The Evaluation of Peripapillary Retinal Nerve Fiber Layer Thickness Changes in Patients with Retinitis Pigmentosa and Patients with Early-Late Stage Glaucoma

Retinitis Pigmentosa ve Erken-Geç Evre Glokom Hastalarında Peripapiller Retınal Sinir Lifi Tabakası Kalınlığı Değişimlerinin Değerlendirilmesi

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ABSTRACT

Objective: The aim of the study is to evaluate the peripapillary retinal nerve fiber layer (RNFL) thickness of patients with retinitis pigmentosa (RP) and patients with early- and late-stage glaucoma using spectral domain optical coherence tomography (SD-OCT), and investigate the similarity and differences of RNFL thickening and thinning regions between these groups.
Methods: This cross-sectional study was carried out in Niğde Ömer Halisdemir University Training and Research Hospital. The patients were divided into three groups; retinitis pigmentosa (group 1), early-stage glaucoma (group 2), and medium- and advanced-stage glaucoma (group 3). The RNFL thickness of all patients were measured. Each group consisted of 20 patients.
Results: RNFL thinning was most frequently detected in the inferior quadrant, and then in the superior quadrant in all 3 groups and thickening was not detected in these 2 quadrants in glaucoma groups. The thickening was most frequently detected in the temporal quadrant, and in the 9 o' clock segment in all groups. In groups 1 and 2, the nasal quadrant was second after the temporal quadrant in RNFL thickening. RNFL thickening and thinning regions were found to be similar in these 2 diseases, which progress with ganglion cell damage. The horizontal quadrants were less affected and vertical quadrants were more affected regardless of the disease.
Conclusion: The similar changes in the RNFL layer in these 2 different diseases with different mechanisms suggest that ganglion cells might have a specific response to various disease processes.

Keywords: glaucoma, peripapillary retinal nerve fiber layer, retinitis pigmentosa, spectral domain optical coherence tomography

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ÖZET

Amaç: Çalışmanın amacı, retinitis pigmentoza (RP) hastalarının ve erken ve geç evre glokomu olan hastaların peripapiller retinal sinir lifi tabakası (RSLT) kalınlığını spektral optik koherens tomografisi (SD-OCT) kullanarak değerlendirmek ve bu gruplar arasındaki RSLT kalınlaşma ve incelme bölgelerinin benzerliğini ve farklılıklarını araştırmaktı.
Yöntem: Bu kesitsel çalışma Niğde Ömer Halisdemir Üniversitesi Eğitim ve Araştırma Hastanesi'nde yapıldı. Hastalar üç gruba ayrıldı; retinitis pigmentosa (grup 1), erken evre glokom (grup 2) ve orta ve ileri evre glokom (grup 3). Tüm hastaların RSLT kalınlıkları ölçüldü. Her grup 20 hastadan oluşuyordu.
Bulgular: RSLT incelmesi her 3 grupta da en sık alt kadranda ve ardından üst kadranda saptandı ve glokom gruplarında bu 2 kadranda kalınlaşma saptanmadı. Kalınlaşma en sık olarak temporal kadranda ve tüm gruplarda saat 9 segmentinde tespit edildi.Grup 1 ve 2'de, RSLT kalınlaşmasında nazal kadran temporal kadrandan sonra ikinci sıradaydı. Ganglion hücre hasarı ile seyreden bu 2 hastalıkta RSLT kalınlaşma ve incelme bölgeleri benzer bulundu. Hastalıktan bağımsız olarak yatay kadranlar daha az, dikey kadranlar daha fazla etkilenmişti.
Sonuç: Farklı mekanizmalara sahip bu 2 farklı hastalıkta RSLT katmanındaki benzer değişiklikler, gangliyon hücrelerinin çeşitli hastalık süreçlerine spesifik bir yanıt verebileceğini düşündürmektedir.

Anahtar Sözcükler: glokom, peripapiller retina sinir lifi tabakası, retinitis pigmentosa, spektral domain optik koherens tomografi

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INTRODUCTION

Retinitis pigmentosa (RP) is a retinal dystrophy that can cause blindness with an approximate prevalence of 1:4000 worldwide (1). At least 80 gene mutations have been described with autosomal dominant (AD), autosomal recessive (AR) or X-linked heredity for RP, and it can also be sporadic with no family history (1). Symptoms and histopathologic findings are similar, although mutation and genetic patterns may be different. The frequent symptoms of RP are nyctalopia, decreased vision, and narrowing of the peripheral visual field. The classic triad is bone spicule pigmentation of the peripheral retina, attenuation in retinal arteries, and optic disc pallor(2, 3). The diagnosis is established through electroretinography (ERG), in addition to clinical findings and symptoms.

Histopathological studies on RP demonstrated decrease in rod and cone cells, and thinning in the outer photoreceptor layer (4, 5). The disease emerges from the mid-peripheral retina where the rod cell intensity is higher, and consequently progress to central retina by affecting the cone receptors. The loss of rod receptors causes nyctalopia, and the loss of cone receptors may cause severe vision loss (2,6).

In other histopathological studies, researchers demonstrated degeneration in the inner retinal layer, particularly ganglion cell loss accompanied by photoreceptor loss in patients with RP (7-9). Transneural damage, narrowing or occlusion in vascular laminae, or axonal compression were suggested as the underlying cause for the degeneration in the inner retina layer secondary to damage in the outer retina layer (3,4,8,10). Gartner et al. suggested that ganglion cell loss might have developed due to glial cell proliferation on and near optic disc in patients with progressive disease and optic disc pallor (11). Another cause of ganglion cell damage in patient with RP could be the direct effect of up to 80 gene mutations on the cell life (1, 9).

Glaucoma is a disease that progresses with the loss of retinal ganglion cells, and ultimately results in characteristic optic disc and visual field abnormalities (12-15). There are two dominant theories in the mechanism of damage due to glaucoma. The first is the mechanical compression theory, the other is the vascular theory, which points particularly to impaired peripapillary choroidal perfusion (16, 17).

The retinal nerve fiber layer (RNFL) is primarily composed of the axons of retinal ganglion cells, neuroglia, and astrocytes (12). The loss of axons of retinal ganglion cells may be observed as thinning in the RNFL (14). Optical coherence tomography (OCT), which enables noninvasive, rapid screening of retinal structures in high axial resolution, has been used in the evaluation of the RNFL and ganglion cell loss in many studies in the diseases of the retina and optic nerve (18-28).

The success of new therapeutic treatment methods such as gene therapy, retinal stem cell transplant, and retinal prosthesis implantation on RP is currently limited. One of the reasons may be that these methods mainly target the photoreceptor layer where the main damage develops. In light of OCT-derived information, new treatment methods targeting inner retinal layers in addition to the photoreceptor layer may be required.

The study aim was to evaluate RNFL thickness change in patients with glaucoma which progresses with ganglion cell damage and retinitis pigmentosa which progresses with ganglion cell damage in addition to rod and cone cell damage.

METHODS

The study was carried out at the Ophthalmology Department of Niğde Ömer Halisdemir University Training and Research Hospital in Niğde, Turkey. The study protocol was approved by the Ethics Committee of Nigde Omer Halisdemir University (approval number: 2019/11) and the study was performed in accordance with tenets of the Declaration of Helsinki. The study was explained to the patients and a written informed consent were obtained from the voluntary participants.

The patients diagnosed with retinitis pigmentosa (RP) and the patients diagnosed with early- and late-stage glaucoma were enrolled the study prospectively. The patients were divided into 3 groups; retinitis pigmentosa (group 1), early-stage glaucoma (group 2), and medium- and advanced-stage glaucoma (group 3).

Glaucoma staging was performed based on the mean deviation (MD) value in visual field testing. Patients with MD values > -6.0 were included in the early-stage glaucoma group, and patients with MD values ≤ -6.0 were included in the medium and advanced-stage glaucoma group.

RP was diagnosed with the history of nyctalopia, presence of deteriorated peripheral visual field, decrease in rod and cone amplitude in ERG, and with the observation of characteristic changes in the fundoscopy. Glaucoma was diagnosed with intraocular pressure higher than 21 mm Hg, and evidence of glaucomatous optic nerve head damage in clinical examination and visual field testing. Patients with spherical refractive errors higher than ±6.0 diopters and/or cylindrical values higher than ±2.0 diopters, with too large or too small optic nerve head, patients diagnosed as having diabetic retinopathy and other retinal diseases, with a history of uveitis, patients who underwent intraocular surgery, and patients with a history of previous retinal laser treatment were excluded from the study. In addition, patients under 18 years of age, patients with systemic disease and pregnancy and breastfeeding were not included in the study. Presence of glaucoma or intraocular pressure above 21 mm Hg were also regarded as exclusion criteria for patients with RP. A detailed ophthalmological examination was performed to all patients including the best-corrected visual acuity, anterior segment examination using slit-lamp biomicroscopy, intraocular pressure measurement using Goldmann applanation tonometry, pachymetry, and fundoscopy. All patients' visual field tests were performed using the Humphrey 24-2 visual field test, and optical coherence tomography imaging were performed. Additionally, electroretinography (ERG) was performed for patients with RP.

Cirrus HD-OCT (Software v.6.5, Carl Zeiss Meditec Inc., Dublin, CA) device was used for peripapillary RNFL measurements. Circumpapillary RNFL thickness measurements were calculated from a 3.46-mm diameter circular scan automatically placed on optic disc. The RNFL values of patients were compared with normative database values included in the OCT device software. The RNFL was considered abnormally thin if its value was less than the 5th percentile of the age-related normal value and thick if it was above 95th percentile. For each patient, RNFL thickness in temporal (316-45°), superior (46-135°), nasal (136-225°), and inferior (226-315°) quadrants and for 3 clock hour segments in each quadrant were automatically measured using the OCT device software. The segments in the right eye were labelled from 1 to 12 as clock hours and in the left eye vertically flipped mirror image of this representation was used.

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0 (IBM Corporation, Armonk, NY). Quantitative data were expressed as the means ± standard deviations and and qualitative data were expressed as proportions (%).

RESULTS

Each group consisted of 20 patients, those with retinitis pigmentosa (group 1), early-stage glaucoma (group 2), and medium- and advanced-stage glaucoma (group 3). The total number of eyes included in each group was 40, 28, and 26, respectively.

The mean age in group 1 was 37.4 years (range, 18-73 years), 60 years (range, 35-70 years) in group 2, and 63.1 years (range, 38-71 years) in group 3. Fourteen patients were male and 6 patients were female in group 1, 12 patients were male and 8 patients were female in group 2, and 11 were male and 9 were female in group 3. Average RNFL thickness for the group 1, group 2 and group 3 were 98.7±25.2, 87.1±8.3, 64.5±10.6 µm respectively. Superior mean RNFL thickness for the group 1, group 2 and group 3 were 119.8±35.8, 108.8±12.3, 74.4±15.2 µm respectively. Inferior mean RNFL thickness for the group 1 , group 2 and group 3 were 111.2±34.7, 100.7±17.2, 70.4±20.3 µm respectively. Nasal mean RNFL thickness for the group 1 , group 2 and group 3 were 75.3±19, 70.4±8.5, 58.9±10.1 µm respectively. Temporal mean RNFL thickness for the group 1 , group 2 and group 3 were 87.8 ±27.3, 67.9±11.4, 54.8 ±13.1 µm respectively.

Average RNFL thickening was detected in 12 eyes in the RP group, whereas thinning was only detected in 7 eyes (Table 1). Thinning in at least one quadrant was detected in 45% of the eyes. The thinning was most frequent in the inferior quadrant consisting of 13 eyes (33%). Inferior quadrant thickening was detected in 7 eyes (17%). The second frequent quadrant with thinning was the superior quadrant with a percentage of 20% (8 eyes). No temporal or nasal quadrant thinning was detected in any eyes. Thickening was most frequently detected in the temporal quadrant in 18 eyes (45%). Nasal quadrant thickening was detected in 11 eyes (27%). The thinning was observed most frequently in the 6 o'clock segment (35%, 14 eyes), the thickening was observed most frequently in the 9 o'clock segment (50%). In contrast with the glaucoma group, thickening was detected in 5 eyes in the 7 o'clock segment (inferotemporal segment).

Average RNFL thinning was detected in 3 patients in early glaucoma group (group 2); no average RNFL thickening was detected in any patient in this group (Table 1). The thinning was most frequently observed in the inferior quadrant, the inferior quadrant thinning was present in 8 eyes (28%), and superior quadrant thinning was present in 3 eyes (11%). No thinning was detected in the nasal and temporal quadrants. The temporal quadrant thickening was present in 5 eyes (18%), and the nasal quadrant thickening was present in 1 eye. The thinning was observed most frequently in the 6 and 7 o'clock segments, and the thickening was most frequently observed in the 9 o'clock segment.

In group 3, average RNFL thinning was detected in 20 eyes (77%) (Table 1). Inferior quadrant thinning was detected in 20 eyes, and superior quadrant thinning was detected in 19 eyes. Nasal and temporal quadrant thinning were detected respectively in 3 and 2 eyes. Although temporal quadrant thickening was detected in 2 eyes, no thickening was detected in other segments in this group. The most frequent segment that showed thinning in RNFL was 6 o'clock (18 eyes (69%)) which is followed by 7 and 11 o'clock segments. Although thickening was detected in 3 eyes in the 9 o'clock segment, no thinning was detected in this segment in this group. RNFL segments in middle stage glaucoma, advanced glaucoma and retinis pigmentosa are shown in figure 1.

Table 1. Number of patients with increased or decreased mean and quadrant RNLF thickness in groups

Group	Average RNLF		Inferior Quadrant		Superior Quadrant		Temporal Quadrant		Nazal Quadrant	
	Thickening	Thinning	Thickening	Thinning	Thickening	Thinning	Thickening	Thinning	Thickening	Thinning
1	12	7	7	13	8	8	18	_	11	_
2	_	3	_	8	_	3	5	_	1	_
3	_	20	_	20	_	19	2	2	_	3

RNFL: Retinal nerve fiber layer

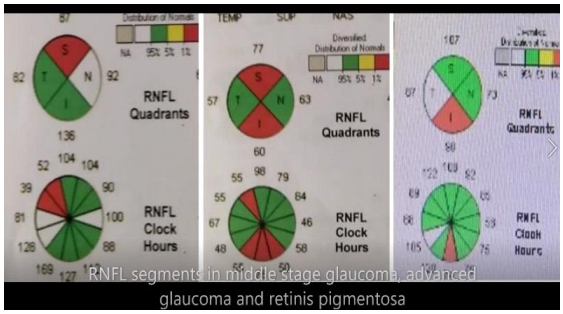

Figure 1

DISCUSSION

In this study we found that RNFL thinning was mostly localized in the vertical meridian and thickening was mostly localized in the horizontal meridian in both diseases. Walia et al. reported RNFL thickness using OCT in patients with RP in their two studies. They reported RNFL thinning in one or more quadrants in 40% of patients in their 2007 study. Although they reported equal rates of thinning in the superior, inferior, and nasal quadrants, no thinning was detected in the temporal quadrant. Thickening was most frequently detected in temporal quadrants. The authors reported RNFL thinning in one or more quadrants in 38.1% of patients in their 2008 study. The most frequent thinning was detected in the nasal quadrant, followed by the inferior quadrant. However, thinning in superior and temporal quadrants was detected in small number of patients. They reported RNFL thickening in 21.65% of patients, and compatible with their previous studies, the temporal quadrant was the most frequently detected region (19, 20). Oishi et al. reported no significant difference regarding RNFL thickness between the normal population and patients with RP in 2009. In their 2013 study, they emphasized that although RNFL thickening or thinning might be detected in patients with RP, RNFL thinning would appear faster in patients with RP compared to the normal population. Therefore, Oishi et al. suggested that abnormal thinning may be detected in longer follow-up of patients with RP or upon investigating only advanced stage patients, yet thickening might not be detected in any patient (21, 22). The authors emphasized that sectoral differences were important and must be investigated during the identification of the location in visual prosthesis implantation, and stem cell transplantation (22). In this study, RNFL thinning was usually detected in the inferior quadrant followed by superior quadrant in RP patients. There was no thinning in the temporal and nasal quadrants. We also found that RNFL thickening was frequently present in the temporal quadrant followed by nasal quadrant.

Yıldırım et al. detected thinning in at least one quadrant in 45% of patients and thickening in at least one quadrant in 48% of patients with RP. Thinning was mostly detected in the inferior quadrant, followed by the superior and nasal quadrant; however, no thinning was detected in the temporal quadrant. Thickening was mostly detected in the temporal quadrant and detected in only 1 patient in the inferior quadrant (18).

In the present study, thinning was most frequently detected in the inferior quadrant, followed by the superior quadrant. No thinning was detected in the nasal or temporal quadrants. Thickening was mostly detected in the temporal quadrant. The other frequent quadrants with thickening were the nasal and superior quadrants. Thickening was mostly in horizontal meridian, whereas thinning was mostly in the vertical meridian. Our study corresponds with the results of the Turkish study by Yıldırım et al. We suggest that similar genetic factors might be effective in these results.

Hood et al. detected thicker RNFL values, particularly in vertical meridians in patients with RP. The authors only reported thinning in the nasal quadrant (23). Hwang et al. in their study in patients with RP, with a mean age of 23 years, detected thickening in 44%; however, no RNFL thinning was detected. They reported that thickening was mainly in the horizontal meridian and was less frequently observed in the vertical meridian (24).

Researchers demonstrated that inner retinal layer degeneration, particularly ganglion cell loss, accompanied photoreceptor loss in patients with RP (7-9). Walia et al. stated that RNFL thickness measurements with OCT and detection of defects in the RNFL in patients with RP would indicate ganglion cell loss. They suggested that RNFL thickening or thinning might be observed after ganglion cell loss in accordance with the course, RNFL became thinner due to loss, and thickening might develop if glial cell proliferation developed secondary to ganglion cell loss (19, 20). Gartner and Oishi supported the opinion that RNFL thickening, particularly in the temporal quadrant, might be associated with glial cell proliferation (11, 21). Hood et al. claimed that in addition to glial cell proliferation, RNFL might be trying to partially cover the empty region that develops due to receptor degeneration by slightly stretching, on the retinal surface for RNFL thickening. Retinal ganglion cells might be widening in places where the RNFL cannot extend (23).

Walia reported that RNFL thinning was maximum in X-linked patients, and measurably lower than AD RP group after expressing the findings revealing that the ganglion cell layer thickness was higher in patients with AD RP compared with patients with X-linked RP in the morphometric analysis study of Humayun et al. (19). Hood suggested that one of the reasons for obtaining different results than Walia and Fishmann might be the different distribution of genetic pattern in their study. X-linked RP was found in 47% of patients and AD RP was observed in 3% patients in the study of Hood, whereas X-linked RP was found in 3% of patients, and AD RP was seen in 25% in the study of Walia (20, 23).

Felipe et al. compared the RNFL thickness of eyes with glaucoma and healthy eyes. A statistically significant thinning was detected in all sectors in eyes with glaucoma except the temporal segment (9 o'clock). The most frequently affected segment was reported to be the inferotemporal segment (7 o'clock), followed by the superotemporal segment (10 o'clock). The thinning was reported to be most frequent in the inferior quadrant in the same study. The authors reported that the papillomacular band was protected until the final stage, after expressing that it was hard to clarify why the temporal segment was not affected (13). Guades et al. found that the most frequent RNFL thinning was present in the inferior section in patients with glaucoma (12).

Karahan et al. found that RNFL thickness was significantly lower in the inferior and superior segments, but no difference was detected in the temporal and nasal quadrants in the glaucoma group compared to healthy controls (17). Leung et al. conducted a progression analysis using OCT in patients with glaucoma in 2010, and reported that progression was most frequently detected in inferotemporal segment (7 o'clock), and the progression was least frequently detected in the temporal segments (8 and 9 o'clock) (29). They also reported that most frequent segment of RNFL thinning was the inferotemporal segment in their 2012 study (30). In our study in glaucoma groups (group 2 and 3) RNFL thinning was seen most frequently in the inferior quadrant followed by superior quadrant. RNFL thinning was found most frequently in the 6 o'clock segment followed by 7 o'clock segment. There were 5 patients with thickening in the temporal quadrant and 1 with thickening in the nasal quadrant in group 2 . There were only 2 patients with thickening in the temporal quadrant and no patients with thickening in the nasal quadrant in group 3. The thickening was most frequently detected in the 9 o'clock segment.

In the present study, RNFL thinning was detected mostly in the inferior quadrant, and then in the superior quadrant in each group. Although there was thickening in these quadrants in the RP group, no thickening was detected in these 2 quadrants in the glaucoma groups. In addition, the thickening was most frequently detected in the temporal quadrant and in 9 o'clock segment in each group. In addition thickening was also found in the nasal quadrant in groups 1 and 2, but no thickening was observed in the nasal quadrant in group 3.

One of the limitations of our study was that we did not identify the hereditary pattern of our patients with RP. One other significant point is that the mean age of the patients with RD was significantly lower. This is due to high prevalence of glaucoma in older age groups, whereas RP is diagnosed earlier. For this reason, we included two glaucoma groups, early and late, in the study for comparison of RNFL changes. Future studies including RP patients with advanced age will increase our knowledge on this topic. One other limitation was that we wanted to investigate the RNFL patterns in these two diseases hence we did not include a normal control group in our study.

CONCLUSION

The results of this study suggest that the RNFL change was a specific response of this layer rather than the disease itself because the RNFL thickening and thinning regions of these 2 diseases were found similar. The horizontal quadrants were less affected and vertical quadrants were more affected regardless of the disease. We hope that there will be a possibility of a significant improvement in the treatment of such diseases when the pathogenetic mechanism underlying ganglion cell loss is completely clarified.

Conflict of interest

No conflict of interest was declared by the authors.

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