DOI: 10.14744/eer.2024.41636
Eur Eye Res 2024;4(2):135–140

EUROPEAN EYE RESEARCH

ORIGINAL ARTICLE

The relationship between color vision status and optical coherence tomography in the non-optic neuritis period in multiple sclerosis

Betul Onal Gunay,[1] Nuray Can Usta[2]

[1]Department of Ophthalmology, University of Health Sciences,Trabzon Kanuni Training and Research Hospital, Trabzon, Türkiye
[2]Department of Neurology, University of Health Sciences,Trabzon Kanuni Training and Research Hospital, Trabzon, Türkiye

Abstract

Purpose: The purpose of the study is to reveal the changes in the sense of color vision (CV) in multiple sclerosis (MS) patients in periods other than acute optic neuritis (ON) using the Ishihara test and to associate CV with optical coherence tomography (OCT) data.

Methods: The demographic and clinical data of MS patients were recorded retrospectively between 2016 and 2021. The CV of the patients was evaluated with the Ishihara test. Patients were grouped according to their CV status (Group 1: impaired CV, Group 2: normal CV). All patients were scanned with a spectral domain OCT device. Peripapillary retinal nerve fiber layer thickness (pRNFLT), macular thickness (MT), and retinal layer thicknesses were evaluated, and comparisons were made between the groups.

Results: Fifty-eight eyes of 29 patients were included in the study. The mean age and expanded disability status scale scores were 37.6±9.1 years and 1.8±0.5, respectively. The CV impairment was detected in 5 eyes and was normal in 53 eyes. Comparing Group 1 and Group 2, the ganglion cell layer thickness, inner plexiform layer thickness, MT, and pRNFLT were thinner, and the outer nuclear layer thickness was thicker in Group 1 ($p<0.05$). There was no difference between the two groups regarding the inner nuclear layer thickness, outer plexiform layer thickness, and retinal pigment epithelium layer thickness.

Conclusion: The CV assessment with the Ishihara test can be performed easily, cost-effectively, and quickly by ophthalmologists and neurologists, providing indirect information about the retina and optic nerve of the MS patient.

Keywords: Color vision; multiple sclerosis; OCT; peripapillary retinal nerve layer thickness; retinal layers.

Multiple sclerosis (MS) is an autoimmune, chronic, inflammatory, multifocal, multiphasic, and demyelinating disease that affects the brain, spinal cord, and visual pathways. Visual disturbances may frequently occur due to MS. The MS patients may have complaints of decreased visual acuity, impaired color vision (CV), and visual field defects.[1,2] Optic neuritis (ON) may be the first sign of MS in 20% of patients or it may progress during the course of the disease.[3,4] Signs and symptoms of ON can include acute or subacute vision loss, dyschromatopsia,

Cite this article as: Onal Gunay B, Can Usta N. The relationship between color vision status and optical coherence tomography in the non-optic neuritis period in multiple sclerosis. Eur Eye Res 2024;4(2):135–140.

Correspondence: Betul Onal Gunay, M.D. Department of Ophthalmology, University of Health Sciences,Trabzon Kanuni Training and Research Hospital, Trabzon, Türkiye
E-mail: drbetulonal@yahoo.com
Submitted Date: 12.01.2024 **Revised Date:** 11.05.2024 **Accepted Date:** 21.05.2024 **Available Online Date:** 01.08.2024

loss of contrast sensitivity, and scotoma accompanied by painful eye movements. Apart from ON, patients may also suffer from, though less frequently, diplopia, ocular movement disorder, ocular inflammation, higher cortical dysfunction, or iatrogenic vision impairment, caused by drugs for treating MS.[5]

Perception, processing, and transmission of colors, taking place in complex pathways, begin with cone photoreceptors; integrated into the retina through bipolar and ganglion cells. Ganglion cell axons synapse in the lateral geniculate nuclei before reaching the visual cortices. The CV defects may develop due to ocular diseases or other ailments, brain damage, long-term use of certain therapeutic medicines, or they may be genetically inherited.[6] If ON accompanies MS, its clinical manifestations often include a deterioration in CV.[7] The CV deterioration that develops after ON usually improves after treatment. However, changes in CV have been reported without an onset of ON.[1,2,5] In MS, the precise location of damage causing CV impairment is uncertain.

Optical coherence tomography (OCT) is used to examine the retina and optic nerve and diagnose ON (especially if it involves the anterior visual pathways). The OCT, a widely used, accessible, non-invasive test, is frequently used in the diagnosis and follow-up processes of MS patients.

Our hypothesis is evaluation of CV in MS patients during non-attack periods reflects structural changes in the retina and optic nerve. This study aims to reveal the changes in the sense of CV in MS patients in periods other than acute ON using the Ishihara test and to associate CV with OCT data.

Materials and Methods

This study was carried out in accordance with the Helsinki Declaration, conducted after obtaining approval from the local Ethics Committee (No: 2022/08). Retrospective analysis was done on the medical records of the patients who were followed up in the MS outpatient clinic of the tertiary health-care facility between January 2016 and December 2021. Given the retrospective nature of the study, informed consent was not obtained.

Patients diagnosed with relapsing-remitting MS according to McDonald's 2010 diagnostic criteria and had at least 1 year of follow-up appointments were included in the study.

The exclusion criteria were (1) being a secondary progressive or primary progressive MS patient, (2) being followed up for less than a year, (3) having an MS attack, including an ON attack in the past month, (4) having received steroid treatment in the past 3 months, (5) Alzheimer's disease or another neurodegenerative disease such as Parkinson's disease, (6) psychiatric disorders, (7) initiation of a new immunomodulatory therapy in the past 3 months, (8) any eye disease (e.g., glaucoma, diabetic retinopathy, hypertensive retinopathy, cataracts, history of ophthalmic surgery, senile maculopathy, or ocular fundus' anomalies, spherical equivalent out of the +3 and −3 Diopters, congenital dyschromatopsia, optic nerve drusen) that may affect the results of eye examination, (9) poor OCT compliance.

Demographic information such as the patients' sex, age, and MS disease duration (year) were collected. The Expanded Disability Status Scale (EDSS) was used to measure disability. The study involved both eyes. Disease duration was defined as the time from the onset of the disease and study enrolment.

The patients' best-corrected visual acuity (BCVA), CV (Ishihara pseudo isochromatic plates), and OCT examinations were collected from their medical records. The CV impairment was defined as failing to read at least two out of 38 plates.[8]

Eyes were divided into two groups according to how well they perceive color. Group 1 included those with impaired CV and Group 2 with normal CV.

We checked patients' medical records to find if they had a history of ON attacks. The CV and OCT data were acquired during the chronic phase of ON attack.

A spectral-domain OCT instrument was used to assess all subjects (SPECTRALIS OCT; Heidelberg Engineering, Heidelberg, Germany). Macular pictures were obtained by scanning a 30° × 25° scan region with a horizontal raster pattern. The retinal thickness map analysis technique was used to analyze retinal thickness in five Early Treatment Diabetic Retinopathy Study subfields, including central (1 mm) macular thickness and thicknesses at the 3 mm nasal, temporal, superior, and inferior locations. After automated segmentation, software produced foveal scans, which the researchers assessed for accuracy. The values of all retinal layers were recorded (Fig. 1).

The peripapillary retinal nerve fiber layer thickness (pRNFLT) was measured around the optic disc using a routine scan of the 3.4 mm diameter peripapillary ring. The software in the device supplied mean pRNFLT as well as superonasal, superotemporal, temporal, inferotemporal, inferonasal, and nasal RNFLT.

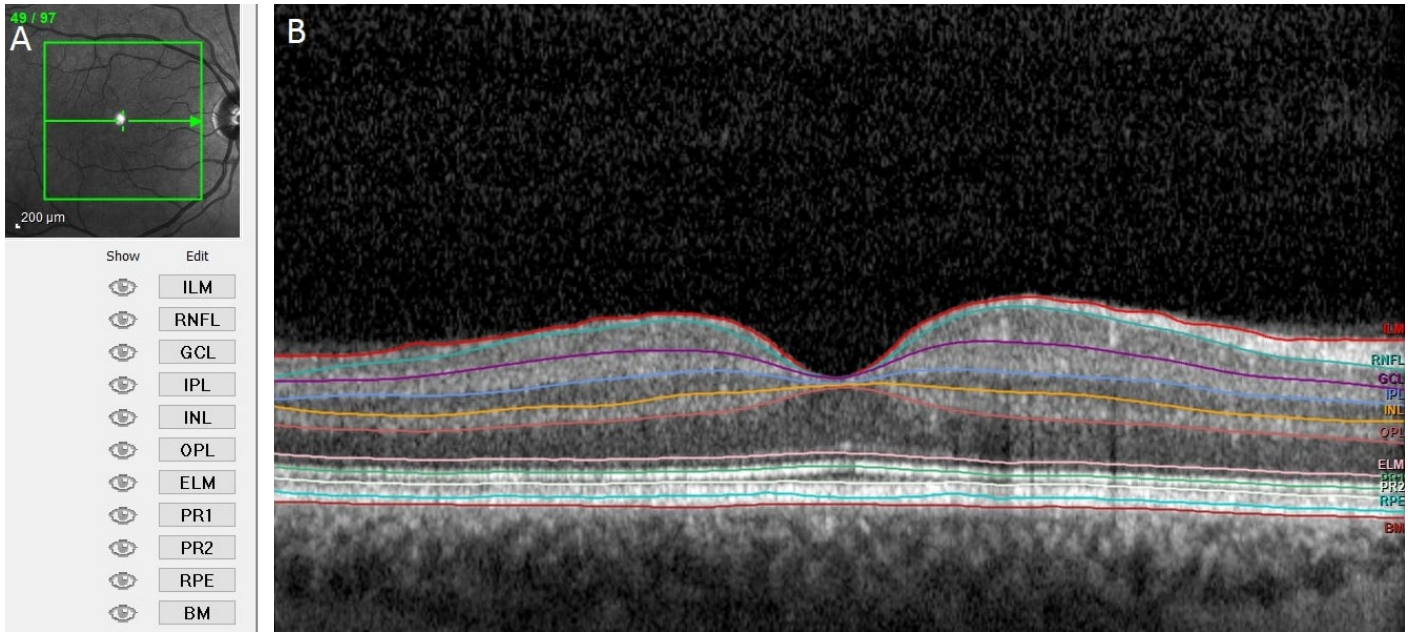

Fig. 1. **(a)** Representative infrared imagining. **(b)** Descriptive the retinal layer analysis after automated segmentation.
ILM: Internal limiting membrane, RNFL: Retinal nerve fiber layer, GCL: Ganglion cell layer, IPL: Inner plexiform layer, INL: Inner nuclear layer, OPL: Outer plexiform layer, ELM: External limiting membrane, PR1: Interface of the inner and outer segments of the photoreceptor layer, PR2: Outer segment-retinal pigment epithelium interdigitation, RPE: Retinal pigment epithelium, BM: Bruch's membrane

Statistic Analysis

For statistical analysis, the SPSS 22 software (IBM SPSS Inc., Chicago, IL) was utilized. For statistical purposes, the Shapiro–Wilk test and histograms were used to determine the data distribution. The Mann–Whitney U test was used to compare two groups of quantitative data. To establish the power of the current study, a post-study power analysis was carried out. The findings indicated that a power of 0.95 would be generated through mean pRNFL values.

Results

Fifty-eight eyes of 29 (6 male, 23 female) patients were included in the study. The mean age and EDSS scores were 37.6±9.1 years and 1.8±0.5, respectively. The average duration of the disease was 7.6±4.2 years.

The CV impairment was also detected in 5 eyes (Group 1). The CV was normal in 53 eyes (Group 2). In their medical histories, all patients reported an attack of ON in Group 1. In Group 1, the Snellen BCVA of 3 of 5 patients was 1.0, while it was 0.7 in 2 patients.

The history of ON was positive in 22 of 53 eyes in Group 2.

There was no difference in age and EDSS score between the two groups (Group 1: 40.0 [31–51], median [min-max] years, Group 2: 39.0 [20–53] median [min-max] years; p=0.53 and Group 1: 2.5 [2–2.5], median [min-max], Group 2: 1.5 [1.5–3.5] median [min-max]; p=0.08).

Table 1 shows the OCT-measured macular parameters for each retinal layer as well as the pRNFL thickness measurement.

Comparing the patients with (Group 1) and without (Group 2) CV impairment, the ganglion cell layer thickness (GCLT) and inner plexiform layer thickness (IPLT) were found to be thinner, and the outer nuclear layer thickness (ONLT) was thicker in all regions in Group 1.

The macular thickness (MT) of 3 mm in the superior, inferior, and nasal quadrants was thinner in Group 1 (<0.05).

The pRNFLT was found to be thinner in Group 1, except for the superonasal region. There was no difference in terms of the inner nuclear layer thickness (INLT), outer plexiform layer thickness (OPLT), and retinal pigment epithelium layer thickness (RPELT) between the two groups.

Discussion

The CV impairment was detected in five (8.6%) of the 58 eyes examined under the study using the Ishihara test and a positive ON history was found in all of these eyes. In patients with impaired CV, GCLT, IPLT, and RNFLT (except superonasal sector) were thinner, while ONLT was thicker than in MS patients with normal CV. The INLT, OPLT, and RPELT were similar across groups.

The CV impairment can be seen in the acute ON period in MS patients, as well as in the chronic phase of ON and even if they have never had an ON attack.[1,2,5,9] Although

Table 1. Optical coherence tomography data of Groups 1 and 2

	Group 1 (n=5 eyes) Median (Min-Max)	Group 2 (n=53 eyes) Median (Min-Max)	p*
Macular Thickness (µm)			
Central	257.0 (226.0–318.0)	257.0 (253.0–263.0)	0.78
Superior	308.0 (304.0–322.0)	334.5 (217.0–378.0)	**0.007**
Temporal	303.0 (300.0–312.0)	321.0 (283.0–358.0)	0.09
Inferior	301.0 (301.0–312.0)	329.5 (300.0–372.0)	**0.002**
Nasal	304.0 (303.0–306.0)	331.5 (301.0–377.0)	**<0.001**
Ganglion Cell Layer Thickness (µm)			
Central	7.0 (7.0–11.0)	12.0 (7.0–24.0)	**0.007**
Superior	28.0 (27.0–39.0)	50.0 (28.0–59.0)	**<0.001**
Temporal	26.0 (25.0–31.0)	45.5 (20.0–56.0)	**<0.001**
Inferior	32.0 (25.0–35.0)	50.0 (24.0–59.0)	**<0.001**
Nasal	27.0 (21.0–34.0)	49.0 (21.0–59.0)	**<0.001**
Inner Plexiform Layer Thickness (µm)			
Central	16.0 (15.0–17.0)	18.0 (15.0–27.0)	**0.007**
Superior	27.0 (26.0–30.0)	40.0 (26.0–46.0)	**<0.001**
Temporal	27.0 (25.0–28.0)	39.0 (25.0–47.0)	**<0.001**
Inferior	26.0 (25.0–30.0)	39.5 (24.0–47.0)	**<0.001**
Nasal	27.0 (25.0–33.0)	40.0 (24.0–48.0)	**<0.001**
Inner Nuclear Layer Thickness (µm)			
Central	19.0 (17.0–20.0)	16.5 (11.0–30.0)	0.11
Superior	43.0 (43.0–45.0)	42.0 (37.0–48.0)	0.07
Temporal	43.0 (42.0–44.0)	41.0 (40.0–48.0)	0.69
Inferior	43.0 (41.0–44.0)	42.0 (33.0–53.0)	0.34
Nasal	43.0 (34.0–43.0)	40.0 (33.0–55.0)	0.78
Outer Plexiform Layer Thickness (µm)			
Central	20.0 (19.0–23.0)	23.0 (17.0–31.0)	0.69
Superior	31.0 (28.0–33.0)	30.0 (26.0–39.0)	0.87
Temporal	28.0 (27.0–30.0)	30.0 (25.0–40.0)	0.27
Inferior	31.0 (29.0–33.0)	30.5 (27.0–53.0)	0.66
Nasal	31.0 (29.0–31.0)	30.0 (27.0–38.0)	0.83
Outer Nuclear Layer Thickness (µm)			
Central	98.0 (94.0–103.0)	89.0 (58.0–110.0)	**0.002**
Superior	79.0 (78.0–79.0)	71.0 (50.0–82.0)	**<0.001**
Temporal	78.0 (78.0–79.0)	70.5 (53.0–88.0)	**0.005**
Inferior	77.0 (69.0–78.0)	68.0 (44.0–79.0)	**0.02**
Nasal	83.0 (81.0–83.0)	72.0 (45.0–86.0)	**<0.001**
Retinal Pigment Epithelium Thickness(µm)			
Central	18.0 (17.0–20.0)	17.0 (15.0–21.0)	0.17
Superior	16.0 (14.0–18.0)	16.0 (13.0–19.0)	0.85
Temporal	15.0 (13.0–19.0)	15.0 (13.0–17.0)	0.97
Inferior	15.0 (14.0–19.0)	15.0 (12.0–17.0)	0.80
Nasal	16.0 (14.0–20.0)	16.0 (13.0–18.0)	0.72
Peripapillary Retinal Nerve Fiber Layer Thickness (µm)			
Mean	68.0 (65.0–85.0)	96.5 (60.0–133.0)	**0.005**
Superotemporal	103.0 (90.0–116.0)	129.0 (90.0–192.0)	**0.004**
Superonasal	101.0 (69.0–105.0)	106.0 (66.0–169.0)	0.34
Temporal	34.0 (28.0–39.0)	60.5 (34.0–92.0)	**<0.001**
Nasal	52.0 (46.0–67.0)	70.0 (46.0–105.0)	**0.01**
Inferotemporal	105.0 (89.0–135.0)	140.0 (75.0–205.0)	**0.03**
Inferonasal	91.0 (88.0–96.0)	109.5 (88.0–178.0)	**0.01**

*Mann–Whitney U test.

the exact mechanism of CV changes in MS patients is not fully understood, mechanisms such as the involvement of afferent visual pathways, anterograde and retrograde neurodegeneration, ganglion cell loss, and inflammatory retinopathy are implicated.[7,10] Similar to lesions in the brain and spinal cord in MS, lesions in the optic nerve and chiasm display inflammation, demyelination, gliosis, axonal damage, and atrophy.[7]

In the current study, the fact that the GCLT and IPLT of MS patients with impaired CV were found to be thinner than those without CV impairment may be related to the previous ON attacks of the patient, or it may be explained by the underlying ganglion cell loss in the deterioration of CV. In support of this hypothesis, a study conducted on MS patients without a history of ON showed a significant relationship between retinal ganglion cells and CV and reported that deterioration in CV might indicate retinal ganglion cell damage.[2] Each inflammatory damage may leave behind residual CV problems.[11]

Villoslada et al.[12] showed the relationship between CV and retinal thinning in their study, but they used only pRNFLT and papillomacular bundle thickness in their study. In our study, we showed a decrease in pRNFLT and MT in patients with impaired CV, similar to other studies. In addition, we found a more significant decrease in the GCLT and the IPLT than in the RNFLT.

Unlike other studies in the literature, the ONLT was found to be thicker in MS patients with CV impairment in our study.[13,14] A few studies found that MS patients with ON have slightly thicker ONLT than MS patients without ON.[15,16] Photoreceptors form most of the ONL, so this difference may be due to compensation for the loss of the GCLT and IPLT, or it may be due to microscopic edema by virtue of inflammation in the photoreceptors. According to current research, primary chronic inflammatory retinopathy may exist in the visual pathway.[10] More studies are needed on ONL thickening.

Martínez-Lapiscina et al.[17] reported that MS patients with CV deficiency had a greater deterioration in disability as measured by EDSS than those with normal CV after 1 year of follow-up. In our study, although the EDSS score of patients with impaired CV was higher than patients without impaired CV, this difference had no statistical significance, which may be due to the small number of samples.

Study Limitations

Retrospective, a small number of patients, lack of a control group, and use of Ishihara test for CV. It is known that more detailed CV tests such as the FM 100 Hue test can reveal even milder disorders.[18] The Ishihara test is intended to identify impairments in red-green CV and has limitations in detecting blue-yellow CV problems. Lack of characterization of CV disorders such as red-green and blue-yellow and the fact that we do not know about any subtle ON in these eyes were among other limitations.

The strength of the study is that the Ishihara test, a practical CV application that can be obtained in every outpatient clinic and can be applied without complex devices, affects clinical practice.

Conclusion

The CV assessment with the Ishihara test is an old but timeless modality that can be performed easily, cost-effectively, and quickly by ophthalmologists and neurologists, providing indirect information about the retina and optic nerve of the MS patient. It is important to consider CV in the follow-up of MS patients.

Ethics Committee Approval: This study was carried out in accordance with the Helsinki Declaration, conducted after obtaining approval from the Health Sciences University Trabzon Kanuni Training and Research Hospital Clinical Research Ethics Committe. (No: 2022/08).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: B.O.G., N.C.U.; Design: B.O.G., N.C.U.; Supervision: B.O.G.; Resource: B.O.G., N.C.U.; Materials: B.O.G., N.C.U.; Data Collection and/or Processing: B.O.G., N.C.U.; Analysis and/or Interpretation: B.O.G., N.C.U.; Literature Search: B.O.G.; Writing: B.O.G.; Critical Reviews: B.O.G., N.C.U.

Conflict of Interest: None declared.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Piro A, Tagarelli A, Nicoletti G, Scannapieco S, Polidoro S, Valentino P, et al. Impairment of acquired color vision in multiple sclerosis: An early diagnostic sign linked to the greatness of disease. Int Ophthalmol 2019;39:671–6. [CrossRef]
2. Lampert EJ, Andorra M, Torres-Torres R, Ortiz-Pérez S, Llufriu S, Sepúlveda M, et al. Color vision impairment in multiple sclerosis points to retinal ganglion cell damage. J Neurol 2015;262:2491–7. [CrossRef]
3. Beck RW, Cleary PA, Anderson MM Jr., Keltner JL, Shults WT, Kaufman DI, et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. N Engl J Med 1992;326:581–8.
4. Kale N. Management of optic neuritis as a clinically first event of multiple sclerosis. Curr Opin Ophthalmol 2012;23:472–6.

5. Costa Novo J, Felgueiras H. Neuro-ophthalmologic manifestations of multiple sclerosis other than acute optic neuritis. Mult Scler Relat Disord 2021;48:102730. [CrossRef]
6. Simunovic MP. Acquired color vision deficiency. Surv Ophthalmol 2016;61:132–55. [CrossRef]
7. Kolappan M, Henderson AP, Jenkins TM, Wheeler-Kingshott CA, Plant GT, Thompson AJ, et al. Assessing structure and function of the afferent visual pathway in multiple sclerosis and associated optic neuritis. J Neurol 2009;256:305–19. [CrossRef]
8. Birch J. Efficiency of the Ishihara test for identifying red-green colour deficiency. Ophthalmic Physiol Opt 1997;17:403–8.
9. Sanchez-Dalmau B, Martinez-Lapiscina EH, Pulido-Valdeolivas I, Zubizarreta I, Llufriu S, Blanco Y, et al. Predictors of vision impairment in Multiple Sclerosis. PLoS One 2018;13:e0195856.
10. Barreiro-González A, Sanz MT, Carratalà-Boscà S, Pérez-Miralles F, Alcalá C, España-Gregori E, et al. Dyschromatopsia in multiple sclerosis reflects diffuse chronic neurodegeneration beyond anatomical landmarks. Acta Neurol Belg 2021;121:1767–75.
11. Gundogan FC, Tas A, Altun S, Oz O, Erdem U, Sobaci G. Color vision versus pattern visual evoked potentials in the assessment of subclinical optic pathway involvement in multiple sclerosis. Indian J Ophthalmol 2013;61:100–3. [CrossRef]
12. Villoslada P, Cuneo A, Gelfand J, Hauser SL, Green A. Color vision is strongly associated with retinal thinning in multiple sclerosis. Mult Scler 2012;18:991–9. [CrossRef]
13. Filgueiras TG, Oyamada MK, Preti RC, Apóstolos-Pereira SL, Callegaro D, Monteiro ML. Outer retinal dysfunction on multifocal electroretinography may help differentiating multiple sclerosis from neuromyelitis optica spectrum disorder. Front Neurol 2019;10:928. [CrossRef]
14. Hanson JV, Hediger M, Manogaran P, Landau K, Hagenbuch N, Schippling S, et al. Outer retinal dysfunction in the absence of structural abnormalities in multiple sclerosis. Invest Ophthalmol Vis Sci 2018;59:549–60. [CrossRef]
15. Balk LJ, Twisk JW, Steenwijk MD, Daams M, Tewarie P, Killestein J, et al. A dam for retrograde axonal degeneration in multiple sclerosis? J Neurol Neurosurg Psychiatry 2014;85:782–9.
16. Saidha S, Al-Louzi O, Ratchford JN, Bhargava P, Oh J, Newsome SD, et al. Optical coherence tomography reflects brain atrophy in multiple sclerosis: A four-year study. Ann Neurol 2015;78:801–13. [CrossRef]
17. Martínez-Lapiscina EH, Ortiz-Pérez S, Fraga-Pumar E, Martínez-Heras E, Gabilondo I, Llufriu S, et al. Colour vision impairment is associated with disease severity in multiple sclerosis. Mult Scler 2014;20:1207–16. [CrossRef]
18. Harrison AC, Becker WJ, Stell WK. Colour vision abnormalities in multiple sclerosis. Can J Neurol Sci 1987;14:279–85. [CrossRef]