Original Article

Macular ganglion cell complex parameters by optical coherence tomography in cases of multiple sclerosis without optic neuritis compared to healthy eyes

Nancy M Lotfy[1,3], Tariq Alasbali[2,3], Rajiv Khandekar[4]

Purpose: To compare different macular thickness parameters and peripapillary retinal nerve fiber layer (RNFL) thickness between recently diagnosed cases of multiple sclerosis (MS) without optic neuropathy (ON) and healthy individuals. **Methods:** This cross-sectional study was performed between June 2014 and June 2015. All subjects underwent ocular and retinal examination. Spectral domain optical coherence tomography (SD-OCT) was used to measure the thickness of different layers of the retina at macular and peripapillary regions and at different quadrants. Between groups comparison was performed with $P < 0.05$ indicating statistical significance. **Results:** There were 32 eyes in the MS group and 74 eyes in the control group. The MS group was significantly younger than the control group ($P < 0.001$). The mean ganglion cell complex (GCL++) thickness in superior macular area was 64.1 ± 8.9 µ in the MS group and 71.1 ± 5.9 µ in the control group. The thickness of the RNFL did not statistically differ in each of the quadrants between groups. Despite controlling for age, the macular thickness parameters were significantly thinner in eyes with MS compared to healthy eyes ($P < 0.01$). **Conclusion:** The macular ganglion cell complex (mGCC) parameters were significantly reduced in recently diagnosed cases of MS as compared to healthy individuals.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1378_18

Quick Response Code:

Key words: Multiple sclerosis, optic neuritis, optical coherence tomography

Multiple sclerosis (MS) is a disorder characterized by inflammation and neuroaxonal degeneration that leads to irreversible disability.[1] Optic neuritis (ON) in many cases is a presenting sign as it develops concurrently in many cases of MS.[2] Optical coherence tomography (OCT) is an essential investigation to evaluate axonal/neuronal integrity and to assess disease progression in the afferent visual pathway.[3] OCT is non-invasive, patient friendly, and highly reproducible, and OCT indices have been used as a marker of axonal loss and as an endpoint in clinical trials.[4] High-resolution spectral domain-OCT (SD-OCT) techniques and computerized algorithms for image analysis have further improved the segmentation and measurement of specific retinal layers such as the ganglion cell layer (GCL) and the inner plexiform layer (IPL). These retinal layers have been studied to understand the pathophysiology of MS.[5]

Patients with MS are usually referred to an ophthalmologist following the onset of ON. OCT imaging of these patients allows evaluation of the extent of damage due to ON and monitoring the progress of ON.[6] The prevalence of MS is rising in the Gulf countries. It is linked to vitamin D deficiency and high consanguinity in the region.[7] Females have higher rate of MS and ON compared to males in the Arab population.[8] To the best of our knowledge, a study of the changes in thickness of different retinal layers in Arab patients with MS without ON has not been published.

This study evaluated the thickness of different macular parameters and peripapillary retinal nerve fiber layer (RNFL) at different quadrants in recently diagnosed MS patients without ON and compared these measurements to those of healthy individuals to determine their role in early detection of axonal damage in MS patients.

Methods

This cross-sectional study was performed between June 2014 and June 2015. The ethics committee of our institute approved this study. Patients diagnosed with MS by a neurologist but without any ocular symptoms of MS were included in the present study (MS group). A patient with a history of any retinal disease or ON, including glaucoma, refractive error of 4.00D or greater, previous eye surgery, or those showing OCT scans with low signal strength were excluded. Healthy volunteers with best-corrected visual acuity (BCVA) of 1.0 and

[1]Department of Ophthalmology, Faculty of Medicine, Cairo University, Cairo, Egypt, [2]Imam Mohammed bin Saud Islamic University College of Medicine, [3]Department of Ophthalmology, Specialised Medical Hospital, [4]Department of Research, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia

Correspondence to: Dr. Nancy M Lotfy, Department of Ophthalmology, Faculty of Medicine, Cairo University. Al-Saray Street, El Manial, Postal Code: 11956, Cairo, Egypt. E-mail: nancymaher@kasralainy.edu.eg

Manuscript received: 21.08.18; Revision accepted: 05.01.19

Cite this article as: Lotfy NM, Alasbali T, Khandekar R. Macular ganglion cell complex parameters by optical coherence tomography in cases of multiple sclerosis without optic neuritis compared to healthy eyes. Indian J Ophthalmol 2019;67:648-53.

without any ocular disease were included as a comparison group (control group). All subjects signed a written informed consent to participate in the study.

We assumed that RNFL thickness at the macula in eyes of healthy Arab individuals was 35 ± 4 μ.[9] In eyes with MS, the RNFL was assumed to be 30 ± 12 μ. To achieve 95% confidence interval (CI), 90% power of the study with 1:2 ratio of two groups of at least 37 eyes were required in the MS group and 77 eyes in the control group.

Three ophthalmologists, one neurologist, and one optometrist were the field investigators. Data were collected on age and gender in both groups. Patients underwent a detailed neurological examination by a neurologist. Early stage MS was confirmed based on the duration of the disease, medications, clinical findings, functional, radiological, laboratory, and electrophysiological examinations.

All subjects underwent a comprehensive ophthalmic examination including measurement of BCVA (Snellen) at 6-m distance with a projection chart, anterior segment assessment with slit-lamp bio-microscopy (HAAG-STREIT AG, Koeniz, Switzerland), Goldmann applanation tonometry, and pupillary light reflex were tested using a well-focused torch light beam.[10]

The posterior segment and peripheral retina were examined using binocular indirect ophthalmoscopy (Keeler, UK) and a +20D Volk lens. The optic disc and macula were also assessed using slit lamp and +90D Volk lens (Volk Optical Inv., Mentor, OH, USA).

After pupillary dilatation, the retinal thickness of each eye was measured using three-dimensional (3D) OCT-2000 (Topcon Corporation, Tokyo, Japan). A 3D disc scan protocol was used which allowed analysis of a 6 mm × 6 mm area centered on the optic disc with a scan density of 512 vertical × 128 horizontal scans. (1) The mean and standard deviations of the peripapillary RNFL thickness were calculated in four quadrants and clock-hour sectors at a circular distance of 3.4 mm in diameter from the optic disc. (2) Macular 3D V scan protocol was performed [scanning of a 7 mm × 7 mm area centered on the fovea with a scan density of 512 (vertical) × 128 (horizontal) scans]. The mean and standard deviations of the macular RNFL (mRNFL), GCL + IPL, and GCL + IPL + nerve fiber layer (NFL) (GCL++) thicknesses were calculated for the superior and inferior hemiretina. These measurements were obtained in one disc diameter inferiorly and superiorly to the fovea. The unit of measurement for retinal thickness was microns (μ).

Data were collected on a pretested data collection form and transferred to an Excel spreadsheet (Microsoft Corp., Redmond, WA, USA). The data were then transferred to a Statistical Package for Social Sciences spreadsheet (SPSS 23, IBM Corp., New York, NY, USA). For qualitative variables, we calculated frequencies and percentage proportions. For quantitative variables, we plotted histogram to study its distribution. If the data were normally distributed, the mean and standard deviations were calculated. To compare the quantitative data between groups, the difference of mean, its 95% CI, and two-sided *P* values were calculated. Variables that were statistically significant associated to MS were added to a regression model to study the interaction of different variables. The adjusted odds ratio, the 95% CI, and two-sided *P* values were calculated. A *P* value <0.05 was considered statistically significant.

Results

Thirty-two eyes were enrolled in the MS group and 74 eyes in the control group. All the subjects in the MS group were diagnosed within 1 year (median duration: 5 months) of the beginning of this study.

The demographic and clinical characteristics of both groups are compared in Table 1. The control group was significantly older than those with MS ($P < 0.01$). Retinal layer thickness of both groups is presented in Table 2. The mean ganglion cell complex (GCL++) thickness in superior macular area in MS group and control group was 33.3 ± 7.8 μ and 37.9 ± 5.5 μ,

Table 1: Profile of patients with and without multiple sclerosis (MS)

	Parameter	MS patients (*n*=32)		No MS (*n*=74)		Validation
		Number	%	Number	%	
Gender	Male	12	37.5	40	54.1	*P*=0.12
	Female	20	63.5	34	45.9	
Eye involved	Right	16	50	36	48.6	*P*=0.9
	Left	16	50	38	51.4	
Age	Mean	32.7		43.5		Diff of mean 10.8 *P*<0.001
	SDV	7.7		10.9		
BCVA	Median	1.0		1.0		M-W *P*=0.4
	25% quartile	1.0		1.0		
RE Spherical equivalent	Median	−0.37		−0.1		M-W *P*=0.14
	25% quartile	−0.63		−0.38		
Pupil	RRR	32	-	74		-
Lens	Clear	32	100	74	100	-
	Lens opacity	0	0	0	0	
Optic nerve head	Normal	29	90.6	74	97.2	-
	Past neuropathy	3	9.4	0	2.8	

respectively. All macular parameters were significantly thinner in the MS group compared to the control group [Figs. 1-3]. The RNFL thickness in the different quadrants did not differ between groups.

Binominal regression analysis suggested that in spite of controlling for the age, the macular thickness parameters were significantly thinner in eyes of the MS group compared to the control group.

Discussion

The current study found that the macular parameters of retinal thickness in eyes of subjects with MS without ON were thinner compared to age-matched healthy individuals. Refractive error is a known factor that influences RNFL thickness. However, there was no statistical difference between groups in refractive error. The RNFL in the four quadrants did not significantly differ in eyes with early MS without ON compared to healthy eyes.

All the subjects with MS in the current study did not exhibit any ophthalmic manifestations of the disease. The MS group had normal vision and no optic nerve head changes. Based on these observations, we conclude that eyes of the subjects with MS did not have ON which is a common manifestation of MS.[11,12]

Macular retinal thickness is influenced by late stage glaucoma.[13] In a previous study, we reported that the retinal thickness was significantly thinner among Saudi glaucoma patients compared to normal healthy patients.[14] Due to

Table 2: Retinal layer thickness in eyes of patient with MS and without MS

OCT parameters of retinal layer thickness	Eye with MS (32)		Eye without MS (74)		Validation
	Mean	SDV	Mean	SDV	
Total macular retinal nerve fiber layer	33.3	7.8	37.9	5.5	0.04
Superior macular retinal nerve fiber layer	32.2	8.0	36.4	5.4	0.009
Inferior macular retinal nerve fiber layer	34.3	7.9	39.4	6.1	0.002
Thickness of ganglion cell layer + inner plexiform layer	64.3	8.4	71.7	5.9	<0.001
Thickness of ganglion cell layer + inner plexiform layer superior	64.7	8.1	72.3	6.1	0.001
Thickness of ganglion cell layer + inner plexiform layer superior inferior	64.1	8.9	71.1	5.9	<0.001
Thickness of ganglion cell layer + inner plexiform layer + nerve fiber layer	97.7	14.9	108.3	14.4	<0.001
Thickness of ganglion cell layer + inner plexiform layer + nerve fiber layer superior	96.8	14.7	108.8	10.1	<0.001
Thickness of ganglion cell layer + inner plexiform layer + nerve fiber layer inferior	98.5	15.6	110.3	10.0	<0.001
Total retinal nerve fiber layer thickness	101.8	13.9	100.9	8.0	0.7
Average retinal nerve fiber layer thickness in superior quadrant	122.6	18.4	118.2	11.9	0.2
Average retinal nerve fiber layer thickness in nasal quadrant	88.5	19.0	81.8	13.1	0.08
Average retinal nerve fiber layer thickness in inferior quadrant	125.0	19.0	127.7	13.4	0.5
Average retinal nerve fiber layer thickness in temporal quadrant	72.1	18.1	75.6	9.9	0.3

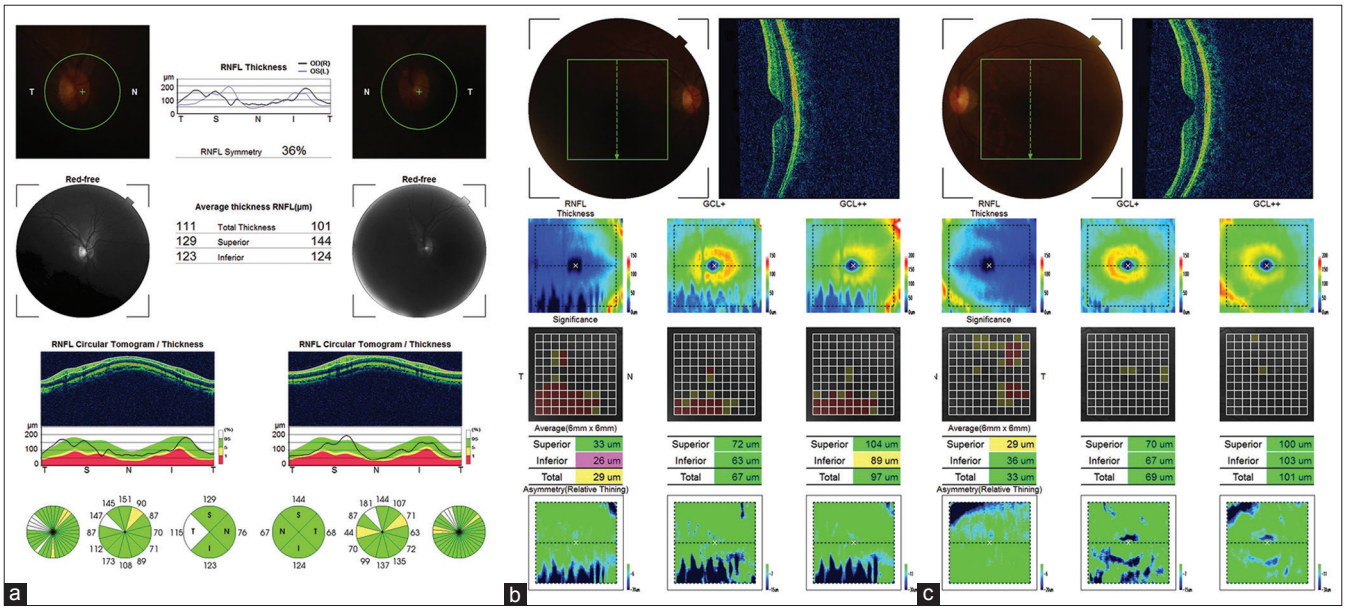

Figure 1: Multiple sclerosis patient 1: (a) Peripapillary retinal nerve fiber layer thickness. Disc circle (Dia. 3.4–1024 mm) [spectral domain-optical coherence tomography (SD-OCT)]. (b) Ganglion cell layer complex thickness at macula (OD). Macular 3D V scan protocol (SD-OCT). (c) Ganglion cell layer complex thickness at macula (OS). Macular 3D V scan protocol (SD-OCT)

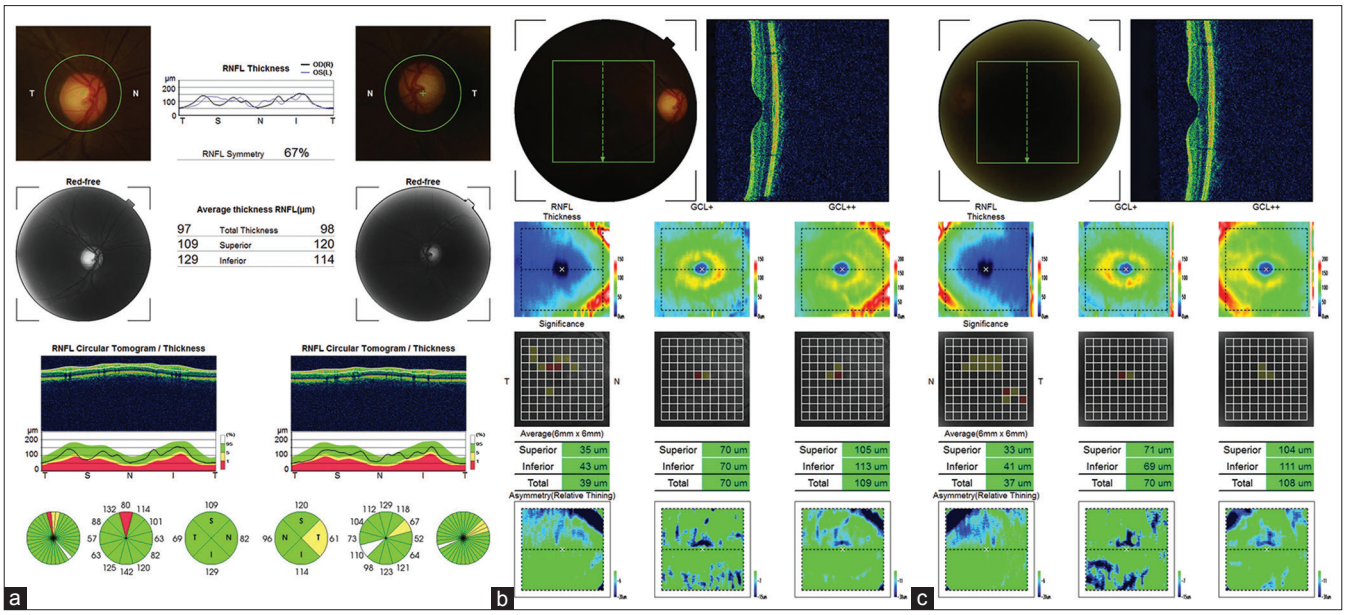

Figure 2: Multiple sclerosis patient 2: (a) Peripapillary retinal nerve fiber layer thickness. Disc circle (Dia. 3.4–1024 mm) [spectral domain-optical coherence tomography (SD-OCT)]. (b) Ganglion cell layer complex thickness at macula (OD). Macular 3D V scan protocol (SD-OCT). (c) Ganglion cell layer complex thickness at macula (OS). Macular 3D V scan protocol (SD-OCT)

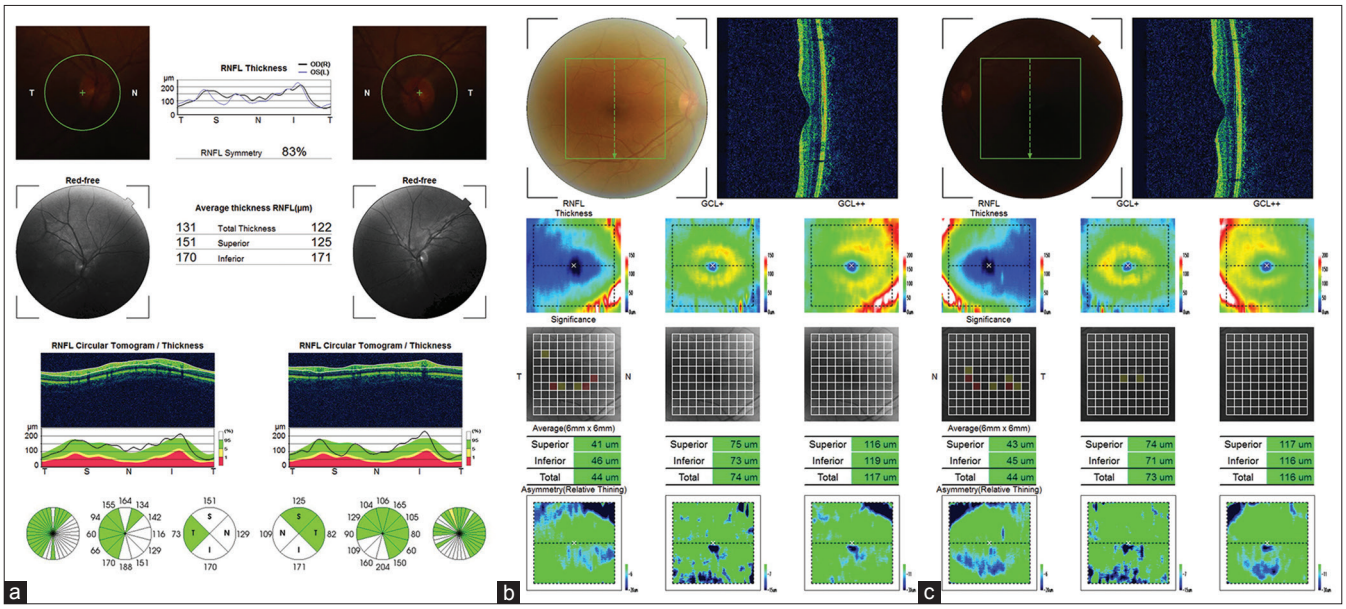

Figure 3: Control 1: (a) Peripapillary retinal nerve fiber layer thickness. Disc circle (Dia. 3.4–1024 mm) [spectral domain-optical coherence tomography (SD-OCT)]. (b) Ganglion cell layer complex thickness at macula (OD). Macular 3D V scan protocol (SD-OCT). (c) Ganglion cell layer complex thickness at macula (OS). Macular 3D V scan protocol (SD-OCT)

exclusion of all cases with known ocular pathology including glaucoma, the present study is less likely to have thinner macular parameter thickness due to other pathology such as glaucoma.

Refractive error did not significantly differ in the MS group compared to the control group in the present study. None of the subjects in the current study were high myopes. High myopia is associated with macular changes, which can be easily identified by OCT.[15] High myopia constituted 16.3% of total myopia in a young cohort from Oman, which is a neighboring Gulf country.[16] Therefore, the presence of high myopia should be noted before reviewing the thinning of macular parameters by OCT and association with MS.

In our study, cases of age-related macular degeneration (AMD) were excluded. Additionally, the MS group was relatively young and less likely to have occult/early AMD changes. However, as a precaution for comparing the retinal layer thickness changes between groups, we ruled out the confounding effect of age. The retinal and vitreous changes in the elderly population have been studied and suggest that even in healthy eyes the macula and retinal layers show degenerative changes.[17,18] The advent of OCT angiography

had allowed the study of thinning of the macula in pathology such as AMD.[19,20] These studies have found differential effects between retinal layers in AMD.[19,20]

Thinning of the macular parameters has been postulated to be due to axonal degeneration in MS.[21] In other neural degenerative conditions of the brain such as Alzheimer's, thinning of retinal layer has been documented.[22–24] The death of neurons of central nervous system and their axons in the eye seems to be a common phenomenon in all these conditions including MS.

In the current study, segmental OCT analysis of retinal layers at the macula showed that the mean total GCL++ thickness (the thickness of GCL + IPL + nerve fiber layer) in the superior macula is the most affected. Longitudinal studies are recommended to confirm the role of this parameter in predicting early MS.

In the current study, the difference in the RNFL in different retinal regions other than the macula was not significant between groups. This is in contrast to changes in the eyes of MS patients with and without ON.[25,26] Patients in the MS group in the current study was in early stage of disease, which may account for the difference in outcomes between studies.

There are some limitations to the current study. In a cross-sectional study, whether the diagnosis of MS preceded macular thinning documented by OCT remains uncertain. Thus, a casual association cannot be established. Longitudinal studies to document changes in macular thickness over time in MS patients are recommended.

Conclusion

GCL complex thickness at macula measured by high-resolution SD-OCT in our study was significantly thinner in eyes of patient with recently diagnosed MS and without ON. SD-OCT could be a useful tool for a detailed work-up in a case of MS even if patient does not have eye symptoms.

Acknowledgements

We thank staff of the neurology department, ophthalmology department and digital imaging department of our institution for their support during the different steps of patient care and current research. Patient cooperation was also highly appreciated.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Balk LJ, Petzold A. Current and future potential of retinal optical coherence tomography in multiple sclerosis with and without optic neuritis. Neurodegener Dis Manag 2014;4:165-76.
2. Plant GT. Optic neuritis and multiple sclerosis. Curr Opin Neurol 2008;21:16-21.
3. Rebolleda G, Diez-Alvarez L, Casado A, Sánchez-Sánchez C, de Dompablo E, González-López JJ, *et al*. OCT: New perspectives in neuro-ophthalmology. Saudi J Ophthalmol 2015;29:9-25.
4. Petzold A, de Boer JF, Schippling S, Vermersch P, Kardon R, Green A, *et al*. Optical coherence tomography in multiple sclerosis: A systematic review and meta-analysis. Lancet Neurol 2010;9:921-32.
5. Galetta KM, Balcer LJ. Measures of visual pathway structure and function in MS: Clinical usefulness and role for MS trials. Mult Scler Relat Disord 2013;2:172-82.
6. Tegetmeyer H, Kühn E. Quantitative analysis of changes in macular layers following optic neuritis. Neuro Ophthalmol 2011;35:101-7.
7. Bohlega S, Inshasi J, Al Tahan AR, Madani AB, Qahtani H, Rieckmann P. Multiple sclerosis in the Arabian Gulf countries: A consensus statement. J Neurol 2013;260:2959-63.
8. Najim Al-Din AS, Kurdi A, Mubaidin A, El-Khateeb M, Khalil RW, Wriekat AL. Epidemiology of multiple sclerosis in Arabs in Jordan: A comparative study between Jordanians and Palestinians. J Neurol Sci 1996;135:162-7.
9. Alkuraya HS, Al-Gehedan SM, Alsharif AM, Alasbali T, Lotfy NM, Khandekar R. Lack of correlation between diabetic macular edema and thickness of the peripapillary retinal nerve fibre layer. Middle East Afr J Ophthalmol 2016;23:241-6.
10. Chilińska A, Ejma M, Turno-Kręcicka A, Guranski K, Misiuk-Hojlo M. Analysis of retinal nerve fibre layer, visual evoked potentials and relative afferent pupillary defect in multiple sclerosis patients. Clin Neurophysiol 2016;127:821-6.
11. Balcer LJ, Miller DH, Reingold SC, Cohen JA. Vision and vision-related outcome measures in multiple sclerosis. Brain 2015;138:11-27.
12. Chen L, Gordon LK. Ocular manifestations of multiple sclerosis. Curr Opin Ophthalmol 2005;16:315-20.
13. Renard JP, Fénolland JR, El Chehab H, Francoz M, Marill AM, Messaoudi R, *et al*. Analysis of macular ganglion cell complex (GCC) with spectral-domain optical coherence tomography (SD-OCT) in glaucoma. J Fr Ophtalmol 2013;36:299-309.
14. Alasbali T, Lofty NM, Al-Gehaban S, Al-Sharif A, Al-Kuraya H, Khandekar R. Macular ganglion cell–inner plexiform layer and retinal nerve fiber layer thickness in eyes with primary open-angle glaucoma compared with healthy saudi eyes: A cross-sectional study. Asia-Pacific J Ophthalmol 2016;5:196-201.
15. Kumar A, Chawla R, Kumawat D, Pillay G. Insight into high myopia and the macula. Indian J Ophthalmol 2017;65:85-91.
16. Khandekar R, Gogri U, Al-Harby S. Changing trends in myopia among schoolchildren in Oman: Screening information over 11 years. Oman J Ophthalmol 2018;11:232-6.
17. Sung KR, Wollstein G, Bilonick RA, Townsend KA, Ishikawa H, Kagemann L, *et al*. Effects of age on optical coherence tomography measurements of healthy retinal nerve fiber layer, macula, and optic nerve head. Ophthalmology 2009;116:1119-24.
18. Itakura H, Kishi S. Aging changes of vitreomacular interface. Retina 2011;31:1400-4.
19. Schmidt-Erfurth U, Waldstein SM. A paradigm shift in imaging biomarkers in neovascular age-related macular degeneration. Prog Retin Eye Res 2016;50:1-24.
20. Waheed NK, Moult EM, Fujimoto JG, Rosenfeld PJ. Optical coherence tomography angiography of dry age-related macular degeneration. Dev Ophthalmol 2016;56:91-100.
21. Syc SB, Saidha S, Newsome SD, Ratchford JN, Levy M, Crainiceanu CM, *et al*. Optical coherence tomography segmentation reveals ganglion cell layer pathology after optic neuritis. Brain 2012;135:521-33.
22. Jones-Odeh E, Hammond CJ. How strong is the relationship between glaucoma, the retinal nerve fibre layer, and neurodegenerative diseases such as Alzheimer's disease and multiple sclerosis? Eye (Lond) 2015;29:1270-84.

23. den Haan J, Verbraak FD, Visser PJ, Bouwman FH. Retinal thickness in Alzheimer's disease: A systematic review and meta-analysis. Alzheimers Dement (Amst) 2017;6:162-70.
24. Thomson KL, Yeo JM, Waddell B, Cameron JR, Pal S. A systematic review and meta-analysis of retinal nerve fiber layer change in dementia, using optical coherence tomography. Alzheimers Dement (Amst) 2015;1:136-43.
25. Pueyo V, Martin J, Fernandez J, Almarcegui C, Ara J, Egea C, *et al*. Axonal loss in the retinal nerve fiber layer in patients with multiple sclerosis. Mult Scler 2008;14:609-14.
26. Fjeldstad C, Bemben M, Pardo G. Reduced retinal nerve fiber layer and macular thickness in patients with multiple sclerosis with no history of optic neuritis identified by the use of spectral domain high-definition optical coherence tomography. J Clin Neurosci 2011;18:1469-72.