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Original research

Glial proliferation and atrophy: Two poles of optic disc in patients with retinitis pigmentosa

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Abstract

Purpose: To clarify the difference of retinal nerve fiber layer (RNFL) thicknesses between patients with retinitis pigmentosa (RP) and normal subjects.
Methods: The study included right eyes of 30 patients with non-late-stage RP, which had a waxy pallor in OD, attenuation in retinal arterioles, and midperipheral bone spicule pigmentary changes. To compare the RNFL analysis with normal subjects, the right eyes of 30 age- and gender-matched healthy subjects were included as a control group.
Results: There were no differences between the RP and control groups in terms of demographic and baseline characteristics ($P > 0.05$, for all). The mean temporal quadrant RNFL thickness was 102.9 ± 31.7 μm (43–222) in the RP group and 72.4 ± 11.8 μm (51–90) in the control group ($P < 0.001$). The mean nasal quadrant RNFL thickness was 57.6 ± 33.7 μm (21–140) in the RP and 75.0 ± 14.1 μm (56–132) in the control group ($P < 0.001$). There were no significant RNFL thickness differences between the groups in other sectors and globally ($P > 0.05$, for all). There was no significant correlation between temporal RNFL thickening and ageing ($r = -0.136$, $P = 0.196$) while there was a significant correlation between nasal RNFL thinning and ageing ($r = -0.274$, $P = 0.047$).
Conclusions: RNFL is thicker in temporal quadrants and thinner in nasal quadrants in non-late stage RP. Age-related decreases in RNFL thickness occurred earlier in the nasal quadrant and RNFL thickening in the temporal quadrant occurred earlier than this global thinning.

Keywords: Retinitis pigmentosa; Retinal nerve fiber layer; RNFL; Retina; Retinal dystrophy

Introduction

Retinitis pigmentosa (RP) is a group of hereditary disorders caused by mutations of genes related to the retina that can be inherited as autosomal dominant, autosomal recessive, X-linked recessive, or isolated. These mutations cause degeneration of the rods, cones, and retinal ganglion cells, respectively.[1] Night blindness, progressive contraction of visual field, and low visual acuity are common symptoms of RP. The concomitance of midperipheral bone spicules pigmentary degeneration, arteriolar narrowing and hyalinization, and a waxy pallor in the optic disc (OD) are known as the classical triad of posterior segment findings of RP.[2]

Retinal pigment epithelium (RPE) cell proliferation, photoreceptor outer segment alteration, and outer nuclear layer irregularity are early histopathological changes occurring before degeneration and the loss of inner retinal segment structures that are preserved until the late-stages of the disease.[3] In RP patients, the changes occurring in the inner retina, peripapillary region, and OD have been studied

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previously with functional tests, but the results are controversial.[4–7] The aim of this study was to clarify the difference of retinal nerve fiber layer (RNFL) thicknesses between patients with RP and healthy subjects.

Methods

This retrospective case control study was carried out from January 2016 to June 2018 at a tertiary referral center. All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki for human subjects.

In the retina department, the medical records of RP patients were retrospectively investigated, and those with no history of other ocular (including uveitis, glaucoma, or neuroophthalmological diseases, etc.) or systemic (including neurological diseases and deafness) diseases, surgery (including cataract, strabismus surgery, or vitrectomy), or drug use that could affect RNFL were included in the study. The patients considered non-complicated early or mid-stage RP patients who met the following inclusion criteria were included in the study: 1) mild or moderately pale appearance of OD; 2) mild or moderately midperipheral bone spicules pigmentary degeneration; 3) between 0.30 and 0.00 logMAR best corrected visual acuity (BCVA) with a spectacles correction; 4) <2 D manifest refraction spherical equivalent; 5) no absolute scotoma or ring scotoma in visual field test and 0 to −2 dB mean deviation; and 6) 200−300 μm subfoveal retinal thickness and no macular edema, cystoid changes and/or epiretinal membranes. According to clinical evaluations, the patients who were considered late-stage RP had severely pale appearance of OD, severely midperipheral bone spicules pigmentary degeneration, <0.30 logMAR BCVA, >2 D manifest refraction spherical equivalent, absolute scotoma or ring scotoma in visual field test, >300 μm subfoveal retinal thickness, macular edema, cystoid changes and/or epiretinal membranes, and were excluded. The patients who had dense cataract, OD drusen, a history of ocular trauma or alcohol addiction, segmentation error in RNFL analysis, and low reliability indices (>15% false positive and false negative responses, and >3 fixation loses) in visual field test were also excluded. To compare the RNFL analysis with healthy subjects, 30 age- and gender-matched healthy subjects who did not have any known ocular diseases except mild nuclear sclerotic senile cataract and <2 diopters refractive error, history of ocular trauma, surgery and drug use, macular abnormality, or systemic diseases that could affect RNFL were included in the study. The same exclusion criteria were also considered in construction of the control group.

Patients with RP were diagnosed on the basis of the presence of night blindness, the classical triad of the disease, and reduced wave amplitude in full field electroretinography (ERG) (Monpack 3, Metrovision, Perenchies, France).[8] All the eyes had midperipheral bone spicules pigmentary changes, attenuation in retinal arterioles, and a waxy pallor appearance of the OD. Humphrey perimeter (Carl Zeiss Meditech, Dublin, CA, USA) was used with the Swedish Interactive Threshold Algorithm (SITA) fast strategy using the 30-2 program to clarify the effects of the disease on the visual field. Absence of OD drusen was verified with B-mode ultrasonography (USG) (Quantel Medical, Cournon-d'Auvergne, France) in patients with RP.

A detailed ophthalmological examination was performed in all cases, including BCVA with Snellen chart (the values were converted to logMAR), intraocular pressure (IOP) with applanation tonometry, biomicroscopy, and dilated fundus examination. An experienced ophthalmologist (M.C.) evaluated optic nerves and retina and served as examiner of stereoscopic fundus photographs. The examiner initially reviewed all photographs. These photographs were independently graded as mild, moderate, or marked optic atrophy on three repeated trials. The photographs agreed consistently as representing mild, moderate, or marked optic atrophy on the three separate trials. In this way, the severity of optic atrophy was graded as, mild, moderate, and severe. This practice is carried out in ophthalmology practice and corresponds to the articles in the scientific literature.[5,9] Similarly, on funduscopic examination, rare and few bone spicules in the middle peripheral retina were classified as mild, prominent and frequent bone spicules in the middle peripheral retina were classified as moderate, and bone spicules in the middle and distant peripheral retina were classified as severe. This practice is also carried out in ophthalmology practice and corresponds to the articles in the scientific literature.[10,11] Macular configuration and peripapillary RNFL thicknesses were examined in all cases using spectral domain optical coherence tomography (OCT) (Spectralis, Heidelberg, Germany) device and Heidelberg Eye Explorer software. The device acquires 40,000 A-scans per second simultaneously and provides qualitative and quantitative information about macular configuration and thickness. Additionally, the system measures RNFL thickness at a 3.4-mm-diameter peripapillary circular area from the center of the optic nerve head. The mean thickness of this zone equals the global measurement and contains temporal and nasal quadrants, and superotemporal, superonasal, inferotemporal, and inferonasal sectors. Fig. 1 shows a report of peripapillary RNFL thickness examination using spectral domain OCT.

Only right eyes of subjects were used for the statistical analysis. The data obtained from the study were analyzed using Statistical Package for the Social Sciences (SPSS) 24.0 software (IBM Corp., New York, USA). Descriptive statistics were presented as mean ± standard deviation and minimum-maximum values. The conformity of the data to normal distribution was tested using the Kolmogorov-Smirnov test. Nonparametric tests were used in the analysis as the numerical data did not conform to normal distribution. The peripapillary six fields and global RNFL measurements of the RP and control groups were compared using the Mann-Whitney *U* test. The correlation between RNFL alterations in RP and

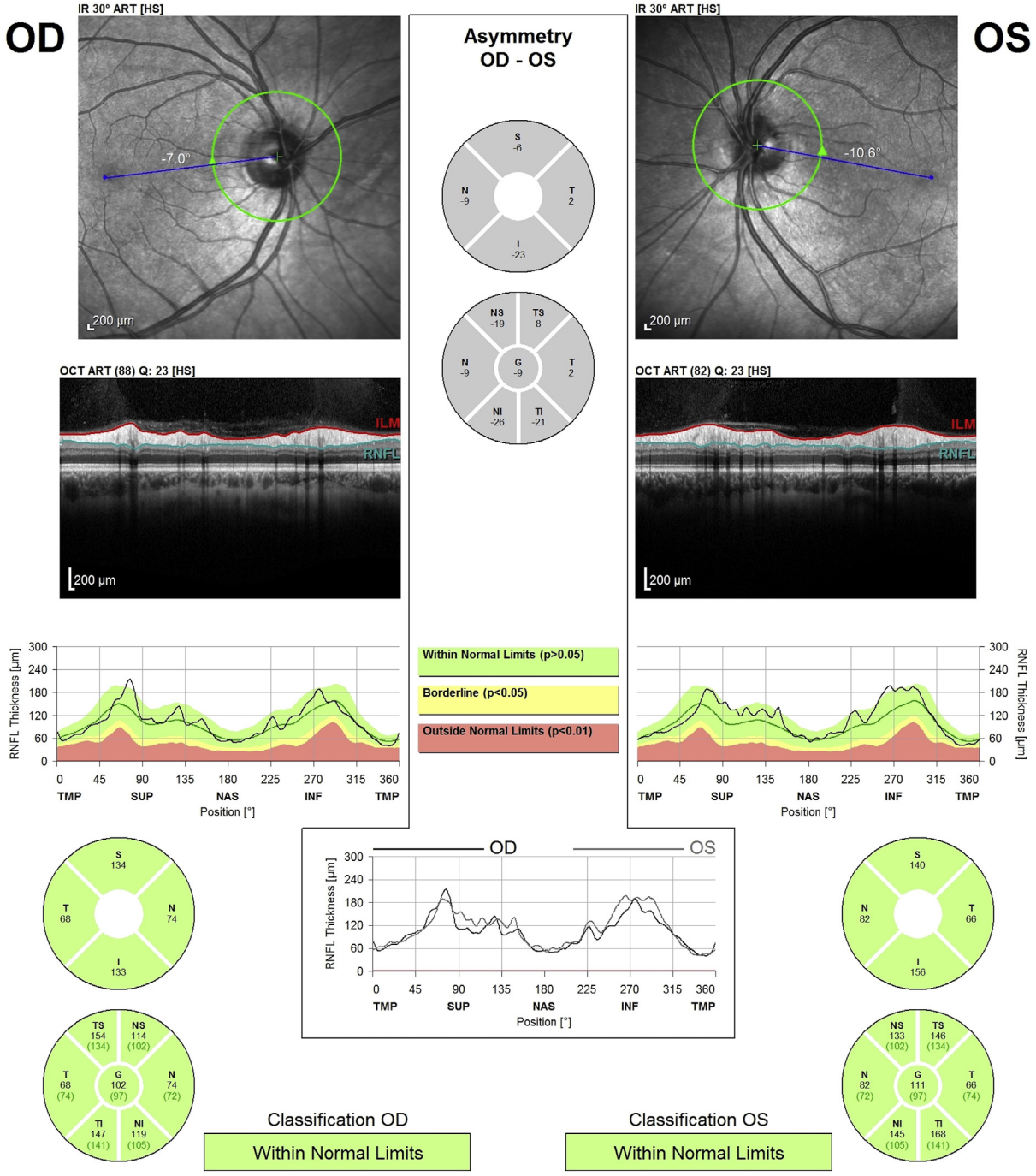

Fig. 1. A report of peripapillary retinal nerve fiber layer thickness evaluation using spectral domain optical coherence tomography (OCT).

ageing was evaluated with the Pearson test. A value of $P < 0.05$ was accepted as statistically significant.

Results

The study included RP (n = 30) and control (n = 30) groups with a mean age of 36.4 ± 18.1 years (range, 8–63 years) and 44.8 ± 17.7 years (range, 11–68 years), respectively ($P = 0.158$). The RP group comprised 17 males and 13 females, and the control group comprised 18 males and 12 females ($P = 0.189$). In the RP group the mean BCVA was 0.19 ± 0.08 logMAR (0.30–0.00), the mean IOP was 13.9 ± 3.0 mmHg (11–18), anterior segment structures were normal, the classical RP triad was present, and the mean subfoveal retinal thickness was 239 ± 25 µm (213–267). In the control group the mean BCVA was 0.23 ± 0.11 logMAR (0.30–0.00), the mean IOP was 14.0 ± 2.2 mmHg (12–17), anterior and posterior segment structures were normal, and the mean subfoveal retinal thickness was 234 ± 21 µm (212–255). No significant difference was determined between

the groups in terms of the mean subfoveal retinal thickness ($P = 0.225$).

The temporal and nasal quadrants, superotemporal, superonasal, inferotemporal and inferonasal sectors, and global measurements of peripapillary RNFL thicknesses of the RP and control groups are presented in Table 1 and demonstrated in Fig. 2. The mean temporal quadrant RNFL thickness was 102.9 ± 31.7 μm (43–222) in the RP group and 72.4 ± 11.8 μm (51–90) in the control group. The mean temporal quadrant RNFL was significantly thicker in the RP group ($P < 0.001$). The mean nasal quadrant RNFL thickness was 57.6 ± 33.7 μm (21–140) in the RP group and 75.0 ± 14.1 μm (56–132) in the control group. The mean nasal quadrant RNFL was significantly thinner in the RP group ($P < 0.001$). There were no significant peripapillary RNFL thickness differences between the RP and control groups in other sectors and globally ($P > 0.05$, for all). When the RNFL analysis of each subject was investigated, it was seen that only 3 of 30 subjects in the RP group had thicker RNFL measurement in the nasal quadrant when compared with the temporal quadrant thickness. This rate was 13/30 in the control group ($P < 0.001$).

To clarify the consistency of RNFL alterations in RP with ageing, the correlation between temporal and nasal RNFL measurements and age were evaluated. Details are given in Table 2. There was no significant correlation between temporal RNFL thickening and ageing ($P = 0.196$). In contrast, there was a significant correlation between nasal RNFL thinning and ageing ($P = 0.047$).

Discussion

An important retinal finding that constitutes the clinical triad of RP is the pale appearance of the OD, which does not always mean OD atrophy. With the exception of the late stages of RP in which the death of neuroglial cells causes the loss of ganglion cell axons, OD atrophy does not occur because the inner retinal layers are preserved until late-stage RP. Therefore, OD atrophy cannot be considered a reason for visual acuity loss or the pale appearance of the OD in patients with non-late-stage RP. There are two theories that explain the presence of a pale appearance of the OD without OD atrophy. The OD has a special structure in the eye globe that is nourished by the branches of paraoptic vessels which arise from short posterior ciliary arteries and enter the sclera. The first theory is that these act as end arteries and there is a watershed zone susceptible to ischemia.[12] Common retinal arteriolar attenuation causes a relative alteration in the OD blood supply and diminishes the natural pink color of the OD and the reddish contrast of reflected light from arterioles. The second theory is that the retinal degenerative process starts from the outer to inner histological layers of the retina causing astrocytic gliosis and the cotton-wool spot-like gliosis makes the OD appear pale yellow-grey or have a waxy pallor. However, OD drusen are known to be not uncommon in patients with RP, and this is a natural course of axonal degeneration, which contributes to the pale-yellow appearance in OD.[13] Finally, an increased risk of glaucoma probably contributes to this appearance if present.[14,15] The first theory is partly supported by the study of Lopez Torres et al.,[16] but there is a need for further testing with advanced imaging methods such as scanning laser ophthalmoscopy. The second theory was examined in this study with analysis of the peripapillary RNFL measurements.

Reports in literature are inconsistent about the peripapillary RNFL thicknesses in patients with RP. Walia et al.[4] stated that there was RNFL thinning in at least one quadrant in patients with RP who have a mild pale appearance of the OD, and this thinning is greater when the OD appears to be moderately or severely pale. The same authors reported RNFL thickening in the same patient group in a later study.[5] Anastasakis et al.[6] stated that peripapillary RNFL can be decreased, increased, or maintained within normal limits in RP. Thickening in RNFL has been explained by the hypertrophic proliferation of glial cells, and thinning in RNFL by retinal ganglion cell degeneration, inner retinal atrophy and nerve fiber loss in several studies.[5,7,17,18] In the current study, significant thickening in the temporal and thinning in the nasal RNFL quadrants was determined in RP. In literature, the temporal and nasal quadrants have been found to be the most prevalent areas of thickening and thinning of RNFL, but no significant reason has been proposed to explain why these quadrants are affected first.[19]

RNFL thinning in the nasal quadrant is positively correlated with age, but this is not new information because it is known that in both RP and control group subjects, RNFL thicknesses are not stable during ageing and they decrease year by year.[20,21] It has been reported that in RP patients, RNFL thickness decreases by 8.3 μm per decade, which is a faster rate than in healthy subjects.[19] In the same way, the increase in RNFL thickness in the temporal quadrant is not consistent

Table 1
The comparison of peripapillary retinal nerve fiber layer (RNFL) thicknesses of the retinitis pigmentosa (RP) (n = 30) and control (n = 30) groups.

	Retinitis pigmentosa (RP) group Mean ± SD (min-max)	Control group Mean ± SD (min-max)	*P* value
Temporal quadrant	102.9 ± 31.7 (43–222)	72.4 ± 11.8 (51–90)	<0.001
Superior temporal sector	146.2 ± 48.2 (54–332)	132.7 ± 15.2 (93–177)	0.075
Superior nasal sector	105.9 ± 42.4 (34–198)	107.2 ± 17.6 (61–136)	0.389
Nasal quadrant	57.6 ± 33.7 (21–140)	75.0 ± 14.1 (56–132)	<0.001
Inferior nasal sector	99.5 ± 49.3 (18–221)	107.6 ± 22.6 (58–167)	0.131
Inferior temporal sector	150.9 ± 48.4 (28–340)	144.0 ± 19.5 (87–180)	0.396
Global	101.7 ± 31.6 (30–224)	98.9 ± 10.1 (82–119)	0.485

SD: Standard deviation.

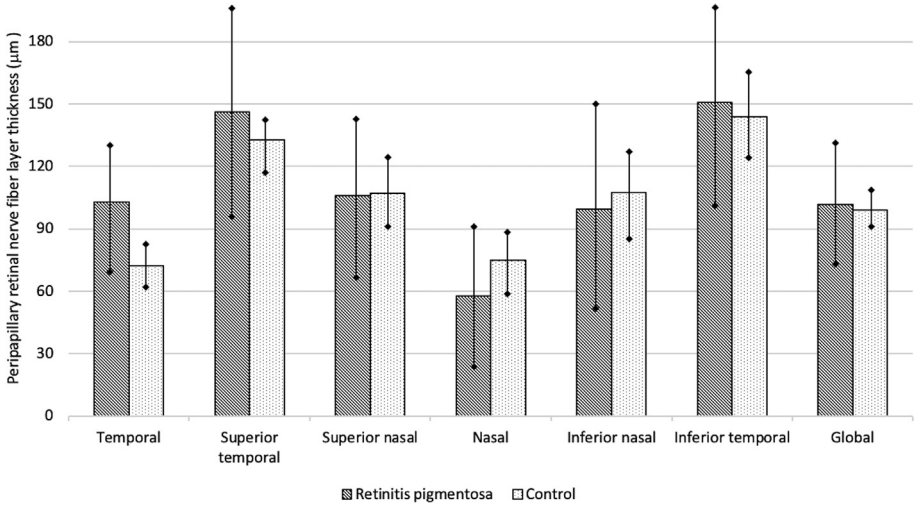

Fig. 2. The temporal and nasal quadrants, superotemporal, superonasal, inferotemporal and inferonasal sectors, and global measurements of peripapillary retinal nerve fiber layer (RNFL) thicknesses of the retinitis pigmentosa (RP) and control groups.

Table 2
The correlation between temporal and nasal retinal nerve fiber layer (RNFL) alterations in retinitis pigmentosa (RP) patients and ageing.

	Retinal nerve fiber layer thickness (RNFL) in temporal quadrant		Retinal nerve fiber layer (RNFL) thinning in nasal quadrant	
	r value	*P* value	r value	*P* value
Ageing	−0.136	0.196	−0.274	0.047

over time. In the current study, it was concluded that in patients with RP, RNFL thinning occurred earlier in the nasal quadrant than in others and that RNFL thickness increased in the temporal quadrant earlier than globular thinning. Nevertheless, further research investigating the longitudinal changes in the RNFL thickness of RP are needed to prove this hypothesis.

In the current study, patients with RP did not undergo any genetic subgroup analyses, and the RP group was not a completely homogeneous group. However, it was attempted to recruit patients with similar clinical findings of similar age and ethnicity, and with similar refractive error, BCVA, retinal findings, visual field test, and ERG results to construct a more homogeneous group. In this regard, this method can be considered an alternative if there is no possibility for genetic subgroup analysis. Nevertheless, this method should be considered a limitation of this study because the thickness alterations in RNFL is different in different genetic subgroups of RP.[22] The results of the samples were investigated and compared according to only one examination, and specific time period changes were not taken into consideration. Although significant differences were determined between the 2 groups, there is no information about the changing curves of these differences, which is another important limitation of the study. Finally, OCT is a non-invasive examination method that reveals the detailed structure.[23] OCT provides the information about the thickness of the retinal layers, but the reasons for alterations in the thickness is still unknown, and the possible reasons can only be hypothesized. There is a need for further research including consecutive examinations of genetic homogeneous larger sample sized groups over a long time period, and the results should be supported via other methods.

In conclusion, compared with healthy subjects, RNFL is thicker in the temporal quadrant and thinner in the nasal quadrant in non-late stage RP patients. The RNFL thickness in these patients decreased with ageing earlier in the nasal quadrant, and RNFL thickening in the temporal quadrant occurred earlier than this global thinning.

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