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# Early disability in *ambulatory* patients with multiple sclerosis: optical coherence tomography versus visual evoked potentials, a comparative study

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## Abstract

**Background:** Multiple sclerosis (MS) is a common cause of neurological disabilities in adults and commonly affects the visual pathway. The objective of this study is to assess and compare the sensitivity of visual evoked potentials (VEP) and optical coherence tomography (OCT) as measures of early disability in *ambulatory* patients with MS.

**Methods:** Forty-four patients with MS with Expanded Disability Status Scale (EDSS) of  $\leq 4.5$  (*ambulatory* patients) and 14 healthy controls participated in this study. Patients were classified into 3 groups according to EDSS. Patients with EDSS of 0–1.5 formed the “No disability,” patients with EDSS of 2–3 formed the “Minimal to mild disability,” and finally patients with EDSS of 3.5–4.5 formed the “Moderate to significant disability” groups. N75/P100 amplitude, P100 latency, retinal nerve fiber layer (RNFL) thickness, and ganglion cell layer complex (GCLC) thickness were measured.

**Results:** Patients showed significantly lower N75/P100 amplitude, higher P100 latency, lower RNFL, and GCLC thicknesses compared to controls. However, there were non-significant changes in P100 latency, N75/P100 amplitude, and GCLC thickness among the 3 groups for both patients with and without history of optic neuritis (ON). On contrary, RNFL thickness was significantly different between the three groups for both patients with and without history of ON. Factorial ANOVA revealed non-significant disability  $\times$  History of ON interaction.

**Conclusion:** Compared to VEP parameters, RNFL thickness was a sensitive correlate with the various degrees of early disability in fully *ambulatory* patients with MS whatever the history of ON.

**Keywords:** Multiple sclerosis, Axonal loss, Optical coherence tomography, Retinal nerve fiber layer, Ganglion cell layer, VEP

## Introduction

Multiple sclerosis (MS) is a common neurological disease affecting about 2.5 million patients worldwide. MS is characterized by demyelination and axonal degeneration in the central nervous system and is the commonest cause of non-traumatic neurological disability in young adults as more than one million people suffer from physical

disabilities caused by MS [1–4]. In an Egyptian study, the prevalence of MS in Egypt was found to be 14.1/100,000 and about 2.5 million worldwide [5, 6].

Approximately, 25% of patients with MS suffer from optic neuritis (ON) as an initial manifestation of the disease. Moreover, ON occurs in about 50% of patients during the course of the disease and in about 99% of patients with MS in post-mortem examination irrespective to the clinical history of ON [7]. ON is an acute inflammatory process of the optic nerve that leads to retrograde axonal degeneration in the peripapillary retinal

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nerve fiber layer (pRNFL) and the whole ganglion cell layer complex (GCLC), which included the complex of ganglion cells plus the inner plexiform plus the RNFL layers, leading to persistent visual dysfunction [8, 9]. Recent autopsy studies of patients with MS have shown retinal pathology irrespective of the disease duration. Moreover, the retina is formed of many layers of unmyelinated nerve fibers that may serve as a good model for studying axonal pathology of patients with MS and other neurodegenerative disorders and hence might be related to the disability in those patients [7, 9, 10].

Before the advent of MRI, evoked potentials in general and especially visual evoked potentials (VEP) were used to document clinically manifest and silent lesions in MS and were part of routine diagnosis. Moreover, VEP may give information about the functional assessment of myelin, axons, and synapses of the visual pathway, especially its prechiasmatic portion, and it was a valuable tool for monitoring MS progression and prognosis [11, 12]. The N75/P100 amplitude reflects the number of functioning axons reaching the visual cortex and is reduced due to transient conduction block during acute ON and/or permanent axonal loss in the optic nerve. VEP latency is unique in which it reflects the integrity of myelin and is potentially useful in measuring the extent of demyelination/remyelination in the visual pathway [8, 13].

Optical coherence tomography (OCT) is a 3D imaging technique that generates cross-sectional images of the retina, which can be used to quantify axonal and neuronal atrophy [14]. In 1999, Parisi et al. reported significant reduction in pRNFL thickness in OCT of patients with MS. Since then, many studies using OCT found reduction in pRNFL thickness in patients with MS with and without previous ON [15]. OCT measurements of GCLC and pRNFL have been proposed as biomarkers of axonal damage in MS regardless the history of ON [10, 16]. Axonal damage is associated with both physical and cognitive disabilities of patients with MS [4]. Some studies suggested that OCT measurements may be more accurate than MRI parameters to determine progression in patients with neuromyelitis optica [17]. The pRNFL thickness was found to predict disability in patients with MS [4, 7]. Other studies found that GCLC thickness also can be considered a marker of axonal damage and disability in patients with MS [4, 7, 10].

## Methods

### Aim of the work

The aims of our study are to compare the measurements of both VEP and OCT in *ambulatory* patients with MS who are not significantly disabled and healthy controls and to compare the results of VEP and OCT in patients with minor levels of disability trying to detect which of

both techniques is more sensitive and more correlated with *minor disability*.

### Subjects

Forty-four patients with *relapsing-remitting* MS (14 males and 30 females; mean age  $\pm$  SD = 33.3  $\pm$  8.7) and 14 healthy controls (6 males and 8 females; mean age  $\pm$  SD = 34.1  $\pm$  10.7) participated in this cross-sectional study. There were no statistically significant differences between patients and controls regarding age and sex. Patients with MS were diagnosed according to the criteria of McDonalds 2017 [18] and were recruited from the neurology and ophthalmology clinics of Sohag University Hospital during the period from July 2017 to November 2018. Healthy volunteers served as controls and were recruited from the staffs and workers of our hospital, friends, and some family members of patients. Patients with neurological deficit caused by any other conditions rather than MS (MS mimics) including patients with collagen vascular, diabetes mellitus, or degenerative disorders, and patients who suffered current or recent attacks (< 3 months before participation in the study) which is enough time for retrograde retinal axonal degeneration according to many human (retinal axonal degeneration is maximal at the second month of ON) and animal (maximal from day 11 and end at day 33 from onset of ON) studies [19–21] of ON or those who suffers high myopia > 5 D and eyes with other ocular diseases that can affect the results of the test variables mentioned below were also excluded from this study. Control participants with history of eye or neurologic disease (other than corrected, non-pathologic refractive error) were excluded from the study. All study participants signed an informed written consent and the study protocol was approved by the local ethics committee of Sohag University Hospital.

Expanded Disability Status Scale (EDSS) was used for measuring disability in patients with MS. Full *ambulatory* (none of our patients was bedridden or wheelchair) patients (EDSS  $\leq$  4.5) were chosen to participate in this study and were classified into 3 groups according to the level of disability [22]. Patients with EDSS from 0 to 1.5 were taken as group 1 “No disability,” patients with EDSS from 2 to 3 were taken as group 2 “Minimal to mild disability,” and finally patients with EDSS from 3.5 up to 4.5 formed the last group “Moderate to significant disability.” Clinical and neurological evaluation was done for each of the study participants. Both VEP and OCT were done for both eyes for both patients and controls by neurologist and ophthalmologist respectively. The N75/P100 amplitude, P100 latency, pRNFL, and GCLC thicknesses and its patterns were measured. The degree of disability in each patient was measured and classified using EDSS as mentioned before.

### Visual evoked potential

VEP were recorded from occipital scalp according to the standard protocol of the International Society for Clinical Electrophysiology of VEP [23] using Neuropack MEB-2300; Nihon-Kohden, Tokyo, Japan. Monocular visual stimulation was performed using a pattern-reversal checkerboard screen. Latencies of N75 and P100 and N75/P100 amplitudes were determined for all recordings. The mean P100 latencies and N75/P100 amplitudes of the right and the left eyes of each study participant were calculated.

### Optical coherence tomography

All subjects underwent complete routine ophthalmic examination including best corrected visual acuity, intraocular pressure, slit lamp examination of the anterior segment, and fundus examination. Any case with signs of a disease which may affect the OCT findings were excluded from the study (i.e., glaucoma, optic atrophy, or optic disc edema).

The OCT examination of the optic disc and macula was performed by the RTVue instrument (Model RTVue premier, Fremont, California, USA) to measure the pRNFL thickness and the GCLC, which is a composite of the inner plexiform layer, ganglion cell layer, and nerve fiber layer.

Two images were acquired separately, one centered on the optic nerve head and the other centered on the fovea to measure the pRNFL thickness and GCLC respectively. The pattern-based GCLC parameters were calculated by the RTVue software and included the global loss volume (GLV) and the focal loss volume (FLV). The GCLC was measured in an area of 7.0 mm by 7.0 mm that is centered at 1.0 mm temporal to fovea. The GLV represents the number of pixels that demonstrate a loss of GCLC relative to the normative data divided by the total number of pixels in the scanned area to determine the percentage of global GCLC loss in the entire map.

The FLV represents the thickness value at each pixel within the scanned area to generate a “pattern map” to determine percentage of focal GCLC loss in the entire map. The RNFL thickness was divided into 8 sectors at 0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315° measured within an area of diameter 3.45 mm around optic disc.

### Statistical analysis

Demographic data were presented as mean  $\pm$  SD if normally distributed, median (range) if not normally distributed, and percentage for categorical data. Data for the various parameters of VEP and OCT were presented as mean  $\pm$  SEM. The Kolmogorov-Smirnov test of normality was used for numerical data. The statistical package SPSS for Windows (Version 16) was used for statistical analysis. Independent sample *T* test and ANOVA were used to determine the significant differences between groups for the numerical data. Chi-squared test and Kruskal-Wallis tests were used for categorical data and non-normally distributed numerical data. *P* value of  $< 0.05$  was considered statistically significant.

### Results

The demographic characters and other MS-related data including the data relevant to history of ON are presented in Table 1 for each of the 3 groups under study. Patients with MS with no disability showed statistically significant lower disease duration and number of attacks compared to patients with mild up to significant disability ( $F = 5.49$ ,  $P = 0.008$ ; and  $F = 9.158$ ,  $P = 0.001$ ) respectively. Post hoc testing with Bonferroni correction revealed only significant difference between the group with “No Disability” and the groups “Minimal to mild disability” and “Moderate to significant disability” for both disease duration and number of attacks respectively ( $P = 0.017$ ,  $P = 0.021$ ; and  $P = 0.01$ ,  $P = 0.001$ ). The distribution of DMT was not the same across the groups of disability as Kruskal-Wallis testing showed significant difference between the three groups ( $P = 0.011$ ).

**Table 1** Demographic and disease variables of patients with MS

Demographic and disease-related data	Groups		
	No disability	Minimal to mild disability	Moderate to significant disability
Number of patients	14	16	14
Age (years)	35.7 $\pm$ 10.2	30.8 $\pm$ 6.8	33.9 $\pm$ 9
Sex	4 males (28.6%); 10 females (71.4%)	6 males (37.5%); 10 females (62.5%)	4 males (28.6%); 10 females (71.4%)
Disease duration (years)	0.5 (0.5–7)	7 (0.5–11)	7 (0.5–14)
Number of attacks	2 (1–3)	3 (3–4)	3 (2–6)
Disease modifying therapy	12 No DMT (85.7%); 2 on DMT (14.3%)	6 No DMT (37.5%); 10 on DMT (62.5%)	11 No DMT (78.6%); 3 on DMT (21.4%)
History of ON	8 yes (57.1%); 6 no (42.9%), 6 single attack of ON and 2 recurrent attacks; 5 unilateral ON and 3 bilateral ON	10 yes (62.5%); 6 no (37.5%), 6 single attack of ON and 4 recurrent attacks; 3 unilateral ON and 7 bilateral ON	11 yes (78.6%); 3 no (21.4%), 2 single attack of ON and 9 recurrent attacks; 0 unilateral ON and 11 bilateral ON

ON optic neuritis

There were statistically significant differences between patients and controls in all the data of both VEP and OCT measurements (Table 2). Further comparing the control group and the patients with MS without disability “No disability,” independent sample *T* test revealed significant differences in most of the parameters of VEP and OCT ( $T = 5.101, P < 0.001$ ;  $T = 3.388, P = 0.001$ ;  $T = 3.281, P = 0.002$ ;  $T = 3.649, P = 0.001$ ;  $T = 4.257, P < 0.001$ ; and  $T = 1.842, P = 0.075$ ) for P100 Latency, N75/P100 amplitude, pRNFL thickness, GCLC thickness, GLV, and FLV respectively.

One-way ANOVA taking the P100 latency, N75/P100 amplitude, pRNFL thickness, and GCLC thickness as within subject factors and disability with its three levels “No disability,” “Minimal to mild disability,” and “Moderate to significant disability” as between subject factor with comparing the patients according to the history of ON revealed non-significant differences in P100 latency, N75/P100 amplitude, and GCLC thickness for both patients without and patients with history of ON ( $F = 1.871, P = 0.173$ ;  $F = 1.034, P = 0.369$ ; and  $F = 1.505, P = 0.24$ ; for patients without history of ON and  $F = 1.523, P = 0.227$ ;  $F = 0.673, P = 0.515$ ; and  $F = 2.666, P = 0.079$ ; for patients with history of ON, respectively). However, pRNFL thickness was significantly different between the three groups for both patients without and patients with history of ON ( $F = 6.892, P = 0.004$ , and  $F = 4.308, P = 0.018$ , respectively) (Figs. 1, 2, 3, and 4).

Factorial ANOVA taking the pRNFL thickness as the within subject dependent variable and both disability and history of ON as fixed between subjects' variables revealed non-significant disability  $\times$  History of ON interaction ( $F = 2.364, P = 0.1$ ) meaning that pRNFL thickness was a sensitive correlate with the degree of disability in fully

*ambulatory* patients with MS whether they suffered ON or not. Moreover, factorial ANOVA taking the pRNFL thickness as the within subject-dependent variable and both subject (cases vs controls) and site (temporal vs nasal pRNFL thicknesses) as fixed between subject variables revealed significant effect of subject ( $F = 32.394, P < 0.001$ ) and also significant effect of site ( $F = 5.456, P = 0.021$ ); however, there was non-significant subject  $\times$  site interaction ( $F = 2.561, P = 0.112$ ) meaning that the reduction of the pRNFL thickness in patients with MS was not dependent on its site whether nasal or temporal part of the retina.

## Discussion

The results of our study supports the utility of OCT as a safe, widely available, inexpensive, non-invasive tool of measurement of the degree of thinning of the pRNFL thickness for assessment of axonal neurodegenerative changes in patients with MS.

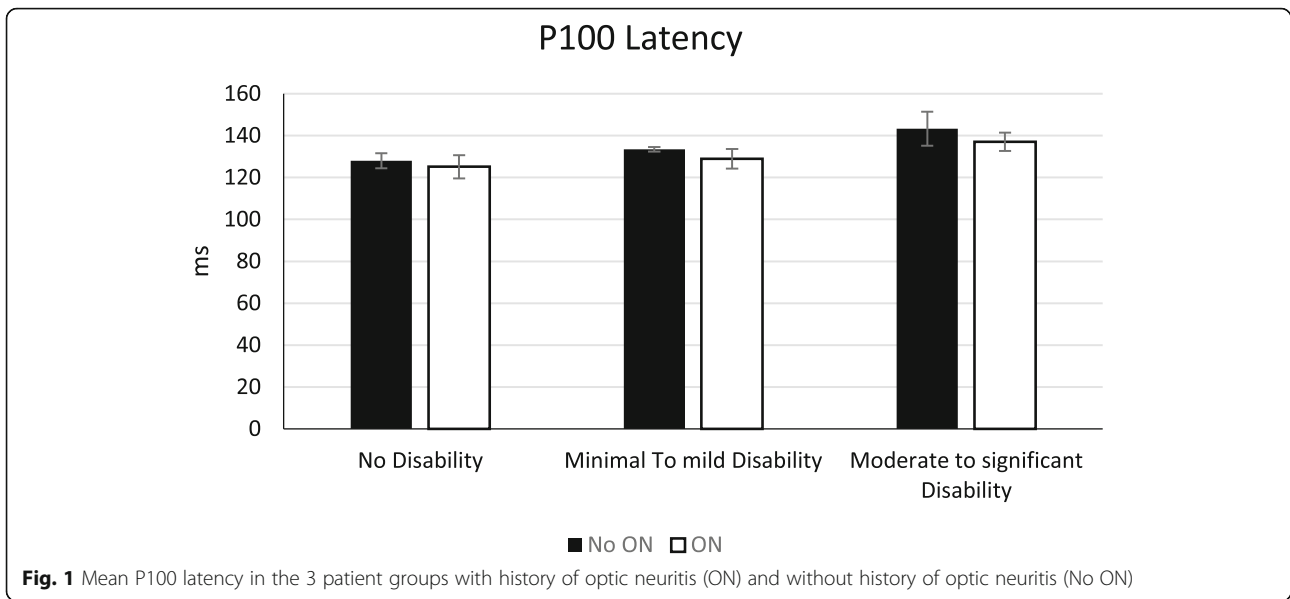
MS is an immune-mediated not only demyelinating, but also a neurodegenerative neurological disorder with axonal damage. Previous studies supported that both inflammatory and neurodegenerative mechanisms co-exist in patients with MS and results in non-reversible axonal damage causing the permanent disability in those patients [24–26]. The retina is an accessible good tool for studying neurodegenerative mechanisms in many diseases because retinal axons lack myelin sheaths, and changes in its structure reflects only axonal damage. The pRNFL is made up of the unmyelinated axons of the retinal ganglion cells traveling to lateral geniculate body [7, 9, 10, 14].

This study demonstrated that both VEP and OCT were sensitive measurements of axonal damage not only in patients with MS compared to healthy controls, but also in patients with MS who are still “*ambulatory*.” Moreover, we found that both VEP and OCT parameters were significantly different between patients and healthy controls even if there is no neurological disability as we found significant differences in both VEP and OCT parameters between *ambulatory* patients with “No disability” group and healthy controls. However, testing the differences in both P100 latency, N75/P100 amplitude, and the GCLC thickness regarding the various grades of disability in *ambulatory* patients with MS revealed no significant differences among the three groups meaning that those parameters although sensitive but not strictly correlated with the degree of early disability. On contrary, pRNFL thickness not only was significantly different among the three groups of disability, but also was not dependent on whether the patient suffered ON or not. This means that the pRNFL thickness can be taken as a significant correlate with the level of early disability in *ambulatory* patients with MS in the early stages of the disease.

**Table 2** VEP and OCT measurements for patients with MS and healthy controls

Variable	Subject	Mean $\pm$ SEM	<i>T</i> value	<i>P</i> value
P100 latency	Case	132.3 $\pm$ 2.2	9.673	< 0.001
	Control	107.7 $\pm$ 1.8		
N75/P100 amplitude	Case	7.8 $\pm$ 0.48	21.448	< 0.001
	Control	13.7 $\pm$ 0.56		
RNFL thickness	Case	99.5 $\pm$ 1.3	5.061	< 0.001
	Control	112.8 $\pm$ 2		
GCLC thickness	Case	87.6 $\pm$ 0.9	4.888	< 0.001
	Control	95.8 $\pm$ 1		
GLV	Case	10.6 $\pm$ 0.7	7.165	< 0.001
	Control	5.1 $\pm$ 0.39		
FLV	Case	2.7 $\pm$ 0.3	4.444	< 0.001
	Control	1.3 $\pm$ 0.1		

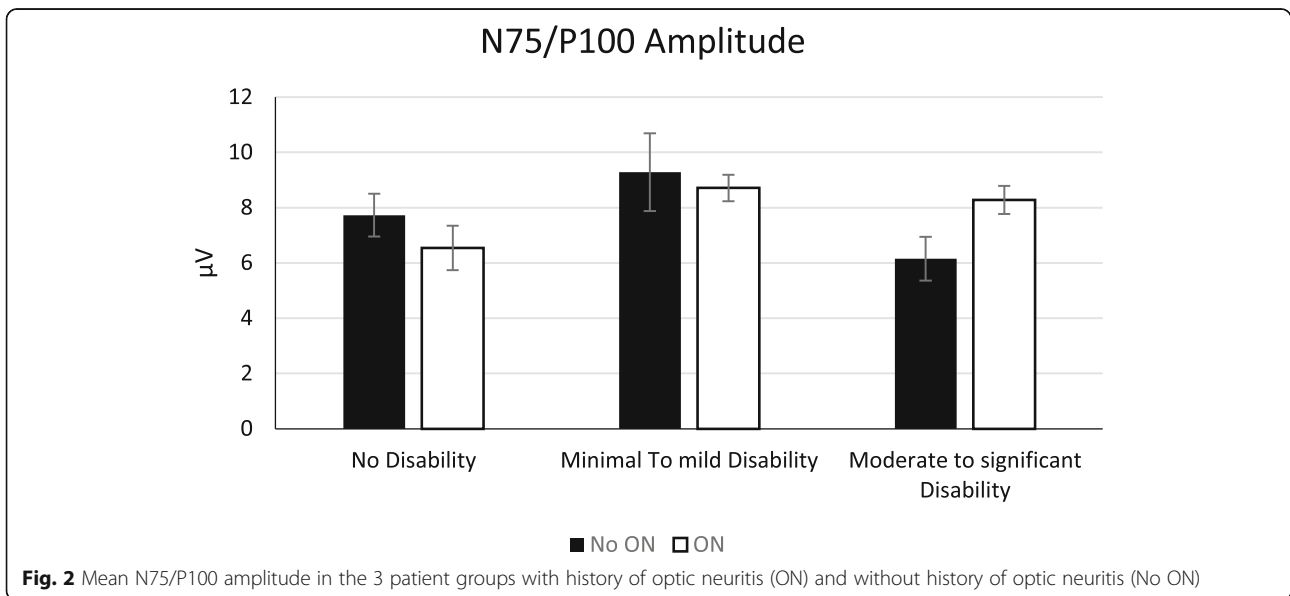
RNFL retinal nerve fiber layer, GCLC ganglion cell layer complex, GLV global loss volume, FLV focal loss volume

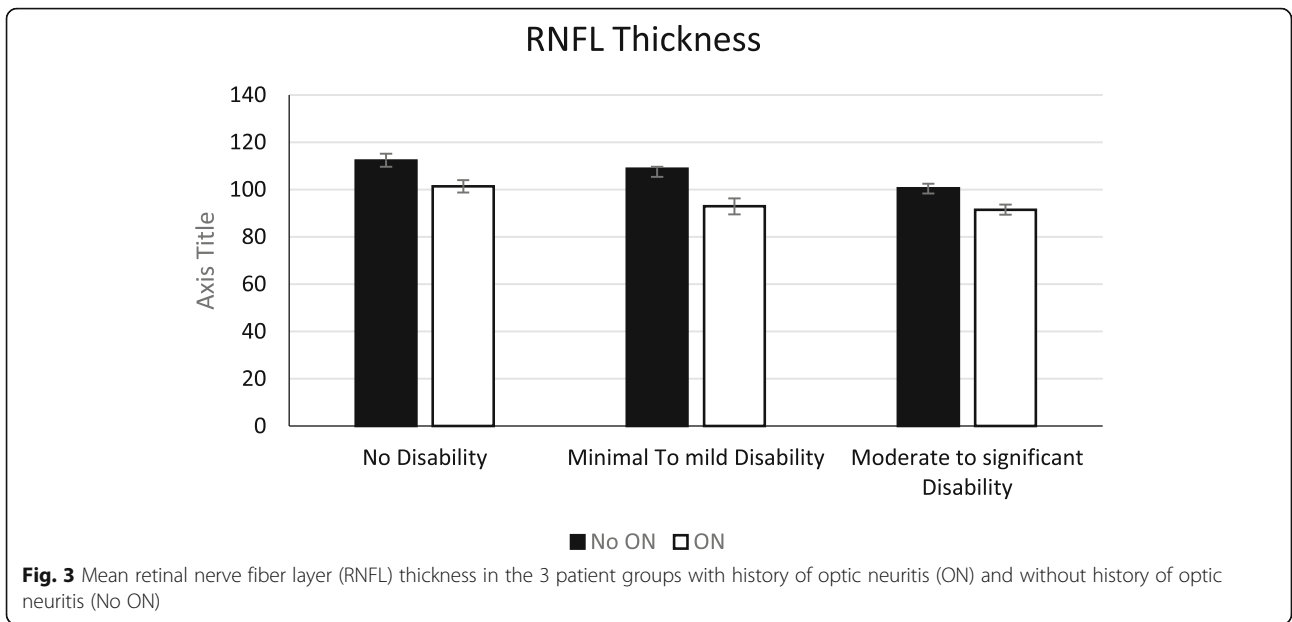


Changes in VEP and OCT parameters in patients with MS were not related to the clinical history of previous ON. The pRNFL thickness was significantly different between the three groups with different degree of disability whether there is history of ON or not. The affection of OCT parameters (GCLC and pRNFL) was evident in our study as well as many other studies [27, 28].

To determine whether the affection of the pRNFL affection is related to the disease itself or related to recent previous attack of ON is an important point. We excluded patients with MS who have recent history (within 3 months) of ON who may suffer retinal injury of a disproportionate degree of the global brain rather than the local retinal neurodegeneration [29] to exclude the damage

precipitated by ON as a manifestation of MS rather than disability of MS. As we reported that it is affected independently from the history of ON, so it can be a pathological sign of the disease itself. Klistorner et al. reported that the pRNFL and the optic radiation were affected in MS patients without history of ON; these results agree with our study [30]. Furthermore, those findings of our study and other studies regarding the affection of the OCT parameters in patients with MS without clear history of ON can be explained by either unknown subclinical attacks of ON, the retrograde axonal and retinal ganglion cell degeneration due to MS lesions within the brain that may result in pRNFL loss, or by other mechanisms leading to neurodegeneration in patients with MS [31, 32].

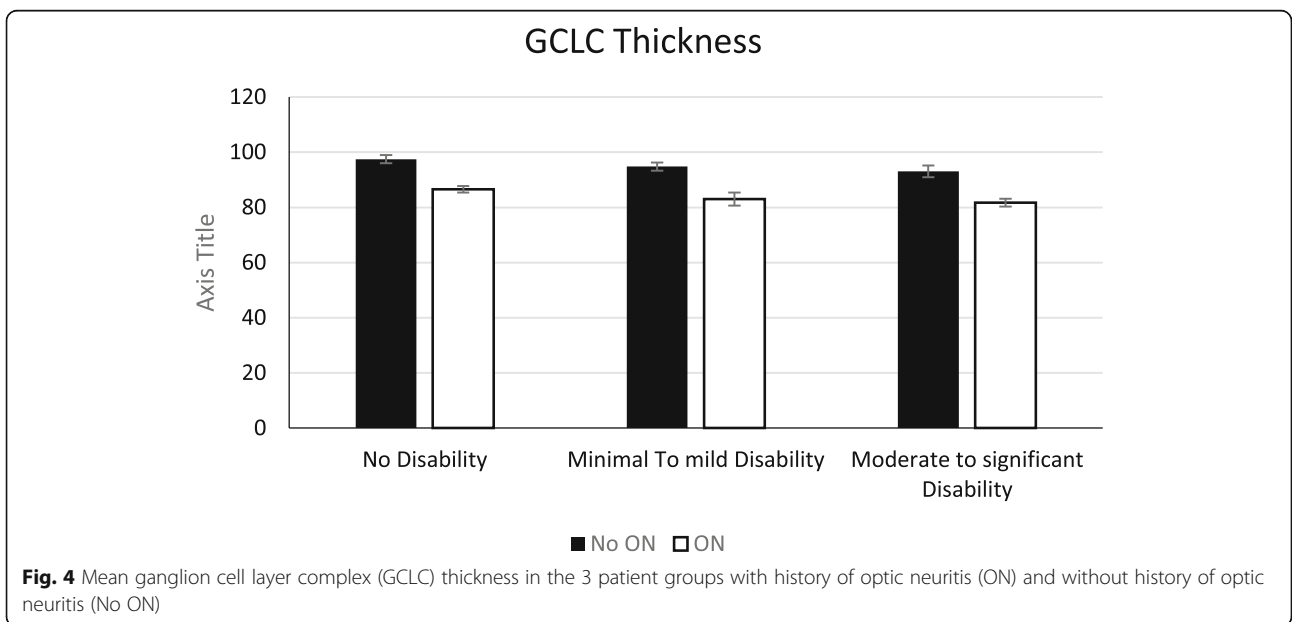




The degree of affection of the pRNFL thickness was correlated with the degree of disability in fully *ambulatory* patients. Gelfand et al. reported the same affection in more advanced disease stage and they also concluded that the thinning of pRNFL was more in patients with history of ON which was not evident in our data in fully *ambulatory* patients [33]. However, the correlation of neurological disability in patients with MS measured by the EDSS and the pRNFL thickness is still a debatable issue as some authors found a significant relation between both parameters [34–38] and others denied this relation [39, 40]. Interestingly, some authors explained this discrepancy by the

inclusion of patients with various levels of disability ranging from mild to severe bedridden or wheelchair patients [36, 41], and that was the reason of inclusion of *ambulatory* patients with MS in our study.

The results of this study points to the degree of pRNFL loss as a correlated factor with the degree of disability in a fully *ambulatory* patients with MS whether they suffered from ON or not. But this degree of loss was not dependent on the site whether nasal or temporal. On the other hand, Birkeldh et al. reported that the temporal pRNFL thickness is more associated with the degree of disability in MS using the EDSS scoring



system, and the degree of association was higher for the temporal pRNFL than the average pRNFL calculated by regression coefficient. We could not find the exact cause of difference between the results of our study and these data, but it may be related to the small sample size in our study and/or the racial difference which is always taken in consideration in all OCT machines and studies [42]. The GCLC as one of the parameters of OCT and represents the ganglion cells with its dendrites and axons was significantly affected in all *ambulatory* patients of MS in our study when compared to controls. The same results were reported by previous studies [42].

The GCLC did not show significant differences according to the degree of disability. Pietroboni et al. reported that the ganglion cells affection occurs early in the course of MS before the pRNFL thinning suggesting that the damage occurs in the cell body then spread to the axon. However, we found that both GCLC and pRNFL thicknesses were affected in early non-disabled patients with MS [43]. Coric et al. reported that the GCLC as well as the pRNFL thickness is correlated with the degree of cognitive impairment in patients with MS without previous history of ON; we did not tested OCT parameters in relation to cognitive functions as it was tested before [44]. They suggested that OCT is a helpful tool in assessment of the degree of degeneration of the central nervous system in MS patients. ON has its own effect on the OCT parameters with masking effect on the degree of thinning caused by the MS itself [44]. The GCLC thickness was considered by Saidha et al. as a useful parameter in monitoring of progressive MS. They found that the ganglion cell layer thickness and the gray matter as well as whole brain atrophy are correlated in progressive MS. Our study added that the GCLC thickness can be considered also as a monitoring tool in early stages of MS in full *ambulatory* patients [45].

As regard VEP, the P100 latency reflects the conductivity of the optic nerve axons which is directly related to the integrity of the myelin sheaths of the nerve; however, the N75/P100 amplitude reflects the functional integrity of the axons itself especially if associated with reduction of the area under the curve [8, 13]. The P100 latency was prolonged in patients with MS who suffered previous episodes of ON and usually persist for many years [46]. In our study, we found that both P100 latency and N75/P100 amplitude were significantly affected not only in all included patients with MS, but also in non-disabled patients. The results of our study were similar to many previous ones [15, 47–49]. Although both parameters were sensitive in non-disabled patients with MS, it was not strictly correlated with the degree of early disability.

Permanent disability in patients with MS is considered to be a direct result of axonal damage and brain volume

measured by many tools used for quantification of disability including EDSS [25, 37]. Moreover, direct correlation between pRNFL thickness and disease duration and functional impairment in EDSS were found in other studies [49, 50] and was in agreement with our results.

## Conclusions

Both OCT and VEP examinations of patients with MS are fast, safe, non-invasive, and relatively inexpensive tools for assessment of the degree of axonal loss and hence the disability in non-disabled ambulatory patients. Moreover, the pRNFL thickness was a sensitive measure that is significantly sensitive to varying degrees of disability even in ambulatory patients in early stages of MS and may be a useful future objective measurement tool taken as a biomarker of disease progression and of the response to immunomodulatory therapy of MS.

## Limitations of the study

The limitations of our study include the small sample size of each patient group. Moreover, this study included patients with relapsing-remitting rather than progressive MS subtypes which may impact the interpretation and the generalization of the results of our study to the various patients with MS. However, this could be explained by the special sample of early ambulatory patients who did not yet suffered the aggressive levels of disability found in progressive MS subtypes either primary or secondary. Future studies of larger homogeneous samples of patients including the various subtypes of MS are still needed for further assessments of axonal damage of MS by easy, non-invasive, widely available, and inexpensive objective tools.

## Acknowledgments

We would like to thank all who helped us in this work especially our colleagues including Dr Mohamed Tarek, Dr Ahmad El-shanhory for their help and support in this research.

## Prior presentation

Part of this work was presented as poster presentation in the World Congress of Neurology, Dubai, 2019, UAE.

## Authors' contributions

MF analyzed and interpreted the optical coherence tomography related data of the patients and controls. MT, MA, and AB analyzed and interpreted visual-evoked potentials and demographic data of the patients and controls. All authors participated in writing the manuscript, and all authors read and approved the final manuscript.

## Funding

This research received no specific grant from any funding agency in public, commercial, or non-profit sectors.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

All study participants signed an informed written consent, and the study protocol was approved by the local ethics committee of Sohag University Hospital.

### Consent for publication

This manuscript does not contain any individual person's data in any form, including individual details, images, or videos.

### Competing interests

None of the authors has any financial conflict of interest relating to this manuscript.

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Received: 11 May 2020 Accepted: 22 June 2020

Published online: 06 July 2020

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