The Egyptian Journal of Hospital Medicine (October 2021) Vol. 85 (2), Page 3645-3648

Evaluation of Retinal Nerve Fiber Layer Thickness in Patients with Multiple Sclerosis

Rasha M. Fahmi, Amr E. Kamel, Mourad A. Salem*, Enas E. Mohammed
Department of Neurology, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Mourad A. Salem**, Mobile:** (+2) 01068069208, **Email:** drmorad86@gmail.com

ABSTRACT

Background: Multiple sclerosis (MS) is a neurodegenerative disease, and is considered a chronic inflammatory disease. Retinal nerve fiber layer (RNFL) thickness as a structural biomarker for axonal loss in MS.

Objective: The aim of the present study was to assess the role of optical coherence tomography (OCT) in detecting RNFL in MS patients without history of optic neuritis and to correlate with disease duration and disease disability.

Patients and methods: Case-control study included 34 patients with clinically definite relapsing remitting multiple sclerosis (RRMS) and 34 age- and sex-matched individuals (other than MS) served as the controls. They were selected from the inpatients wards and Outpatients Clinic of Neurology Department, Zagazig University Hospitals**.** All patients were subjected to full history taking, clinical examination as well as laboratory and specific investigations.

Results: The mean age was 34.56 ± 8.79 years in MS patients and 34.03 ± 8.79 years in controls. VEP 42.9% is with delay of p100 wave in bilateral eyes, and prolongal p100 laterary in bilateral eyes in 54.3%. There was a highly statistical significant difference between groups as regard RNFL average thickness and RNFL symmetry. Expanded disability status scale (EDSS) showed independently associated with RNFL.

Conclusion: The thickness of the RNFL observed by OCT in MS patients is dramatically reduced when compared to controls, according to the current study. OCT is a valuable tool for determining the thickness of the RNFL in MS patients.

Keywords: Multiple sclerosis, Optical coherence tomography, Retinal nerve.

INTRODUCTION

Multiple sclerosis is a journey from being at risk, through the asymptomatic, prodromal and symptomatic phases of the disease. MS is typically suspected when a person presents with a clinically isolated syndrome (CIS). The most commonly seen presentations are optic neuritis and brainstem and spinal cord syndromes. Gross clinical recovery from relapses often appears complete in early MS; however, most relapses leave behind some damage [(1)].

Acute optic neuritis (ON) results in rapid and prominent peripapillary retinal nerve fiber layer (RNFL) as measured with optical coherence tomography (OCT). However, the degree of thinning within these layers following ON is heterogeneous, varying across patients, even within the same disease state. Optic neuritis is practically ubiquitous in MS, with up to 94%–99% of patients demonstrating demyelinating plaques within their optic nerves [(2)].

Spectral-domain optical coherence tomography (SD-OCT) has matured from a research instrument to a tool used in clinical routine. SD-OCT permits the visualization of neurodegeneration in vivo at a hitherto unparalleled structural resolution [(3)].

The ability to quantify RNFL could provide a diagnostic opportunity for assessing neuronal or axonal damage [(4)]. The optimal interval to capture RNFL thinning is estimated to be approximately 6 months following acute ON.

Gabilondo *et al.* [(5)] reported thinning from baseline of the RNFL by 45.3 μm at 6 months following ON. Optical coherence tomography used image distinct strata of the retina histologically in real time with sensitivity enables micron-scale resolution imaging and quantification of RNFL and macular thickness [(6)].

The present study aimed to evaluate the role of OCT in detecting the thickness of RNFL in MS patients without history of optic neuritis.

A case control study included 34 patients with relapsing remitting multiple sclerosis (RRMS) and 34 age- and sex-matched control subjects were selected from Outpatients Clinic of Neurology Department, Zagazig University Hospitals.

Inclusion criteria: Patients aged ≥18 years of both sexes and with clinically definite RRMS. Control group with visual acuity (VA) of 20/30 or better and without ophthalmic or neurologic diseases.

Exclusion criteria: cases with a refractive error of ± ≥ 5.0 D, history of optic neuritis (ON), other diseases as hypertension or diabetes mellitus, glaucoma, anterior ischemic optic neuropathy, congenital abnormalities of the optic nerves, history of ocular surgery or penetrating trauma.

Clinical assessment:

All patients were subjected to full history taking, clinical examination including neurological examination at neurology department, Zagazig University.

This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY-SA) license (http://creativecommons.org/licenses/by/4.0/**)**

Received: 30 /6 /2021
Accepted: 26 / 8/2021

Expanded Disability Status Scale (EDSS):

Clinical EDSS scales were used to quantify disability in pyramidal, cerebellar, brain stem, sensory and visual functions to all patients.

Laboratory investigations:

Complete blood count (CBC), fasting blood glucose, lipid profile, kidney and liver function tests, C - reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were estimated.

Spectral domain optical coherence tomography (OCT) examination:

By using the Heidelberg Engineering Spectralis (Heidelberg, Germany).

Visual evoked potential (VEP):

All patients underwent VEP using The Nihon Kohden (Nihon Kohden MEB-2300, Tokyo, Japan). The patients were seated in a semi-dark room 40 cm away from a television screen, then four electrodes were placed on the patient's head (one on occiput, two laterals, and a ground electrode on the vertex). The participant was asked to fix on a central target taped to the screen 5 cm × 5 cm. A strobe flashlight is suddenly illuminated to elicit flash response. The screen is turned on to reveal a checkerboard with a check size of 16 inches that reverses in pattern between black and white squares at a rate of 2 Hz. The latency of the first major positive peak in the VEP (P100 wave) was measured.

Retinal nerve fiber layer (RNFL) examination:

RNFL images were acquired by taking three circular 3.4-mm-diameter scans, centered on the optic disc, the mean of which was used to express RNFL thickness in temporal, superior, inferior, and nasal quadrants, which automatically was calculated by the OCT device software.

Ethical approval:

The study was approved by the Ethical Committee of Zagazig Faculty of Medicine. An informed consent was obtained from each patient in this research. Every patient received an explanation for the purpose of the study. All given data were used for the current medical research only. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

The data were analyzed using the SPSS (Statistical Package for Social Sciences) version 15 for Windows® (SPSS Inc, Chicago, IL, USA). Qualitative data were presented as number and percent. Comparison between groups was done by Chi-Square test. Quantitative data were tested for normality by Kolmogrov-Smirnov test. Linear regression analysis was used to identify significant factors affecting RNFL. Measures of association were expressed as Beta and 95% confidence interval (CI). P value was set at ≤ 0.05 for significant results and < 0.001 for highly significant results.

RESULTS

The present study showed that mean age was 34.56 ± 8.79 years in MS patients and 34.03 ± 8.79 years in controls. About 64.71% were females and 35.29% were males in MS patients, while in controls, 58.82% were females and 41.18% were males. There was non-statistical significant difference between groups as regards age and sex (Table 1).

As regards VEP, 42.9% were with delay of p100 wave in bilateral eyes, and prolongal p100 lateray in bilateral eyes in 54.3% (Table 2). Majority of cases in each group showed that BCVA was > 0.5, and there was non-statistical significant difference between case and control group.

Best Corrected Visual Acuity (BCVA) **(Figure 1)**:

There was a highly statistical significant difference between groups as regards RNFL average thickness and RNFL Symmetry (Table 3). Regarding Expanded Disability Status Scale (EDSS), it showed independently associated with RNFL (Table 4).

Table (1): Demographic data between the two studied groups

Demographic data	RRMS (N = 34)		Controls (N = 34)		p
	No.	%	No.	%	
Sex					
Male	12	35.29	14	41.18	0.618
Female	22	64.71	20	58.82	
Age (years)					
Mean ± SD.	34.56 ± 8.79		34.03 ± 8.79		0.802

N: number; SD: stander deviation

Table (2): Visual Evoked Potential distribution among RRMS patients: (N=34)

VEP	N	%
Prolongal p100 lateray in bilateral eyes	19	54.3

N: number; VEP: visual evoked potential

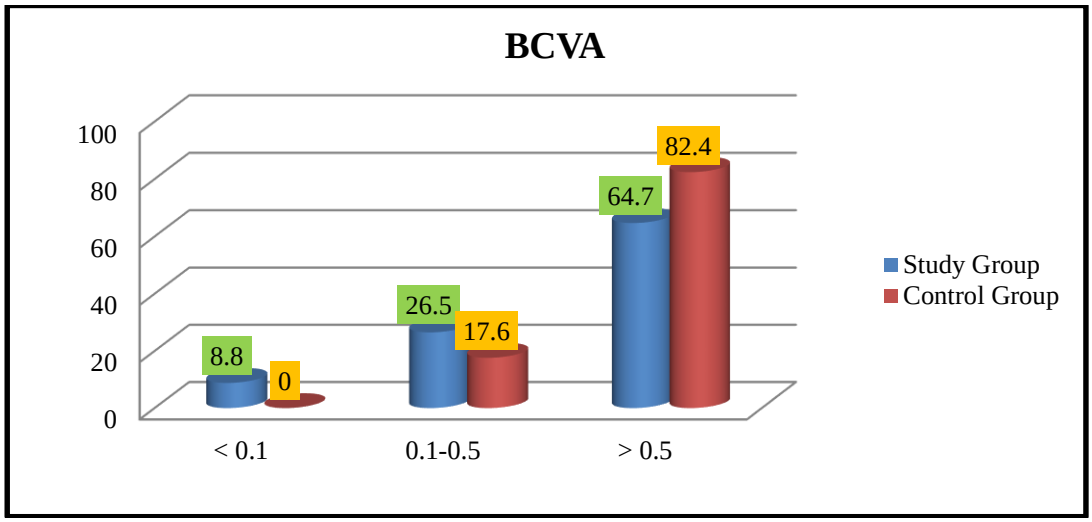

Figure (1): Bar charts showing BCVA among RRMS and controls

Table (3): RNFL thickness and symmetry between the studied groups

	RRMS (n = 34)	Controls (n = 34)	p
Average RNFL Median (IQR)	68.25 (59.28 – 78.72)	101.8 (95.18 – 107.4)	<0.001*
RNFL Symmetry Median (IQR)	0.70 (0.50 – 0.80)	0.90 (0.80 – 1.0)	<0.001*

RRMS: Relapsing-remitting multiple sclerosis; RNFL:retinal nerve fiber layer; *: Statistically significant at $p \leq 0.05$

Table (4): Linear regression of variables affecting RNFL in RRMS

Variables	Beta	95% C.I.		P
		Lower	Upper	
Duration	0.153	0.472	1.284	0.352
EDSS	0.370	0.269	5.093	0.031*

RNFL: retinal nerve fiber layer; RRMS: Relapsing-remitting multiple sclerosis; EDSS:Expanded Disability Status Scale, *: Statistically significant at $p \leq 0.05$

DISCUSSION

Multiple sclerosis (MS) is a chronic neurodegenerative disease of the central nervous system (CNS). Although MS has long been considered a primary demyelinating disease, axonal loss is of critical importance. Axonal loss is increasingly thought to occur early in the disease course and is thought to be associated with neurologic deficits and predictive of progression to permanent disability [(7)].

The visual system is an extension of the central nervous system and the retina is the only place where a tissue layer made up of unmyelinated axons can be imaged directly. Axonal loss in the RNFL, as measured by OCT, has the potential to become a model to study axonal lossthroughout the central nervous system in patients with MS [(8)].

This study was a case control study carried out on 34 patients with clinically definite relapsing remitting multiple sclerosis (RRMS) and 34 age- and-sexmatched patients (other than MS) served as the controls. They were selected from the Inpatients wards and Outpatients Clinic of Neurology Department, Zagazig University Hospitals.The aim of our study was to evaluate the role of OCT in detecting the thickness of RNFL in RRMS patients and correlate our findings with disease duration and disease disability.

This study showed that the mean age of MS onset was 27.94 ± 6.94 years. This is in agreement with **Zakaria *et al.*** [(9)] who found that the mean age of onset was 26.17 ± 7.6 years. In our study female to male ratio was 1.8:1, which is in agreement with other Egyptian studies by **Zakaria *et al.*** [(9)] and **Hamdy *et al.*** [(10)]**.** However, other studies showed a higher ratio (F:M) up to 3:1 and 3.3:1 [(11, 12)]**.** This increased risk of MS among women may be due to specific physiology and hormone-related factors. Furthermore, X chromosome inactivation in women (skewed X chromosome) results in over representation of MS [(13)].

Regarding RNFL thickness measurement, there was decrease in all parameters in RRMS patients compared to control with high statistical significant difference. This is in agreement with other studies **Zamzam *et al.*** [(14)]**, Khalil *et al.*** [(15)] and **Singh *et al.*** [(16)]**.** Also, **Soufi *et al.*** [(17)] evaluated retinal nerve fiber layer thickness measured by optical coherence tomography in patients with multiple sclerosis. Total RNFL thicknesses were significantly lower in MS eyes compared to healthy control eyes.

As regards BCVA, in our study it was > 0.5 but with no statistical significant difference between them. **Khalil *et al.*** [(15)] reported a decrease in mean of BCVA in multiple sclerosis patients (0.41 ± 0.33) compared to controls (0.9 ± 0.09) and this was statistically significant ($p < 0.001$).

Linear regression analysis showed that EDSS was independently associated with RNFL in this study.

This is in agreement with previous studies showed an inverse correlation [18, 19 and 15]. However, other studies didn't identify an association between RNFL thickness and EDSS [20, 21]. Moreover, **Bsteh *et al.*** [22] observed that having a RNFL thickness below 88 μm was independently associated with a three-fold increased risk of EDSS progression ($p < 0.001$) within the following 3 years. EDSS reflect disability in MS, which mean the presence of neurodegenration. Our findings support that value of RNFL thickness to assess the axonal loss in MS.

CONCLUSION

The thickness of the RNFL observed by OCT in MS patients is dramatically reduced when compared to controls, according to the current study. OCT is a valuable tool for determining the thickness of the RNFL in MS patients.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

REFERENCES

1. **Dobson R, Giovannoni G (2019):** Multiple sclerosis–a review. European Journal of Neurology, 26 (1): 27-40.
2. **Saidha S, Naismith R (2019):** Optical coherence tomography for diagnosing optic neuritis: Are we there yet? Neurology, 92 (6): 253-254.
3. **Petzold A (2016):** Optical Coherence Tomography (OCT). In Optical Coherence Tomography in Multiple Sclerosis. Springer, Cham. Pp: 21-46.https://www.springer.com/gp/book /9783319209692
4. **Sakai E, Feller J, Galetta M *et al.* (2011):** Vision in multiple sclerosis (MS): the story, structure-function correlations, and models for neuroprotection. Journal of neuro-Ophthalmology, 31 (4): 362-67.
5. **Lambe J, Saidha S, Bermel A (2020):** Optical coherence tomography and multiple sclerosis: Update on clinical application and role in clinical trials. Multiple Sclerosis Journal, 26 (6): 624-639.
6. **DeBuc C (2011):** A review of algorithms for segmentation of retinal image data using optical coherence tomography. Image Segmentation, 1: 15-54.
7. **Hauser L, Oksenberg R (2006):** The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. Neuron, 52 (1): 61-76.
8. **Fahmi M, Kamel E, Abdelrahem S *et al.* (2021):** Association of Retinal Nerve Fiber Layer Thickness with Disability in Patients with Multiple Sclerosis. Annals of the Romanian Society for Cell Biology, 25 (6): 14256-14267.
9. **Zakaria M, Zamzam A, Hafeez A *et al.* (2016):** Clinical characteristics of patients with multiple sclerosis enrolled in a new registry in Egypt. Multiple Sclerosis and Related Disorders, 10: 30-35.
10. **Hamdy M, Abdel-Naseer M, Shalaby M *et al.* (2017)**: Characteristics and predictors of progression in an Egyptian multiple sclerosis cohort: a multicenter registry study. Neuropsychiatric Disease and Treatment, 13: 1895-1899.
11. **Hirst C, Ingram G, Pickersgill T *et al.* (2009):** Increasing prevalence and incidence of multiple sclerosis in South East Wales. Journal of Neurology, Neurosurgery & Psychiatry, 80 (4): 386-391.
12. **Etemadifar M, Sajjadi S, Nasr Z *et al.* (2013):** Epidemiology of multiple sclerosis in Iran: a systematic review. European Neurology, 70 (5-6): 356-363.
13. **Ysrraelit M, Correale J (2019):** Impact of sex hormones on immune function and multiple sclerosis development. Immunology, 156 (1): 9-22.
14. **Zamzam D, Gaafar A, Ismail A *et al.* (2015):** Retinal nerve fiber layer thickness in multiple sclerosis subtypes. Egypt J Neurol Psychiatr Neurosurg., 52 (3): 216-220.
15. **Khalil D, Said M, Abdelhakim M *et al.* (2017):** OCT and visual field changes as useful markers for follow-up of axonal loss in multiple sclerosis in Egyptian patients. Ocul Immunol Inflamm., 25 (3): 315-22.
16. **Singh S, Sharma R, Gurunadh V *et al.* (2017):** OCT based evaluation of retinal changes in multiple sclerosis. Int J Res Med Sci., 5 (9): 4117-4121.
17. **Soufi G, AitBenhaddou E, Hajji Z *et al.* (2015):** Evaluation of retinal nerve fiber layer thickness measured by optical coherence tomography in Moroccan patients with multiple sclerosis. J Fr Ophtalmol., 38 (6): 497-503.
18. **Siepman A, Bettink-Remeijer W, Hintzen Q (2010):** Retinal nerve fiber layer thickness in subgroups of multiple sclerosis, measured by optical coherence tomography and scanning laser polarimetry. Journal of Neurology, 257 (10): 1654-1660.
19. **Siger M, Dziegielewski K, Jasek L *et al.* (2008):** Optical coherence tomography in multiple sclerosis: thickness of the retinal nerve fiber layer as apotential measure of axonal loss and brain atrophy. J Neurol., 255: 1555-60.
20. **Jeanjean L, Castelnovo G, Carlander B *et al.* (2008):** Study of optical axonal loss by optical coherence tomography (OCT) in 15 patients with multiple sclerosis and comparison with a population of matched controls. Rev Neurol., 164: 927-34.
21. **Naismith R, Tutlam N, Xu J *et al.* (2009):** Optical coherence tomography is less sensitive than visual evoked potentials in optic neuritis. Neurology, 73: 46-52.
22. **Bsteh G, Hegen H, Teuchner B *et al.* (2017):** Peripapillary retinal nerve fibre layer as measured byoptical coherence tomography is a prognostic biomarker not only for physical but also for cognitive disability progression in multiple sclerosis. Mult Scler., 25 (2): 1352458517740216. https://journals.sagepub.com/doi/abs/10.1177/1352458517740216