Evaluation of Ganglion Cell Complex Layer Thickness with Optical Coherence Tomography in Multiple Sclerosis Patients

Multipl Skleroz Hastalarında Optik Koherans Tomografi ile Ganglion Hücre Kompleksi Kalınlığının Değerlendirilmesi

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ABSTRACT

Purpose: To evaluate ganglion cell complex(GCC) layer thickness in Multiple Sclerosis (MS) patients

Material and Methods: Eighty four MS patients referred from the neurology department and 20 age and sex matched healthy control subjects were included in this study. The degree of disability of MS patients were assessed using the Expanded Disability Status Scale (EDSS) scores. The medical records including history of optic neuritis, and the duration of disease were obtained from the neurology department. GCC measurements were performed with RTVue-100 FD- Optical coherence tomography (OCT) system (Optovue). The correlations between parameters were evaluated.

Results: The mean age of the patient group was 38.7±10.41 and the mean age of the control group was 38.3±12.4 years (p>0.05). The mean duration of disease was 8.25±6.42 years in the MS group. Mean GCC of MS patients were thinner than those of the controls (p=0.001). There was no statistically significant correlation of mean GCC thickness with the age of the MS patients (p=0.289). Fifty two eyes of 168 eyes (30.95%) had a history of optic neuritis in 42 of 84 patients (50%) in the MS group. In 32 patients with a history of unilateral optic neuritis, mean GCC thickness of unaffected eyes was 94.68±9.67 and mean GCC thickness of affected eyes was 89.24±13.14; however, the difference was not statistically significant (p=0.372). The GCC scores of the MS patients were negatively correlated with EDSS scores of the patients (r=-0.322 p=0.003) and the duration of the disease (r=-0.314 p=0.004).

Conclusion: GCC thinning occurs in MS patients and GCC thickness is negatively correlated with EDSS score, and duration of the disease. OCT measurements of GCC may be helpful in evaluating MS patients. The best OCT scan protocol to evaluate MS patient and MS disease processes must be further investigated.

Key Words: Optical coherence tomography, multiple sclerosis, ganglion cell complex.

ÖZ

Amaç: Multipl Skleroz (MS) hastalarında ganglion hücre kompleksi (GHK) tabakasının kalınlık değişimlerini değerlendirmek.

Gereç ve Yöntem: Nöroloji kliniğinden refere edilen 84 ms hastası ile yaş ve cinsiyetleri hasta grubu ile örtüşen 20 sağlıklı kontrol bu çalışmaya dahil edildi. MS hastalarının özür seviyeleri genişletilmiş özürlülük durum ölçeği(GÖDÖ) ile hesaplandı. Hastaların, optik nörit geçirmiş olma ve hastalık süreleri gibi bilgileri içeren tıbbi kayıtları nöroloji bölümünden temin edildi. GHK ölçümleri RTVue-100 FD optik koherans tomografi cihazı ile yapıldı. Parametreler arasındaki korelasyonlar değerlendirildi.

Bulgular: Hastaların yaş ortalaması 38.7±10.41 yıl, kontrol grubunun ise 38.3±12.4 yıldı (p>0.05). MS grubunda ortalama hastalık süresi 8.25±6.42 yıl idi. MS hastalarında ortalama GHK kalınlığı kontrol grubundan düşüktür (p=0.001). MS olgularının yaşı ile ortalama GHK kalınlığı arasında istatiksel olarak anlamlı korelasyon yoktu (p=0.289). Seksendört MS hastasının 42'sinin 54 gözünde optik nörit hikayesi vardı. Tek taraflı optik nörit hikayesi olan 32 olguda tutulan gözlerdeki ortalama GHK kalınlığı 89.24±13.14 mikron, tutulum olmayan gözlerde ortalama GHK 94.68±9.67 mikrondu ancak aradaki fark istatistiksel olarak anlamlı değildi (p=0.372). MS olgularının GHK kalınlığı, olguların GÖDÖ (r=-0.322 p=0.003) ve hastalık süresi (r=-0.314 p=0.004) ile negatif koreleydi.

Sonuç: MS olgularında GHK kalınlığı azalır ve kalınlık GÖDÖ ve hastalık süresi ile negatif koreledir. MS olgularında OKT ölçümleri olguları değerlendirmede faydalı olabilir. MS olgularını ve hastalık süreçlerini değerlendirmek için en faydalı OKT protokolünü tespit etmek için ileri araştırmalar yapılmalıdır.

Anahtar Kelimeler: Optik koherans tomografi, multipl skleroz, ganglion hücre kompleksi.

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INTRODUCTION

Multiple sclerosis (MS) is a neurodegenerative disorder which is characterized by demyelination, gliosis, and neuronal loss in brain and spinal cord.[1] Retina is a part of Central Nervous System (CNS). It is unique in that axons and dendrites in retina do not have myelin sheath.[2] Axonal and neuronal degeneration is the reason for the functional disability in the disease process in MS. Visual system is a target for MS.[3,4] Optic neuritis occurs in up to 70% of MS patients during the course of the disease.[5] Uveitis, retina and optic nerve degenerations also occur in eyes with or without a history of optic neuritis in MS patients.[4,6]

Optical coherence tomography (OCT) generates high resolution cross-sectional and three dimensional images of retina and its layers. It has been widely used to detect retina and optic disc in different ophthalmological and systemic disease processes. It has a very important role for the assessment of glaucoma and macular disease.[7,8] It has been shown that RNFL is widely affected in MS disease process.[5,9,10]

However RNFL is consist of only axons of ganglion cells. RNLF measurements give only indirect information about the effect of MS disease processes on ganglion cells. With technologial improvements, other layers of retina can also be evaluated with OCT and one of them is the ganglion cell complex (GCC). GCC is combination of nerve fiber, ganglion cell and inner plexiform layers. These layers are the innermost layers of retina and consist of axons, cell body, and dendrites of ganglion cells[11]. Measurement of GCC thickness in macular region may be much more valuable in evaluating visual system functions of MS patients such as visual acuity or visual field and effect of disease processes on ganglion cells then measurement of RNLF thickness around optic disc. The best OCT scan protocol to evaluate MS patient and MS disease processes is not known.

In this study we measured GCC thickness of MS patients. We compared these scores with healty controls and evaluated the relation of GCC scores with age, EDSS scores, duration of disease and history of optic neuritis.

MATERIALS AND METHODS

Eighty four MS patients referred from the neurology department and 20 age and sex matched healthy control subjects were included in this study. All patients and control subjects underwent detailed ophthalmological examination. Patients and controls with any ocular disease which may affect GCC thickness were excluded from the study. The degree of disability of MS patients were assessed using the Expanded Disability Status Scale (EDSS) scores by the same experienced neurologist. EDSS is a rating system which is used to classify the patients according to their functional capacity and neurological examination. Functional systems of a patient are; pyramidal (ability to walk), cerebellar (coordination), sensory (touch and pain), brain stem (speech and swallowing), visual, and mental systems. The scale has a range between 0.0 and 10.0. 0.0 refers to normal neurological exam and 10.0 to death due to MS. The medical records of the patients and also the records of history of optic neuritis were obtained from the neurology department. OCT measurements were performed with RT-Vue-100 FD-OCT system (Optovue) by the same examiner. It is a new generation Fourier-domain OCT (FD-OCT) system (also called spectral OCT or spectral domain OCT).[12,13] The GCC and RNFL thickness were measured using the scan protocol “GCC” and “RNFL”, and the parameter “average” was recorded for each eye. In the RTVue-100 OCT system, the signal strength index (SSI) identifies image quality.

Strong OCT signal values which is 50 or above were recorded. For statistical analyses of the findings obtained from the study, Number Cruncher Statistical System 2007 and Power Analysis and Sample Size 2008 (NCSS, Kaysville, UT) programs were used. Non-parametric values were analyzed with the Mann-Whitney test and parametric values were analyzed with Student-t test. To evaluate the correlations between parameters, Pearson correlation analysis and Spearman’s rho correlation coefficient were used.

Tenets of Helsinki were followed in the study. Ethics committe approved the study. Informed consent was obtained from all participants.

RESULTS

The mean age of the patient group was 38.7±10.41 and the mean age of the control group was 38.3±12.4 years ($p>0.05$). The mean duration of disease was 8.25±6.42 years in the MS group. Mean GCC of MS patients was 90.39±11.38 and mean GCC of controls was 99.13±5.66 ($p=0.001$). There was an average of 8.81% reduction in GCC thickness in MS group when compared with control subjects. There was no statistically significant correlation between GCC thickness and the age of the MS patients ($r=-0.119$ $p=0.289$). Fifty two eyes of 168 eyes (30.95%) had a history of optic neuritis in 42 of 84 patients (50%) in the MS group. In 32 patients with a history of unilateral optic

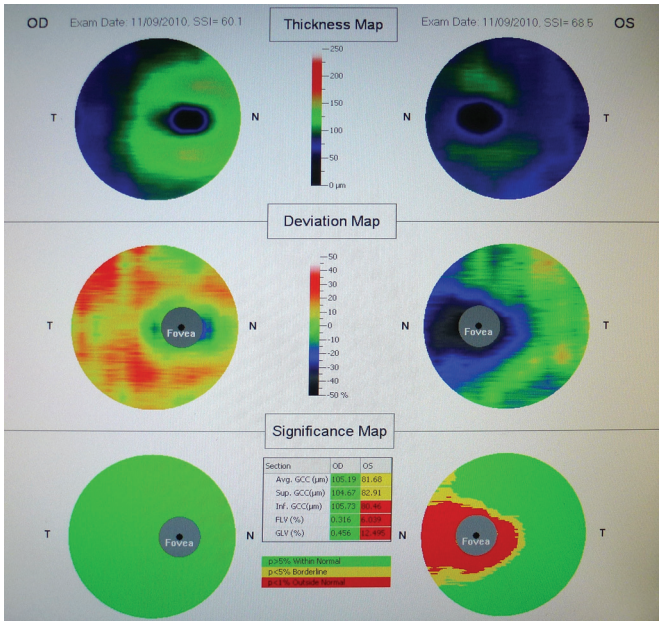

Figure: *GCC measurement in a MS patient with a history of left optic neuritis. GCC thickness is markedly reduced in left eye.*

neuritis, mean GCC thickness of unaffected eyes was 94.68±9.67 and mean GCC thickness of affected eyes was 89.24±13.14. Mean GCC thickness of affected eyes was thinner by 5.74% respectively than unaffected eyes; however, the difference was not statistically significant (p=0.372). The GCC scores of the MS patients were negatively correlated with EDSS scores of the patients (r=-0.322 p=0.003) and the duration of the disease (r=-0.314 p=0.004).

DISCUSSION

Multiple sclerosis is a chronic inflammatory neurodegenerative disorder of CNS which results in variable pathological manifestations and clinical syndromes. Demyelinating lesions can be demonstrated by MRI studies.[14] Conventional and new imaging techniques such as magnetization transfer imaging, magnetic resonance spectrometry, or diffusion tensor imaging have not been very helpful in linking the obtained imaging datas from CNS with the clinical severity of the MS.[14] The dissociation between the lesions seen on MRI scans and documented clinical deficits on neurological examination is called 'clinicoradiological paradox'.[15] Tests for determining visual functions such as color vision, visual acuity or contrast acuity are very subjective and may be affected by many factors.[16,17] Also, there is a threshold of RNFL thickness for clinically significant visual function impairment, which is 75 um[18]. Below this threshold, every 10 um decrease in RNFL thickness results in 5.8 dB decrease in visual field and a 0.46 reduction in visual acuity.[18] Above this threshold, RNFL thickness changes are not clinically significant and can not be detected by visual function tests.[19] Therefore, new imaging techniques have been investigated for coupling clinical deficits and syndromes in MS with pathological changes and disease processes. One of these new imaging techniques is spectral domain OCT. OCT, a specific imaging technique for the eyes, enables objective analysis of retina and optic disc 7. It is reproducible and reliable. RNFL changes above 75 um can be easily detected by OCT. With technologial improvements, other layers of retina can also be evaluated with OCT and one of them is the ganglion cell complex (GCC). In MS studies, generally RNFL mesurements have been used.[20-22] The measurement of RNLF around the optic disc represent the whole retina, and not the macular region. Also optic disc inflammation or retinal astrocytes proliferation may lead to RNLF swelling and pseudonormalization of the RNLF thickness in MS patients.[23] Fernandes et al demonstrated retinal ganglion cell layer and inner nuclear layer thinning in MS patients with spectral domain OCT.[24] In this study we evaluated the changes of GCC thickness in MS patients.

GCC measurements did not differ according to the age of the patients in our study (p=0.289). Gender does not affect GCC thickness but interindividual variations of GCC thickness is affected by age in the normal population. Harwerth et al.,[25] reported that normal RNFL thickness is 104.4±7.6 in the third decade and 89.5±7.5 in the seventh decade with stratus OCT. RNFL thickness decreases 0.3 um/year or 0.27%/year. In healthy population, GCC thickness also decrease slowly with age but in MS patients, disease processes also affect retinal layers and the optic disc. The effect of age may have been masked by the disease process in our patient population.

Mean GCC thickness of MS patients were thinner than the controls. The differences were statistically significant (p<0.01). There was an average of 8.81% reduction in GCC thickness in MS group when compared with control subjects. In 1974, it was the first time that a subjective analysis of thinning of the RNLF performed by hand-held ophthalmoscopy was reported in MS patients.[26]. Parisi et al.,[20] reported that the RNFL thickness was reduced by an average of 26% in unaffected eyes in MS patients when compared with the eyes of healthy controls and the measurements were performed by Humphrey OCT. Saidha et al.,[27] reported that GCL+inner plexiform layer (GCIP) was thinner in relapsing-remitting MS (RRMS; n=96, 71.6 µm), secondary progressive MS (SPMS; n=20, 66.4 µm) and primary progressive MS (PPMS; n=16, 74.1 µm) than in healthy controls (81.8 µm; p<0.001 for all) with spectral domain OCT. Regardless of history of optic neuritis and other factors, it is obvious that MS disease processes lead to RNFL and GCC thickness reduction.

In our study, 50% of MS patients experienced acute optic neuritis in one or both eyes. As many as 70% of MS patients experience an acute attack during their life period. Most MS lesions in the central nervous system are silent; however, the lesions in optic nerve and brain stem often result in symptoms.[28] Signs of optic neuritis are pain and visual disturbance.[29] Optic neuritis may be the first symptom of MS in approximately 20% of the MS patients[30]. After an attack of optic neuritis, most of the patients recover visually because an attack may not lead to extensive axonal damage which causes permanent visual disturbance. In 32 patients with a history of unilateral optic neuritis, mean GCC thickness of unaffected eyes was 94.68±9.67 and mean GCC thickness of affected eyes was 89.24±13.14. Mean GCC thickness of affected eyes was thinner by 5.74% respectively than unaffected eyes; however, the difference was not statistically significant (p=0.372). Pro et al.,[31] reported that RNFL thickness decreases significantly as early as few months after the onset of optic neuritis when compared to baseline measurements with OCT-3. Parisi et al.,[20] reported that the RNFL thickness was reduced by an average of 46% in eyes with a history of optic neuritis when compared with the eyes of healthy controls, and by 28% when compared with the other eyes of the same patients with Humphrey OCT. Trip et al.,[21] using macular volume measurements reported an average reduction of 11% in the eyes with a history of optic neuritis versus the eyes of controls and a 9% reduction in the affected eye when compared with the other eyes of the same patients. These two studies attributed a very important role to acute optic neuritis in RNFL and macular thickness reduction in MS patients. However, in our study there was no statistically significant difference in GCC thickness between affected and unaffected eyes. (p=0.372) Garcia-Martin E et al.,[32] reported that optic neuritis is not a risk factor for increased chronic damage in MS patients without ophthalmic relapses. In post-mortem analyses, almost all MS patients had the same pathological changes in the optic disc and retina, regardless of history of optic neuritis.[33] Optic neuritis may cause acute reduction in GCC thickness but with longer follow-up and increased duration of disease, the progressive degeneration of optic nerve and retina may play a greater role in GCC thickness reduction than acute attacks.

In this study, we evaluated the relation of EDSS scores GCC thickness. There was a statistically significant negative correlation between mean GCC (r=-0.322, p=0.003) thickness of the patients and EDSS scores. Fisher et al.,[34] reported that RNFL thickness decreases with increasing neurological impairment in MS patients with spectral domain OCT. Costello et al.,[19] reported the relation of RNFL thickness with neurological disability in mildly or moderately affected MS patients with spectral domain OCT. We also demonstrated the same relation of EDSS scores with GCC measurements in our study. Substantial silent disease activity and accumulation of MS lesions eventually lead to neurological deficits, and higher EDSS scores. Same silent disease processes may lead to reduction of RNFL and GCC. Postgeniculate lesions from subclinical disease may also affect anterior visual pathway, optic disc, and retina.[35] Reich et al.,[35] reported that MS lesions within the posterior optic pathways also cause RNFL atrophy via retrograde transsynaptic retinal ganglion cell degeneration. There was a statistially significant negative correlation between GCC (r=-0.314, p=0.004) thickness and the duration of disease. It also suggests that chronic disease activity may have an important role in GCC thickness reduction.

Acute demyelinating lesions are similar in many ways to acute optic neuritis. Chronic optic nerve degenerations without an optic neuritis attack may be a model for central nervous system degenerations. OCT can quantify the retinal and axonal damage. These findings may be useful in understanding the pathophysiology of MS and evaluating the treatment strategies. MS disease processes affects all these 3 layers - ganglion cell, inner plexiform, and nerve fiber and OCT measurements of GCC may be helpful in evaluating MS patients.

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