A study of the Retinal Nerve Fiber Layer Thickness Changes in Multiple Sclerosis Using Optical Coherence Tomography in Nassiriyha city

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الخلاصة: يمثل مرض التصلب احد امراض المناعة الذاتية التي تصيب الجهاز العصبي المركزي وتؤدي الى تأكل الطبقة العازلة الليفة العصبية.
تتكون طبقة الالياف العصبية الشبكية أساسا من الياف عصبية غير معزولة، وبالتالي يمكن ان تعطي فكرة دقيقة عن مقدار الضمور في الالياف العصبية. وللجهاز الضوئي المقطعي الذي تم استدامه في هذا البحث القدرة على تحليل مقاطع عرضية من طبقة الالياف العصبية الشبكية بطريقة غير تداخلية.
توصل هذا البحث الى عدة نتائج أهمها:

1. ان متوسط سمك طبقة الالياف العصبية الشبكية في التصلب المتناثر اقل منها في المجموعة الحاكمة.
2. يكون هذا التأثير اكبر قيما اذا كان للعين تاريخ مرضي سابق لالتهاب في العصب البصري .
3. لم يوجد رابط بين سمك طبقة الالياف العصبية الشبكية واي من سن المريض او جنسه او التاريخ المرضي او قياس النظر المعدل.
4. تدعو النتائج التي توصل لها البحث الى بدء دراسة أخرى تشتمل على عدد اكبر من المرضى تتم متابعتهم عبر فترة زمنية أطول للتأكد من حقيقة مغزى هذه النتائج.

ABSTRACT Optical coherence tomography (OCT) is a non-invasive relatively inexpensive technique that allows the quantitative cross sectional imaging of the RNFL. It has been used predominantly to investigate retinal axonal loss in glaucoma. The aim of the current study was to evaluate the retinal nerve fiber layer thickness as a structural biomarker for axonal loss in multiple sclerosis regardless the frank history of previous attack of optic neuritis. We evaluated the relationship between RNFL changes and the patients' age and duration of the disease. We also studied the correlation between the RNFL thickness and patients' clinical data as BCVA, history suggestive of optic neuritis as well as optic disc appearance by fundoscopy.
Key Words: Multiple sclerosis (MS), Optical coherence tomography (OCT), Retinal nerve fiber layer(RNFL).

Introduction

Multiple sclerosis (MS) is an autoimmune disease, in which T-lymphocytes specific for myelin antigens start an inflammatory reaction in the central nervous system, leading to demyelination with subsequent axonal injury. [1] Kutzelnigg et al., is considered to be the predominant cause of enduring disability in multiple sclerosis (MS).[2] The retinal nerve fiber layer (RNFL) is composed predominantly of unmyelinated axons of retinal ganglion cells. Measurements of the RNFL should, therefore, give relatively direct measures of the number of axons present without the confounding variable of tissue loss due to demyelination.[3] RNFL loss in MS has also been documented pathologically and the axonal loss has been recognized by the appearance of abnormalities on fundoscopy especially with red free filter.[4] However, these abnormalities are not readily quantifiable.[5] Optical coherence tomography (OCT) is a non-invasive relatively inexpensive technique that allows the quantitative cross-sectional imaging of the RNFL. It has been used predominantly to investigate retinal axonal loss in glaucoma.[6] Costello et al., demonstrated a significant reduction in mean RNFL thickness in the eyes of MS patients that were clinically unaffected by optic neuritis as well as those affected by optic neuritis. [7]

The aim of the current study is to evaluate the retinal nerve fiber layer thickness as a structural biomarker for axonal loss in multiple sclerosis regardless of the frank history of previous attack of optic neuritis

Patients and Methods

This is a controlled cross section observational study of sampled patients assessed in the diagnostic laser unit at Habobi teaching hospital in Nassiryha city.

Inclusion and Exclusion Criteria.

Inclusion criteria: Patients diagnosed to have relapsing remitting Multiple Sclerosis (MS) by a neurologist and confirmed by Magnetic Resonance Imaging (MRI).

Exclusion criteria:

- Patients known to have glaucoma.
- Patients with diabetic retinopathy.
- Patients with retinal vascular diseases.
- Previous ocular surgery.
- Acute episodes of the disease

Forty seven patients with established diagnosis of MS (94 eyes),all of them were of the relapsing remitting subtype and 20 healthy controls (20 eyes) were enrolled in this study. MS was diagnosed by standard clinical and neuroimaging criteria (Mc Donald's criteria).

The following information was obtained from each MS patient: disease duration and the presence of prior episodes of optic neuritis.

The MS group included 57 eyes without history or evidence of clinical optic neuritis, MSON group included 37 eyes with optic neuritis (19 of them had unilateral ON affection (A) with a free fellow eye (F)) and group C which included 20 eyes of 20 healthy controls, with no history of ocular or neurological disease and with a best corrected visual acuity of 6/9 or better. Only one randomly chosen eye from every control was included in the study. We also studied the effect of the disease on the free fellow eye in patients with unilateral optic neuritis.

Patients were diagnosed with previous attack of ON (MSON) if they had Decreased best corrected visual acuity in addition to one or more of the following

(1) History of previous attack of ON

(2) A relative afferent pupillary defect

(3) A compatible fundus examination (temporal pallor or optic atrophy).

Results

This study enrolled 94 eyes of 47 diagnosed multiple sclerosis patients: MS group included 57 eyes without optic neuritis, MSON group included 37 eyes with optic neuritis (19 of them had unilateral ON affection (A) with a free fellow eye (F)) and group C which included 20 eyes of 20 healthy controls. Mean ages in the diseased and control groups were 31 years (range19– 50years) and 34 years (range 27–41years), respectively. Women represented about 65% of subjects in both groups. There were no statistically significant differences in these descriptive characteristics. Accordingly, cases and controls were age- and sex-matched (Table 1)

Table 1: age of Patients with MS in year

Group	N (eyes)	Mean (years)	SD	Minimum	Maximum
MS	57	31.11	±7.99	19	50
MSON	37	31.51	±9.86	19	55
C	20	34.35	±4.60	27	41
Total	114	31.81	±8.22	19	55

SD: standard deviation

Figures 1&2 demonstrate examples of patients enrolled in our study.

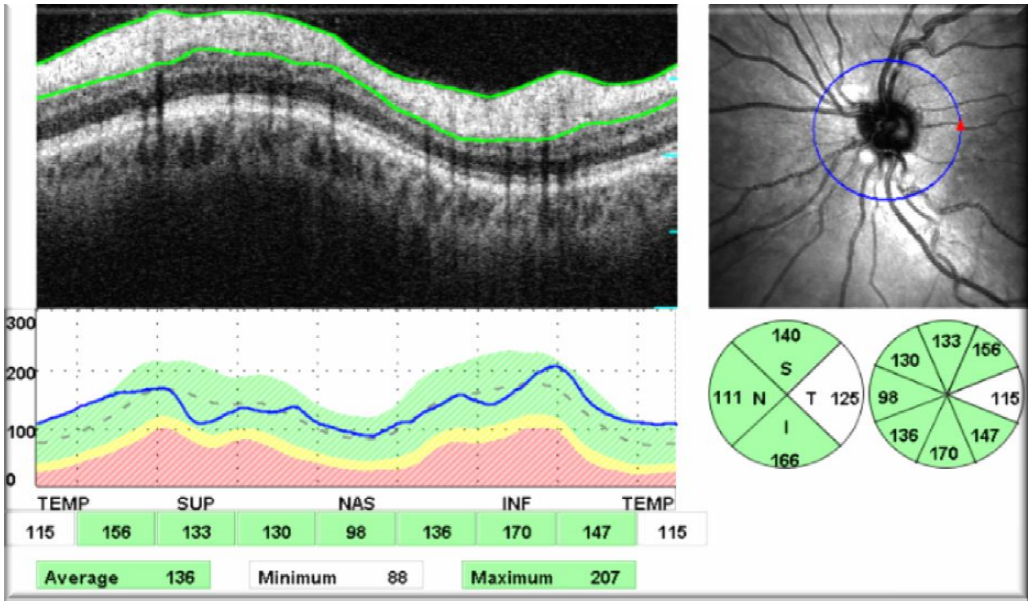

Fig.1: example of the control group (C) .OCT image taken from the left eye of a 24 years old female, BCVA 1, no history of ocular or systemic diseases and normal appearance of the optic nerve on fundoscopy.OCT RNFL analysis revealed within normal RNFL thickness in all quadrants.

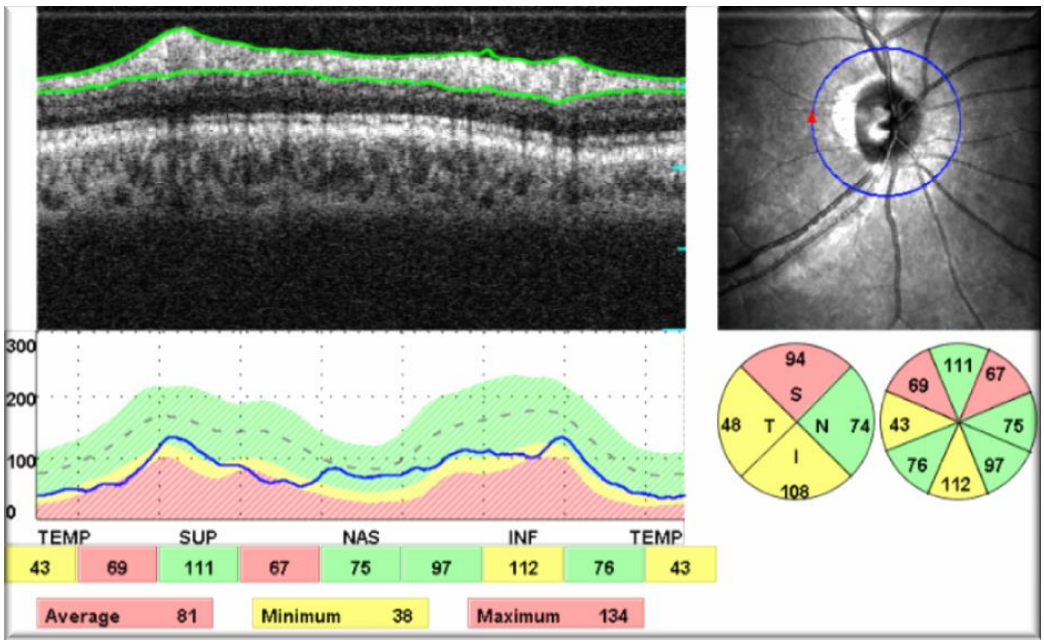

Fig 2: example of the MSON group .OCT image taken from the right eye of a 31 years old female, BCVA 0.2, history of MS 12 years ago, 3 attacks of optic neuritis the latest was 1 year ago. and temporal disc pallor was evident on fundoscopy. OCT RNFL analysis revealed reduced RNFL thickness in all quadrants, except the nasal. The temporal quadrant was the quadrant most affected (48 microns).

(1) BCVA in Patients with multiple sclerosis

As demonstrated in Table 2, all MSON group patients, had visual impairment of various degrees, 14 eyes had visual acuity ranging from 0.5-0.3, and 23 eyes had a visual acuity <0.3. The mean BCVA in MSON group was 0.23 (SD ±0.184); range 0.04 to 0.5) (Table 3). There was a significant reduction in BCVA in MSON group when compared to group C.

Table 2: best corrected visual acuity among MS patients

		BCVA count and %							
MS	count	0	0	0	0	17	24	16	57
	%	0	0	0	0	29.8	42.1	28.1	100
MSON	Count	12	1	10	4	10	0	0	37
	%	32.4	2.7	27	10.8	27	0	0	100
Total	Count	12	1	10	4	27	24	16	94
	%	12.8	1.1	10.6	4.3	28.7	25.5	17	100

Table 3: mean best corrected visual acuity among MS patients

Group	N	Mean	SD	Minimum	Maximum
MS	57	.720	±.190	.50	1
MSON	37	.230	±0.18	0.04	.50
Total	94	0.53	±.300	.040	1

SD: standarad deviation

(2) RNFL thickness in patients with multiple sclerosis.

The average RNFL thickness was significantly reduced in both MSON group (105.9 ±14.1) & MS group (116. ±12.02) when compared to control group (147.3 ±10.9). .However the reduction was found to be greater in MSON group (p<0.01).There was also a significant reduction in MSON group when compared to MS group(p=0.01)

Temporal quadrant RNFL thickness was most affected for both MSON, MS groups (mean temporal quadrant RNFL in MS group = 88 microns, mean temporal quadrant RNFL in MSON group =74 microns). There was less reduction in RNFL thickness in both MS and MSON groups in the superior, nasal and inferior quadrants. Fig.3 (see Table 4 for raw data and the p values)

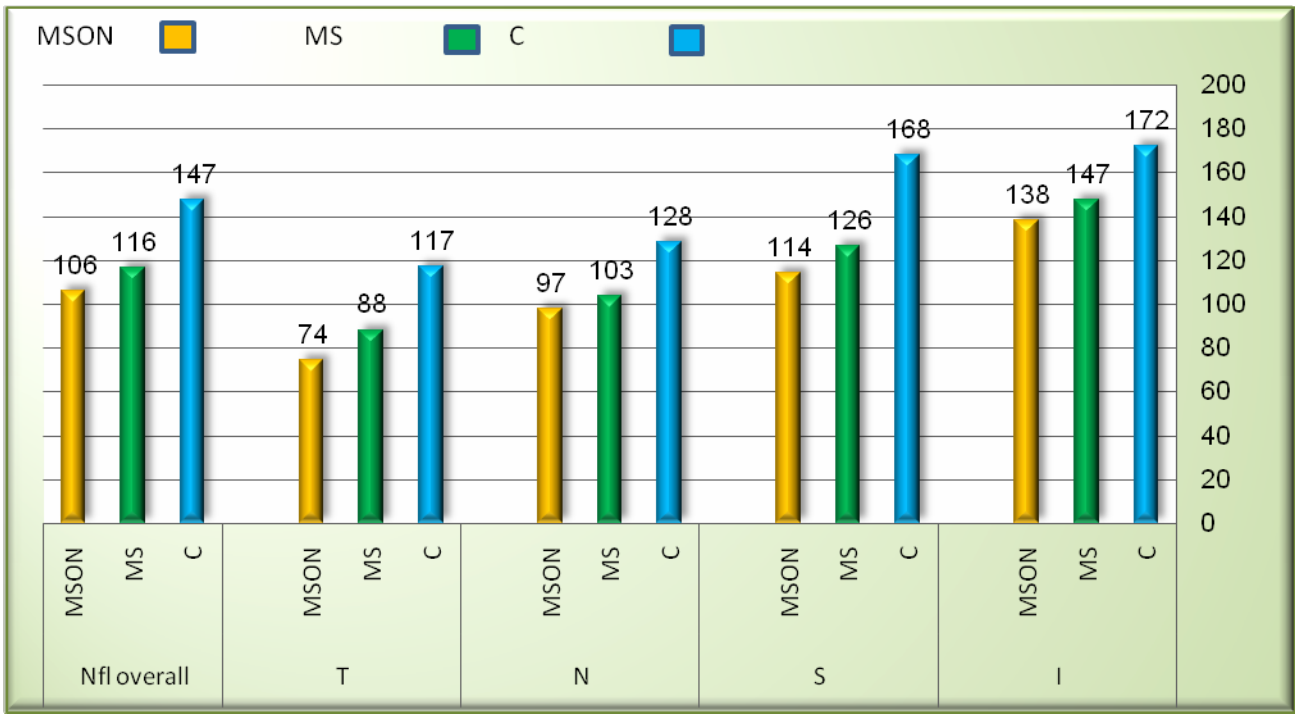

Fig.3: Comparison of the RNFL thickness measured in microns in every optic disc quadrant in MS, MSON and healthy control eyes (c). Differences between the three groups were statistically significant for all the quadrants (p < 0.05 for all quadrants)

Table 4: Average RNFL thickness in microns in all quadrants (inferior(I),superior(S),nasal(n),temporal(T)) in 3 groups (MS,MSON,C) and their significance (p- values)

Quadrant	Group	No o	Mean	SD	Minimum	Maximum	Sig. (p-values)
I	MS	57	147	±17	105	199	0.02
	MSON	37	138	±22	92	166	.000
	C	20	172	± 11	157	199	-
	MSON - MS diff.		9				0.03
S	MS	57	126	± 16	86	159	0.05
	MSON	37	114	± 16	86	156	.000
	C	20	168	±10	151	194	-

	MSON - MS diff.		12				0.01
N	MS	57	103	± 13	77	138	0.02
	MSON	37	97	± 15	64	123	.000
	C	20	128	± 10	110	150	-
	MSON - MS diff.		6				0.04
T	MS	57	88	±12	66	128	0.03
	MSON	37	74	±13	52	98	.000
	C	20	117	±10	101	142	-
	MSON - MS diff.		14				0.01
NFL overall	MS	57	116	± 12	87	142	0.02
	MSON	37	105	±14	77	130	.000
	C	20	147	± 10	129	164	-
	MSON - MS diff.		11				0.01

Within the MSON group, 19 patients had unilateral optic nerve involvement (A), with a free fellow eye (F). As shown in table 5, mean RNFL thickness was significantly reduced in the eyes with optic nerve involvement (A) when compared to their free fellow eyes (F) (Fig 4). ON affected eye (A) – free fellow eye (F) difference =15 microns, P <0.01 which is statistically significant. . Moreover, mean RNFL thickness was significantly reduced in the free fellow eye (F) in relation to healthy controls (c) (control–fellow eye difference =26 microns, *P*<0.01). (See Table 5 for raw data and the p values)

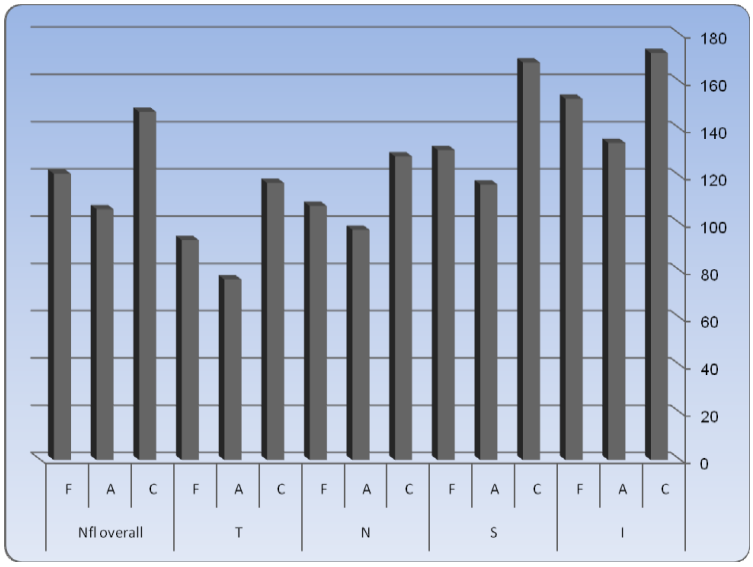

Fig.4: Comparison of the RNFL thickness measured in microns in every optic disc quadrant (I, S, N, T) in the affected eye (A), free fellow eye (F) and healthy controls (c)

Table 5: Average RNFL thickness in microns in all quadrants (inferior (I), superior(S), nasal (n), temporal (T)) in 3 groups the affected eye (A), free fellow eye (F) and healthy controls (c) and their significance (p-values).

Quadrant	Group	No of patients	Mean	SD	Minimum	Maximum	Sig. (p-values)
I	A	18	134	±22	98	166	.000
	C	20	172	± 11	157	199	-
	F	18	152	± 18	120	199	0.03
S	A	18	116	±20	86	156	.000
	C	20	168	±10	151	194	-
	F	18	131	± 12	110	153	0.02
N	A	18	97	± 16.	64	123	.000
	C	20	128	±10	110	150	-
	F	18	107	± 11	89	130	0.02
T	A	18	76	±14	56	98	.000
	C	20	117	±10	101	142	-
	F	18	93	± 13	73	128.	0.03
NFL overall	A	18	106	±15	84	130	.000
	C	20	147	± 10	129	164	-
	F	18	121	± 11	103	142	0.02
	A-F diff		15				0.04

(A) History suggestive of opticneuritis and

Significant correlation was found between the history of ON and RNFL measurements *p<0.01*.The history of ON is an indicator for RNFL thickness as shown in Table 6.

Table 6: predictive value of age, sex, history of ON, BCVA and temporal pallor (TP).

Predictor	p-value
Age	.942
Gender	.176
TP	.958
History BCVA	.000* .000*

Dependent Variable: NFL overall

* Statistically significant *

As shown in table 7, Forty percent of patients (37 eyes) reported history suggestive of previous attacks of optic neuritis 46% (17 eyes) of them were included in (MSON) group according to criteria of optic neuritis used in the current study, 35%(20 eyes) were included in (MS) group .

Sixty percent of patients (57 eyes) denied any history suggestive of previous attacks of optic neuritis 54% (20 eyes) of them were included in (MSON) group according to our criteria of optic neuritis previously mentioned, 66%(37 eyes) were included in (MS) group.

Table7: history of optic neuritis (yes, no) in 2 groups MS, MSON

History ON count and %				
		Yes	no	Total
MS	count	20	37	57

	%	35	65	100
MSON	Count	17	20	37
	%	46	54	100
Total	Count	37	57	94
	%	39	60	100

The mean RNFL thickness in patients with no history of optic neuritis was higher than in patients giving history of optic neuritis. The mean RNFL thickness in patients with no history of optic neuritis is 116 microns (min=91, max=142).The mean RNFL thickness in patients with history of optic neuritis is 106 microns (min=77, max=130).

(B) Optic disc appearance and OCT RNFL thickness:

No Significant correlation was found between temporal disc pallor and RNFL thickness (NFL overall) *p=0.958.* temporal disc pallor is not an indicator for RNFL thickness as shown in table 6.On the other hand, a significant correlation was found between temporal disc pallor and temporal quadrant RNFL thickness (NFL temporal) *p<0.01*.

As shown in table 8, Fifty three percent of patients (50 eyes) had normal appearance of the optic nerve 13% (5 eyes) were part of (MSON) group, 79% (45 eyes) were part of (MS) group.

In 11.7% of patients (11 eyes) examination revealed optic atrophy, all of them were included in (MSON) group, and none of them was included in (MS) group. In 35% of patients (33 eyes) examination revealed temporal disc pallor, 57% (21 eyes) were included in (MSON) group and 21 %(12 eyes) were included in (MS) group.

There was no significant difference between the temporal quadrant RNFL thickness in patients revealing temporal disc pallor on fundoscopy in both MSON and MS groups. The mean temporal quadrant RNFL thickness in patients revealing temporal disc pallor in MSON group was 76 microns ranging from 57 to 95 microns. . The mean temporal quadrant RNFL thickness in patients revealing temporal disc pallor in MS group was 80 microns ranging from 66 to 94 microns. (Table 9)

Table 8: optic nerve appearance (normal (n), optic atrophy (OA), temporal pallor (TP)) in both MS and MSON groups

Optic disc appearance					
		N	OA	TP	total
MS	count	45	0	12	57
	%	79	0	21	35
MSON	Count	5	11	21	33
	%	13.5	30	56.8	35
Total	Count	50	11	33	94
	%	53	11.7	35	100

Table 9: Mean temporal quadrant RNFL thickness in microns(µ) in patients revealing temporal pallor µ(TP) on fundoscopy in both MS and MSON groups.

Group	Number of patients with P(µ)	Mean RNFL temp.	SD	Minimum	Maximum
MS	12	80	±14	66	94
MSON	21	76	±12	57	95

Discussion

The examination of RNFL in MS offers a unique opportunity to study and even quantify axonal loss in the CNS without the confounding effects of demyelination using fast, non-invasive and relatively inexpensive techniques especially OCT. OCT is a non-invasive technique that allows quantitative cross-sectional imaging of the RNFL that was used by Parisi et al,1999 to demonstrate

a significant reduction in the mean RNFL thickness in eyes of MS patients that were clinically unaffected by optic neuritis (ON).[5] The capacity of MRI techniques to quantify precisely axonal and neuronal loss within the brain is limited to research methods such as diffusion tensor imaging and MR spectroscopy.[8] Furthermore, MRI provides very little information regarding disease in the anterior visual pathways .[9] An elaborate study by Fisher et al, 2006 suggested the occurrence of chronic axonal loss in relapsing-remitting MS (CR-MS) patients who didn't suffer from previous attacks of ON. Their cross-sectional designed study found a significant reduction in RNFL thickness in MS patients (92microns) versus controls (105 microns; $p<0.001$) and particularly in MSON eyes (85 microns; $p<0.001$).

We were successful in achieving our primary objective since we found a statistically highly significant reduction in RNFL in MS patients with/without a history and/or clinical evidence of ON and a significant reduction in RNFL in the fellow eye of patients with unilateral ON. We encountered, however, several difficulties and some interesting findings. First, we found a very poor interdisciplinary cooperation in the management of MS patients in our society. Many of the patients we studied (and who were referred from the neurology department for the purpose of the study) were not seen by an ophthalmologist before, even those with evident unilateral or bilateral optic neuritis. Second, patients were not aware of the cause of their visual loss, knew very little about their condition and many of those with unequivocal evidence of previous optic neuropathy had nothing in their medical records that say that they had optic neuritis before. This forced us to rely on objective criteria to diagnose previous attacks of optic neuritis including a best corrected visual acuity of 0.5 or less in absence of other causes for visual loss, BCVA of 0.72 or less with evident temporal pallor or an evident RAPD. Undoubtedly this could have introduced some bias in our results. We believe that this situation is unacceptable and that the efforts should be concentrated on the accurate documentation of the medical records of patients and the easy retrieval of data as a first step in encouraging and improving patient service and medical research.

Interdisciplinary care of patients should be mandatory and every patient, at least in the neurology department, should be referred for ophthalmic examination even those who are being followed–up on an outpatient basis. We need to better educate the patients of their condition, their possible complications and when to seek medical advice. We had another objective that could not be fulfilled by the current cross-sectional study. We need a prospective study for the role of OCT as a prognostic indicator for optic neuritis to pick up those cases that could progress to MS. This should have important prognostic implications since, unilateral idiopathic optic neuritis in young patients should have better prognosis. It will also offer the opportunity to treat early those patients that could progress to MS before widespread disease since unilateral optic neuritis is a common presentation of relapsing-remitting MS.[10] For achieving this objective we will conduct a prospective study of the fellow-eye of patients with unilateral ON.

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