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ORIGINAL ARTICLE

OCT and Visual Field Changes as Useful Markers for Follow-up of Axonal Loss in Multiple Sclerosis in Egyptian Patients

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ABSTRACT

Purpose: The aim of this work was to correlate optical coherence tomography (OCT) parameters, retinal sensitivity (perimetry) and best-corrected visual acuity (BCVA) with disease duration and neurologic functional disability in Egyptian patients with multiple sclerosis (MS).

Methods: This is a cross-sectional observational cohort study in which 68 MS patients and 23 healthy controls had full neurologic examination, including expanded disability status scale (EDSS) and full ophthalmologic examination, including functional and structural assessments of the optic nerve through BCVA, visual field examination (*SITA*), and OCT (*Optovue*).

Results: Retinal nerve fiber layer (RNFL) thickness was significantly decreased in MS eyes. MS eyes had significantly decreased GCC. RNFL thickness was significantly negatively correlated to EDSS and disease duration. GCC was significantly negatively correlated to disease duration. BCVA and retinal sensitivity (MD) were significantly correlated to the MS duration.

Conclusions: OCT is a promising tool to detect subclinical changes in RNFL and GCC in Egyptian patients with MS.

Keywords: Expanded disability status scale (EDSS), ganglion cell complex (GCC), multiple sclerosis, optical coherence tomography (OCT), perimetry, retinal nerve fiber layer (RNFL)

Multiple sclerosis (MS) is a variably progressive disease of the nervous system, in which patchy degenerative and inflammatory changes occur within the brain and spinal cord. It is considered to be the major cause of nervous system disability in young adults.[1] Neurodegeneration plays a major role in determining the permanent disability in MS.[2]

Routine magnetic resonance imaging (MRI) scans are expensive and not always readily available; they are also not sensitive enough regarding the differentiation between demyelination and neurodegeneration, and show a discrepancy between lesion load and the degree of disability.[3]

Optical coherence tomography (OCT) is a non-invasive imaging technique that allows *in vivo* visualization of different retinal layers. Retinal nerve fiber layer (RNFL) is made up of non-myelinated axons from the ganglion cells whereas, the ganglion cell complex (GCC) is defined as the three innermost retinal layers: the nerve fiber layer, the ganglion cell layer, and the inner plexiform layer, and therefore part of the central nervous system is used in quantification of neurodegenerative processes in the retina, which can be detected in MS and other neurologic diseases. OCT is inexpensive, easy to handle and highly reproducible. Additionally, it is well-tolerated and thus represents a

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promising tool for monitoring of neurodegenerative disorders.[4]

The purpose of this study was to assess if RNFL measurements, GCC thickness and visual perimetry could be used as markers for follow-up of axonal loss in MS in Egyptian patients. It also highlighted the correlation between changes in these parameters with neurologic functional disability according to EDSS scale and disease duration. OCT was performed using the RTVue spectral-domain OCT, while most current work in this field is based on Heidelberg Spectralis or Cirrus OCT data, and all previous work was based on time-domain OCT, essentially the Stratus machine.

PATIENTS AND METHODS

This case–control cross-sectional cohort study was approved by the research ethics committee of Cairo University Hospital Ophthalmology Department, and the tenets of the Declaration of Helsinki were respected. All patients received a thorough explanation of the study design and aims, and were provided with written informed consent.

In total, 75 patients with clinically defined MS who were diagnosed and admitted to the neurology department of Kasr Al Ainy Hospital Cairo University were enrolled. They were invited to enrol in the study from August 2013 to April 2014. One eye was included in the study, randomly, from each participant, to increase the statistical power of the study, using a computer-based randomization program.

Patients included in this study were diagnosed as multiple sclerosis (MS) according to the international panel on diagnosis of MS, 'McDonald' criteria 2001[5] and its revision by Polman et al. (2005).[6] Subtypes of MS included in this study were relapsing remitting (RR), secondary progressive (SP) and primary progressive (PP).

In total, 23 healthy controls, with no history of ocular or neurologic disease, were recruited. Only one randomly chosen eye from every control was included in the study. The effect of age on RNFL thickness has been described in histologic studies[7] and has been also demonstrated by means of OCT.[8] To avoid this source of bias, we selected a control group that was age-matched with the MS patients.

Four patients (5.3%) who experienced an optic neuritis attack <6 months prior to the study were excluded, to avoid potential interference of optic disc oedema with accurate peripapillary RNFL thickness measurements. Also, three patients (4%) with nystagmus, making perimetry and OCT difficult to perform, were excluded from our study. A total of 68 patients therefore continued throughout the study.

Examination Techniques

The patients were subject to:

- History-taking, including disease duration and the presence of prior episodes of optic neuritis, as reported by the treating neurologist.
- Full neurologic examination, including expanded disability status scale (EDSS).[9]
- Full ophthalmologic examination, including: functional and structural assessments of the optic nerve through best-corrected visual acuity (BCVA), visual field examination, and OCT.

Typical cases of optic neuritis (ON) were diagnosed when: there was acute or subacute diminution of visual acuity, associated with periocular pain worse on eye movements; drop in contrast sensitivity; ipsilateral relative afferent pupillary defect [absent in nine patients (30% of ON) with ON in the fellow eye); visual field defect (any type, ranging from commonly seen diffuse depression and central or centrocecal scotoma, to rarely seen quadrantic, altitudinal defects and contracted field); dyschromatopsia (17 eyes, 56.7% of ON); optic disc pallor or temporal pallor; together with a history of MS and possible previous attacks of ON.[10]

Uhthoff's phenomenon (exercise or heat-induced deterioration of visual symptoms) was observed in 12 eyes (40% of ON), while the Pulfrich phenomenon (misperception of the direction of movement of an object) was observed in seven eyes (23.3% of ON).

Visual field assessment was done using automated perimetry (Swedish Interactive Threshold Algorithm, SITA standard 24–2 strategy, Humphrey Visual Field Analyzer; Carl Zeiss Meditec, Dublin, CA). The SITA Standard strategy, program 24–2, was used in order to decrease the duration of the exam. The outcome measure evaluated was the mean deviation (MD, dB).

Optical coherence tomography was performed using the RTVue spectral-domain OCT (Optovue Inc, Fremont, CA), which is based on the new generation Fourier-domain optical coherence technology. Two different protocols were used: the first was the *macular map protocol*, which allows fast macular scan for GCC measurement. It consists of 12 radial line scans (1024 A-scans per line) in a 3-dimensional 6 × 6 mm area (2.0 s). The second was the *peripapillary RNFL NHM4 protocol*, which consisted of 12 radial scans (452 A-scans per line) over 3.45 mm diameter, centered on the optic disc. It has the advantage of eye tracking and signal noise reduction. Also, the inner nuclear layer (INL) was observed for the presence of macular microcysts. All

scans were performed with ambient lighting and without pupil dilation to ensure patient comfort.

For quality control of OCT imaging, the OSCAR-IB protocol was adopted[11]:

O: Obvious problems not covered by items below were excluded.
S: Only OCT images with signal strength >15 (ring and volume scans) with appropriate averaging of multiple scans were included.
C: ONH did not cross more than two colors of the RAF logo (outer ring of RAF electronically adjusted to outer ring of scan).
A: Red lines correctly identified the superior and inferior RNFL border (ring scan); red lines correctly identified the retinal borders (volume scan).
R: Retinal pathologies, which may potentially impair the RNFL reading (structural, vascular, immune paraneoplastic, infectious, metabolic and recent optic neuritis), were excluded from the study.
I: The fundus was well illuminated.
B: The measurement beam was placed centrally.

Statistical Analysis

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using the Student's *t*-test for independent samples. For comparing categorical data, the χ^2-test was performed. Exact test was used instead, when the expected frequency was <5. Correlation between various variables was done using Pearson moment correlation equation for linear relation in normally distributed variables and Spearman rank correlation equation for either non-normal variables, or those with non-linear relation; p values <0.05 were considered statistically significant. All statistical calculations were accomplished using computer programs, SPSS for Windows, version 15 (SPSS, Inc, Chicago, IL) .

RESULTS

The study enrolled 68 eyes of 68 Egyptian patients diagnosed as having MS and 23 healthy age- and sex-matched controls. Since we evaluated age- and sex-matched healthy subjects, no differences were observed in these descriptive characteristics between the two groups. Their age ranged from 20 to 50 years. Other demographic data and clinical parameters are presented in Table 1.

Visual field defects observed were: diffuse depression (9 eyes, 30% of ON); central or centrocecal scotoma (8 eyes, 26.7% of ON); quadrantic (5 eyes, 16.7% of ON); altitudinal defects (4 eyes, 13.3% of ON); and contracted field (4 eyes, 13.3% of ON). Optic disc pallor was observed in 22 eyes (73.3% of ON) and temporal pallor in 8 eyes (26.7% of ON).

Eyes of MS patients had significantly lower peripapillary RNFL thickness than those of the control group (p<0.001). The greater abnormalities were observed in the *temporal* and *inferior* quadrants. Ganglion cell complex (GCC) also showed significant decrease in MS patients when compared with the control group (p = 0.048) (Table 2).

Within the MS group, there was significant RNFL atrophy in patients with a previous history of optic neuritis (Multiple sclerosis associated optic neuritis; MS-ON), either with or without complaint of diminution of vision, compared with the control group (p = 0.023 and p = 0.03, respectively), as well as in patients who had not previously suffered from optic neuritis (p = 0.045) compared with the control group. RNFL (but not GCC thickness) measurements were significantly decreased in the MSON subgroup than in the MS-NON subgroup (p = 0.047).

But comparing RNFL and GCC complex thickness between MS-ON and MS-NON, in the relapsing subgroup (RRMS) was statistically insignificant (p = 0.181, and p = 0.251, respectively). It was also insignificant in each of the secondary progressive (SPMS) (p = 0.254, and p = 0.862, respectively) and primary progressive subgroups (PPMS) (p = 0.270, and p = 0.137, respectively).

When OCT parameters of each of the MS subtypes were compared with those of the control group, there was significant decrease in RNFL thickness and average GCC thickness (Table 3). On the other hand, when comparing relapsing to progressive MS subtypes by ANOVA test, there was no significant difference in RNFL thickness or average GCC thickness (p = 0.279 and 0.233, respectively).

Correlating OCT parameters to neurologic variables, including duration, relapses (of MS and ON) and EDSS, using Pearson correlation, showed that; the average RNFL thickness was negatively correlated with disease duration (r = –0.530, p<0.001) and EDSS (r = –0.269, p = 0.042), while the GCC thickness was only negatively correlated with disease duration (r = –0.639, p = 0.008) (Figure 1) and there was no significant correlation with EDSS (p = 0.131). On the other hand, the correlation between OCT parameters and number of relapses of MS was not significant (p = 0.452 for RNFL thickness, p = 0.709 for GCC), as was the correlation between OCT parameters and number of relapses of ON (p = 0.571 for RNFL thickness, p = 0.054 for GCC).

TABLE 1. Demographic and clinical variables of MS patients and healthy controls.

Descriptive data	MS patients (n = 68)			Controls (n = 23)	p value
Age (years) (mean ± SD)	34.03 ± 8.19			36.22 ± 8.8	0.280
Sex, female (n, %)	54 (79.4)			19 (82.6)	1.000
BCVA (logMAR) (mean ± SD)	0.41 ± 0.33			0.09 ± 0.09	<0.001
Eyes with previous optic neuritis (MS-ON) (n, %)	30 (44.1)				
Eyes with complaint of visual impairment (n, %)	23 (33.8)				
Patients with complaint of diplopia (3rd nerve palsy) (n, %)	3 (4.4)				
MD (dB) (mean ± SD)	–11.8 ± 9.7			–2.89 ± 1.3	<0.001
MD (n, %)					
<–6.0	32 (47)				
–6.0 to –20.0	19 (28)				
>–20.0	17 (25)				
Disease duration (years) (mean ± SD)	6.8 ± 5.5				
MS relapse rate in previous 2 years (mean ± SD)	2.7 ± 1.05				
Optic neuritis relapse rate in previous 2 years (mean ± SD)	0.7 ± 0.895				
Disease subtype (n, %)		MS-ON	MS-NON		
Relapsing-remitting	40 (58.8)	17 (42.5)	23 (57.5)		
Secondary-progressive	18 (26.5)	6 (33.3)	12 (66.7)		
Primary-progressive	10 (14.7)	7 (70)	3 (30)		
EDSS (mean ± SD)	4.89 ± 1.74				

BCVA, best-corrected visual acuity; dB, decibels; EDSS, expanded disability status scale; MD, mean deviation; MS, multiple sclerosis; MS-ON, MS associated with optic neuritis; MS-NON, MS not associated with optic neuritis.
$p < 0.05$ is considered statistically significant.

TABLE 2. Differences in variables between patients with MS and healthy controls.

	MS (n = 68)	Control (n = 23)	p value
RNFL thickness (average)	89.34 ± 16.68	117.79 ± 26.23	<0.001
RNFL thickness (superior)	92.16 ± 19.35	118.87 ± 27.89	0.001
RNFL thickness (temporal)	63.8 ± 19.05	82.34 ± 15.77	<0.001
RNFL thickness (inferior)	90.56 ± 20.76	112.47 ± 34.26	<0.001
RNFL thickness (nasal)	72.64 ± 12.41	88.46 ± 28.5	0.004
GCC (average)	85.58 ± 12.9	96.16 ± 21.04	0.048
GCC (superior)	87.48 ± 16.8	99.12 ± 9.81	0.007
GCC (inferior)	84.07 ± 11.24	98.79 ± 7.85	<0.001

GCC, ganglion cell complex; MS, multiple sclerosis; RNFL, retinal nerve fiber layer.
$p < 0.05$ is considered statistically significant.

None of the eyes (0%) within the MS group or control group showed macular microcysts.

As regards other visual functions, including mean deviation (MD) and BCVA, the correlations with OCT parameters were not significant, either in MS cases or controls, and so were correlating MD and BCVA with EDSS and number of relapses in the last 2 years, while correlating MD and BCVA with MS duration was statistically significant (r = 0.300, p = 0.02 for BCVA and r = –0.402, p = 0.004 for MD) (Table 4).

Comparing each of MD and BCVA between MS-ON and MS-NON, in the relapsing subgroup (RRMS) was statistically insignificant (p = 0.403 and p = 0.330, respectively). It was insignificant in each of the secondary progressive (SPMS) (p = 0.759 and p = 0.959, respectively), and primary progressive subgroups (PPMS) (p = 0.288 and p = 0.660, respectively).

DISCUSSION

Multiple sclerosis (MS) is a disease of the CNS characterized by immune-mediated injury, demyelination and neuroaxonal loss.[12] Retinal nerve fiber layer (RNFL) is made up primarily of retinal ganglion cell axons. OCT allows measurement of total macular thickness. OCT-derived metrics of macular thickness and volume are sometimes inferred as providing estimates of retinal neuronal integrity.[13]

Our study showed significant axonal loss affecting the whole peripapillary RNFL in the MS group in

TABLE 3. OCT parameters of different MS subtypes in relation to control subjects.

		RNFL thickness (μm) (mean ± SD)			GCC thickness (μm) (mean ± SD)		
	n	Average	Control	*p* value	Average	Control	*p* value
All MS cases	68	89.34 ± 16.68	117.79 ± 26.23	<0.001	85.58 ± 12.9	96.16 ± 21.04	0.048
MS-NON	38	92.4 ± 17.7		0.045	86.3 ± 13.8		0.049
MS-ON	30	84.05 ± 13.5		0.021	84.3 ± 11.9		0.023
RRMS	40	87.8 ± 18.9		0.033	85.6 ± 13.3		0.043
SPMS	18	89 ± 13.3		0.023	82.8 ± 13.2		0.011
PPMS	10	83.09 ± 12.4		0.001	83.5 ± 11.4		0.014

GCC, ganglion cell complex; MS, multiple sclerosis; MS-NON, MS without optic neuritis; MS-ON, MS with optic neuritis; OCT, optical coherence tomography; PPMS, primary progressive MS; RNFL, retinal nerve fiber layer; RRMS, relapsing remitting; SPMS, secondary progressive.

$p < 0.05$ is considered statistically significant.

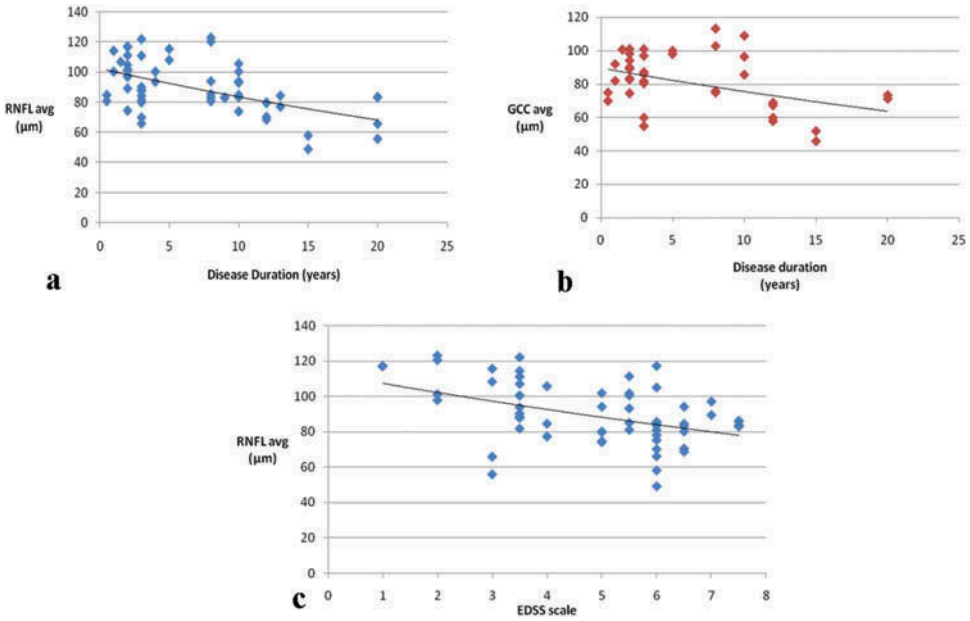

FIGURE 1. (a) Correlation of RNFL with duration of MS. (b) Correlation of GCC with duration of MS. (c) Correlation of RNFL with neurologic functional disability.

comparison with the control group, and these data agreed with the results of the study conducted by Klistorner et al. (2008).[14] The greater abnormalities were observed in the temporal and inferior quadrants. The studies done by Ghalie and Husein (2010),[15] as well as Oberwahrenbrock et al. (2012)[16] were in line with our study, while Noval et al. (2011)[17] confirmed that the temporal quadrant is the most vulnerable to the disease process.

Regarding ganglion cell complex (GCC) in MS eyes, our results showed significantly lower values compared with the control group, which agrees with Oberwahrenbrock et al. (2012); Syc et al. (2012); Davies et al. (2011); and Khanifar et al. (2010).[16,18–20]

While RNFL reduction after an episode of ON is not surprising, RNFL reduction was consistently observed in MS patients who had never had a clinical episode of ON, as well as in the clinically unaffected fellow eye of patients with a history of ON. In the absence of optic neuritis, retrograde trans-synaptic retinal ganglion cell degeneration due to MS lesions within the posterior optic pathways could cause RNFL loss. Progressive axonal loss could also explain the RNFL thinning found in eyes of patients with MS without a history of optic neuritis.[21] In the present study, significant reduction of average RNFL in patients with a previous history of optic neuritis, as well as in patients who had not previously suffered ON, compared with the control group, are in agreement with the findings of Fjeldstad et al. (2011) and Pueyo et al. (2010).[22,23]

In our study, average RNFL thickness was significantly decreased in eyes with MS-ON than those with

TABLE 4. Correlating retinal sensitivity mean deviation (MD) and best-corrected visual acuity (BCVA) with OCT parameters.

			BCVA	Retinal sensitivity (MD)
Cases	RNFL thickness (average)	Pearson correlation	–0.104	0.090
		p value	0.429	0.542
	RNFL thickness (superior)	Pearson correlation	–0.056	0.102
		p value	0.678	0.499
	RNFL thickness (inferior)	Pearson correlation	–0.134	0.149
		p value	0.317	0.324
	GCC (average)	Pearson correlation	–0.197	0.463
		p value	0.406	0.053
	GCC (superior)	Pearson correlation	–0.290	0.406
		p value	0.215	0.094
	GCC (inferior)	Pearson correlation	–0.069	0.458
		p value	0.772	0.056
	MS duration	Pearson correlation	0.300	–0.403
		p value	0.02	0.004
	No of relapses	Pearson correlation	–0.068	0.082
		p value	0.604	0.580
	EDSS	Pearson correlation	0.236	0.051
		p value	0.060	0.717
Control	RNFL thickness (average)	Pearson correlation	0.194	–0.158
		p value	0.375	0.471
	RNFL thickness (superior)	Pearson correlation	0.109	–0.182
		p value	0.620	0.405
	RNFL thickness (inferior)	Pearson correlation	0.081	0.030
		p value	0.713	0.892
	GCC (average)	Pearson correlation	0.133	0.070
		p value	0.546	0.751
	GCC (superior)	Pearson correlation	–0.085	0.089
		p value	0.700	0.688
	GCC (inferior)	Pearson correlation	0.059	0.238
		p value	0.788	0.275

EDSS, expanded disability status scale; GCC, ganglion cell complex; MS, multiple sclerosis; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer.

$p < 0.05$ is considered statistically significant.

MS-NON. But when RNFL and GCC thickness were studied in each subgroup (RRMS, SPMS and PPMS), there was no statistical significant difference between MS-ON and MS-NON. Gundogan et al. (2007) only found a significant difference in eyes with and without optic neuritis for the temporal quadrant.[24] When comparing the GCC thickness in the MS-ON subgroup with that in the MS-NON subgroup, our study showed insignificant difference between both subgroups, this was not the case in the studies done either by Syc et al. (2012)[18] or Davies et al. (2012),[19] who detected a significant decrease in GCC thickness in MS-ON group. This may be related to the distribution of ON, as well as number of patients among the MS subtypes. Another explanation is the difference in disease duration among our patients, which should be avoided in future studies to minimize bias effect.

Regarding MS subtypes, in agreement with Ghalie and Hussein (2010),[15] a significant decrease in RNFL thickness was proved when comparing each of MS subtypes and those of the healthy control group. When comparing relapsing to progressive MS subtypes, there was no significant difference in RNFL thickness. This agrees with the study done by Siepman et al. (2010).[25]

On the other hand, Pulicken et al. (2007)[26] found RNFL thinning in the progressive forms, even more pronounced than in patients with RRMS. This controversy may be attributed to difference in small sample size especially progressive subtypes.

In our study, there was a statistically significant negative correlation between the average RNFL thickness of MS eyes and disease duration and neurological disability quantified by the Expanded Disability Status Scale (EDSS). These findings were in agreement with Khanifar et al. (2010) and Costello et al. (2010)[20,27] while Pueyo et al. (2010) and Naismith et al. (2009)[23,28] did not find a significant correlation between the EDSS and RNFL thickness.

In our study, there was no significant correlation between the average RNFL thickness of MS eyes and visual field mean deviation (MD). This may be attributed to the visual fields representing a subjective method of measuring visual function which usually improves after a first episode of optic neuritis to normal or near normal levels. However, OCT often reveals subclinical permanent axonal damage, which may not be reflected by subjective explorations.[12] But,

in our study BCVA and retinal sensitivity (MD) were significantly correlated to the MS duration.

In this study, although we did not measure the inner nuclear layer (INL) thickness both in MS cases and control groups, there were no visible microcysts in any of the eyes in the OCT images. Macular microcysts in MS appear to be dynamic in their extent, suggesting a dependency on the acute inflammatory status of the optic nerve. It was also reported that macular microcysts are not exclusive to MS, but they also occur in other neuroinflammatory conditions, such as neuromyelitis optica (NMO) and chronic relapsing inflammatory optic neuropathy, and that macular microcysts in those diseases are generally associated with ON.[29]

In conclusion, retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) are significantly decreased in multiple sclerosis (MS). Both, eyes of MS cases with optic neuritis and those without showed a more marked decrease in RNFL thickness than those of age- and sex-matched healthy individuals, but there was no significant difference in RNFL thickness between MS-ON and MS-NON when studied in each subgroup (RRMS, SPMS and PPMS).

OCT is a promising tool to detect subclinical changes in RNFL and GCC in patients with MS and should be examined in longitudinal studies as a potential biomarker of retinal pathology in MS. OCT devices, compared with MRI, are affordable, and examinations can be performed within a few minutes. It has now emerged into a valuable imaging method for the detection and longitudinal monitoring of neuroaxonal pathology in MS. Importantly, typical OCT findings in MS, namely RNFL reduction and GCL thinning, were also the most prominent pathologic changes observed in a post-mortem histologic investigation of the retinas of MS patients.[30]

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