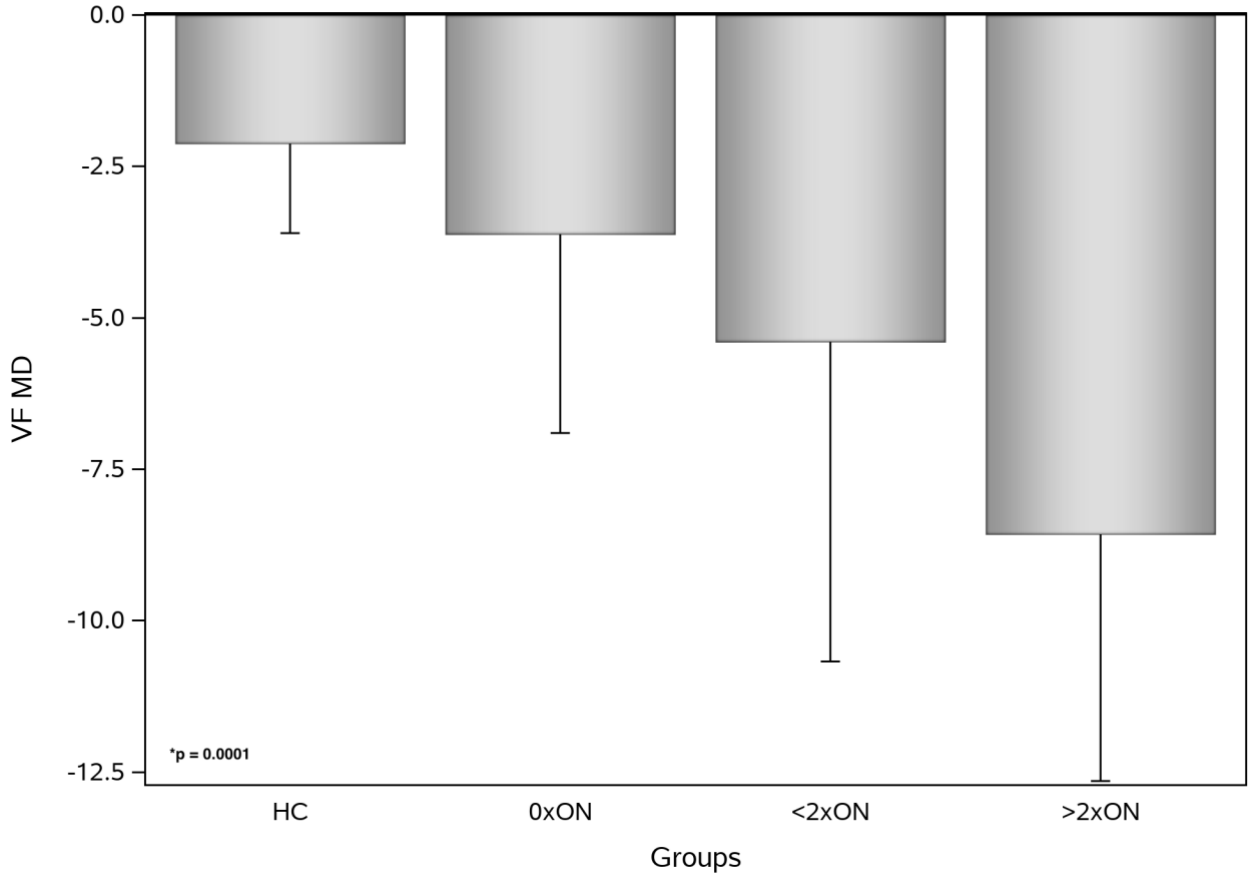

Figure 2: Association of number of ON relapses (x-axis) with the extend of the visual field defect as quantified by automated perimetry using the Visual Field Median Deviation (VFMD, y-axis). A higher number of relapses was associated with a significant worse visual field defect (p = 0.0001).

Abbreviations - VFMD; Visual Field Median Deviation; O_HC (zero relapses of optic neuritis in healthy control); O_ON (zero relapses optic neuritis in non-affected eyes); <2_ON (less than two relapses of optic neuritis); >2_ON (more than two relapses optic neuritis).

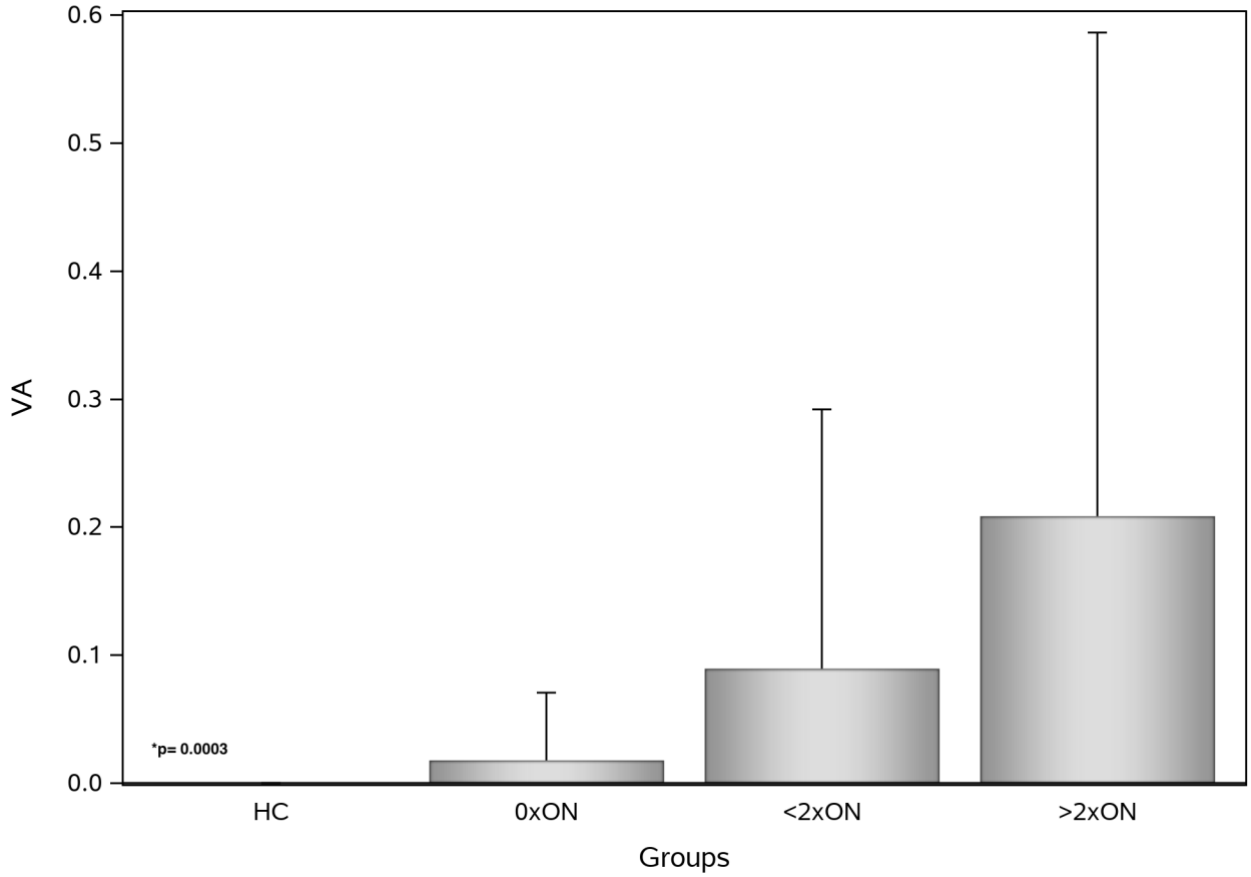

Figure 3: Association of number of ON relapses (x-axis) with the visual acuity (VA, y-axis). A higher number of relapses was associated with a significant worse visual field defect (p = 0.0003).

Abbreviations - VA (visual acuity); O_HC (zero relapses of optic neuritis in healthy control); O_ON (zero relapses optic neuritis in non-affected eyes); <2_ON (less than two relapses of optic neuritis); >2_ON (more than two relapses optic neuritis).

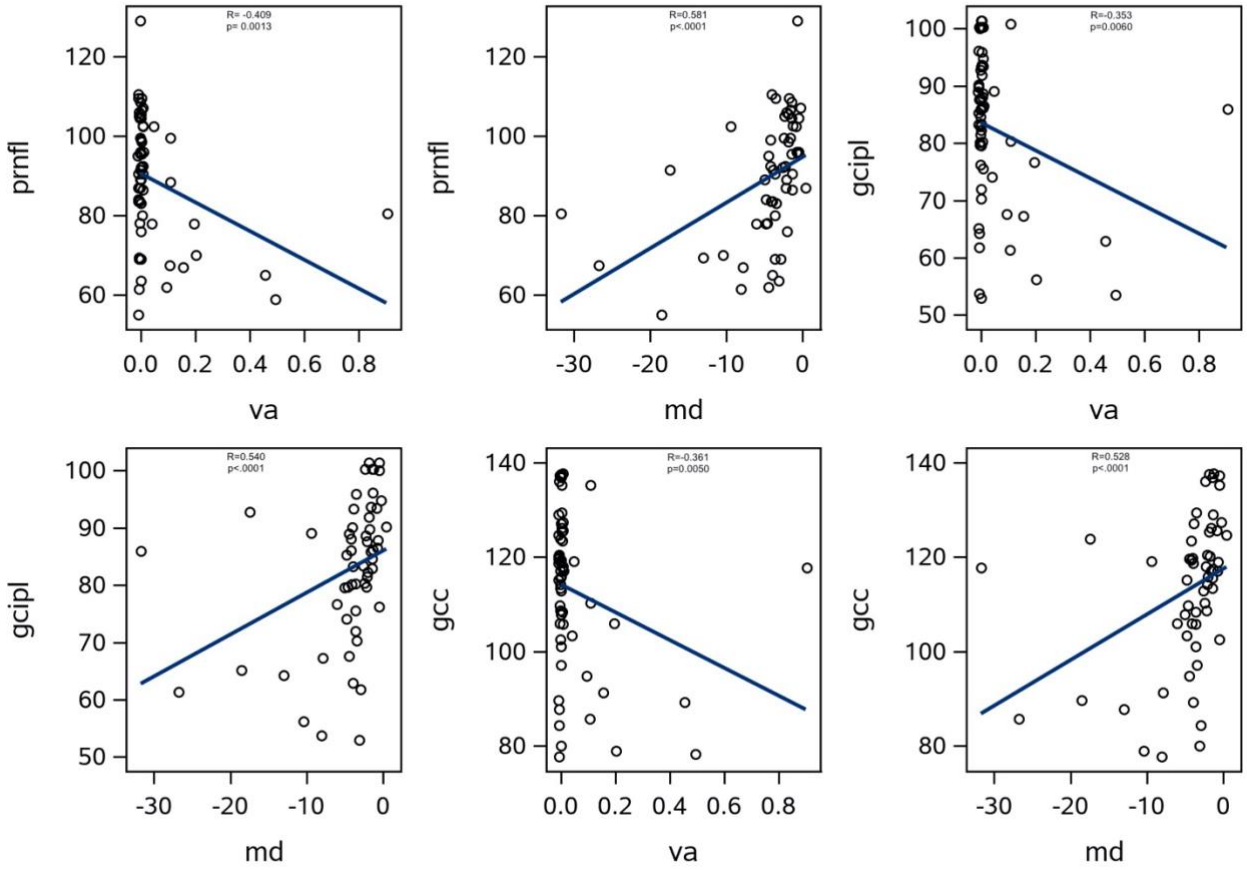

Figure 4: Association of retinal segmentation (prnfl; gcipl; gcc; x-axis) with the visual acuity and visual field median deviation (va; md, y-axis).

Abbreviations - prnfl: peripapillary retinal nerve fiber layer; gcipl: ganglion cell-inner plexiform layer; gcc: ganglion cell complex; va: visual acuity; md: median deviation of visual field;

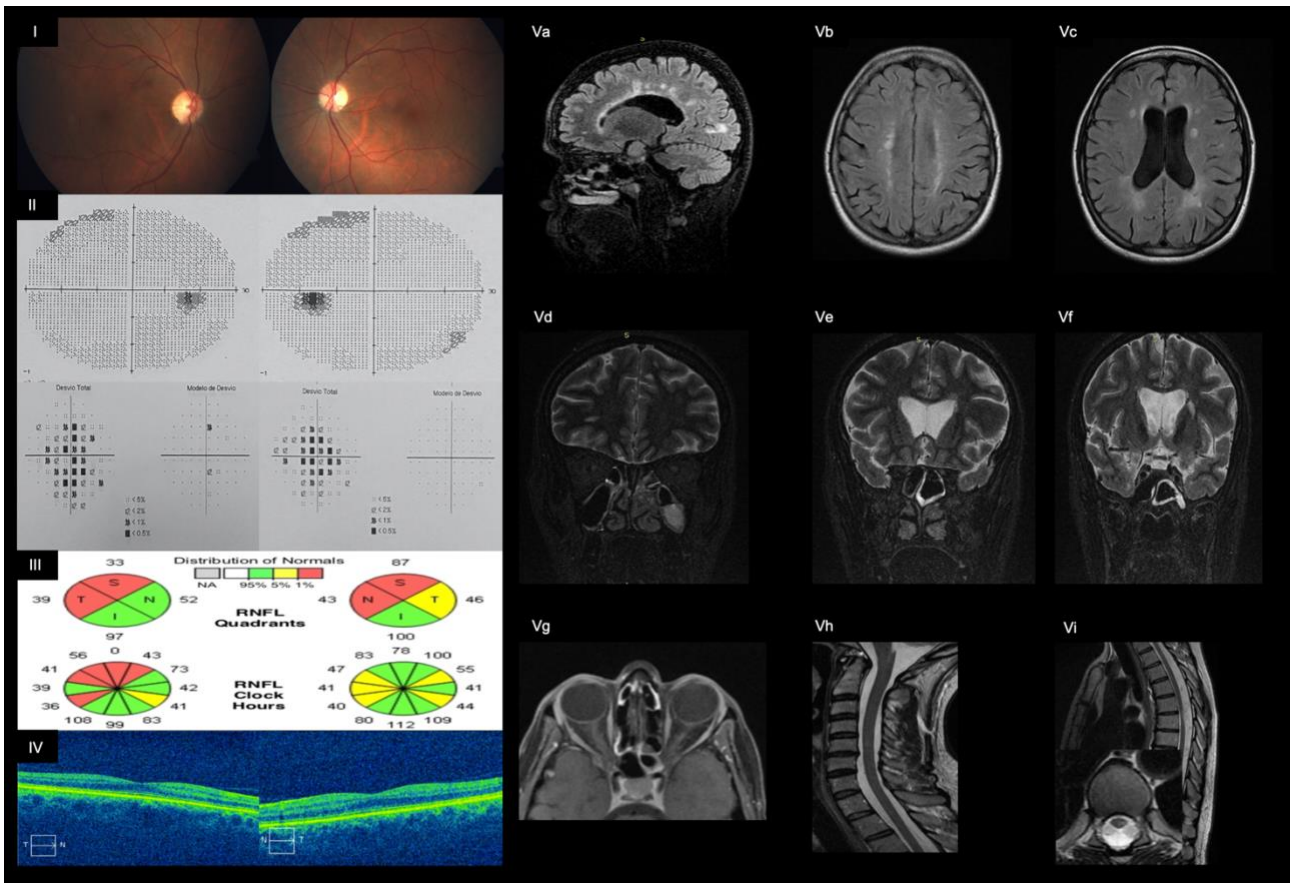

Figure 5: Summary of the case history (# Patient number 7) - Woman, 49 years, female, white. The visual index event occurred with 32 years old (2001) and was characterized by acute visual dysfunction at right eye and complete recovery. Seven years later occurred the Transverse Myelitis Index event characterized by acute paresthesia and mild sensorial objective deficit in inferior limbs with upper limit in T10 associated with acute T10 spinal cord lesion with contrast enhancement. Four other acute and reversible events of right ON (2-2002;1-2006;1-2012; – see in figure 1). The patient refused DMF for MS. At the last follow up after 17 years of disease the visual acuity with best correction was 0.1 in both eyes without other neurological deficit. (FS visual = 1, EDSS = 1) The figure 5 presents the documentation of the neurophthalmological exams: I. Retinography: Mild pale optic disc in temporal sector in both eyes; II. Automated perimetry: Diffuse defect in both eyes; III-IV. OCT: III. Average of pRNFL of 59 μm in RE and 69 μm in LE.; IV. Orion retina segmentation showed a mGCIPL of 52 μm in RE and 56 μm LE; V(a-i)MRI: a. Sagittal FLAIR: images shows typical demyelinating plaques that mainly involve the periventricular white matter; b. Axial FLAIR: lesions hyperintense; c. Axial FLAIR: lesions hyperintense in periventricular white matter; d. Coronal STIR (short tau inversion recovery): the affected optic nerves shows high signal intensity; e. Coronal STIR (short tau inversion recovery): the affected optic nerves shows high signal intensity; f. Coronal STIR (short tau inversion recovery): normal chiasm; g. Axial T1 FAT SAT with contrast: no contrast enhancement in optic nerves; h. Sagittal cervical cord imaged with T2: observe the multiple small focal lesions that do not exceed two vertebral segments in length; i. Sagittal and axial thoracic cord imaged with T2: the lesions occupy lateral white matter columns and do not affect more than half the cross-sectional area of the cord (left).

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