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Evaluation of Retinal Layers by Optical Coherence Tomography in Patients with Acromegaly

Akromegali Hastalarında Optik Koherens Tomografi ile Retinal Tabakaların Değerlendirilmesi

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Abstract

Objectives: Acromegaly, a rare endocrine disorder caused primarily by growth hormone (GH) secreting pituitary adenomas, leads to elevated levels of growth GH and insulin-like growth factor 1 (IGF-1), resulting in systemic complications and ocular manifestations. These include increased corneal thickness, elevated intraocular pressure, retinal changes, and visual field defects. Spectral-domain optical coherence tomography (SD-OCT) enables high-resolution, noninvasive assessment of individual retinal layers. This technique provides a thickness map of the following seven different retinal layers via automatic segmentation: retinal nerve fibre layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), retinal pigment epithelium (RPE). This study employed SD-OCT to evaluate the thickness of seven distinct retinal layers in patients with acromegaly, addressing a gap in the current literature.

Materials and Methods: This cross-sectional comparative study included patients with acromegaly and age- and gender-matched healthy controls. Data collected included demographics, treatment modalities, disease activity status (remission vs. non-remission), and IGF-1 levels. A single-blinded ophthalmologist performed OCT. The thickness of seven distinct retinal layers was compared between acromegaly patients and controls.

Results: The study included 23 acromegaly patients and 18 healthy controls, with 46 and 36 eyes evaluated, respectively. The acromegaly group exhibited significantly reduced median thicknesses in the RNFL, GCL, IPL, and RPE layers compared to controls ($p<0.05$), while INL, OPL, and ONL showed no differences. Subgroup analysis revealed that INL thickness was significantly greater in non-remission patients than in those in remission ($p=0.022$).

Conclusion: Retinal layer thinning, particularly in the RNFL, GCL, IPL, and RPE, was observed in acromegaly patients compared to healthy controls. Interestingly, patients with active disease had thicker retinal layers than those in remission, suggesting a role for IGF-1 in these changes. As the first comprehensive evaluation of all seven retinal layers in acromegaly, this study highlights the need for further research to clarify these findings and the impact of IGF-1 on retinal structure.

Keywords: Acromegaly, optical coherence tomography, retinal layers, retinal nerve fiber layer, ganglion cell layer

Öz

Amaç: Akromegali, öncelikli olarak büyüme hormonu (BH) salgılayan hipofiz adenomu kaynaklı nadir bir endokrin hastalıktır ve BH ile insülin benzeri büyüme faktörü 1 (IGF-1) seviyelerinin yükselmesine bağlı olarak sistemik komplikasyonlara ve oküler bulgulara yol açar. Bu bulgular arasında kornea kalınlığında artış, intraoküler basınç artışı, retinal değişiklikler ve görme alanı defektleri yer alır. Spektral-domain optik koherens tomografi (SD-OCT), retina tabakalarının yüksek çözünürlüklü, non-invaziv değerlendirmesine olanak tanır. Bu teknikle, otomatik segmentasyon aracılığıyla yedi farklı retina tabakasının kalınlık ölçümü yapılabilir: retinal sinir lifi tabakası (RNFL), ganglion hücre tabakası (GCL), iç pleksiform

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tabaka (IPL), iç nükleer tabaka (INL), dış pleksiform tabaka (OPL), dış nükleer tabaka (ONL) ve retinal pigment epiteli (RPE). Bu çalışmada, akromegali hastalarında literatürdeki bir boşluğu doldurmak amacıyla, SD-OCT kullanarak, yedi farklı retinal tabakanın kalınlığını değerlendirmek amaçlandı.

Gereç ve Yöntem: Bu kesitsel karşılaştırmalı çalışmaya, akromegali hastaları ile yaş ve cinsiyet açısından eşleştirilmiş sağlıklı kontrol bireyler dahil edilmiştir. Demografik özellikler, tedavi yöntemleri, hastalık aktivite durumu (remisyonda veya değil) ve IGF-1 seviyeleri kaydedildi. Tüm OCT ölçümleri, tek bir oftalmolog tarafından yapılmıştır. Akromegali hastaları ile kontrol grubu arasında yedi farklı retinal katmanın kalınlıkları karşılaştırılmıştır.

Bulgular: Çalışmaya 23 akromegali hastası ve 18 sağlıklı kontrol dahil edilmiş; sırasıyla 46 ve 36 göz değerlendirilmiştir. Akromegali grubunda RNFL, GCL, IPL ve RPE katmanlarının medyan kalınlıkları kontrol grubuna kıyasla anlamlı olarak düşük bulunmuştur ($p<0,05$). INL, OPL ve ONL arasında fark gözlenmemiştir. Akromegali hastaları, remisyonda veya remisyonsuz olarak 2 gruba ayrıldığında, INL kalınlığı, remisyonsuz hastalarda anlamlı derecede daha yüksek bulunmuştur ($p=0,022$).

Sonuç: Akromegali hastalarında RNFL, GCL, IPL ve RPE katmanlarının kontrol grubuna göre inceldiği, ancak aktif hastalık grubunda bu katmanların remisyondaki hastalara kıyasla daha kalın olduğu gözlenmiştir. Bu durum, IGF-1'in retinal değişikliklerdeki rolüne işaret etmektedir. Akromegali hastalarında retinal tabakaların ayrıntılı olarak değerlendirildiği ilk çalışma olan bu araştırma ile IGF-1'in retinal yapı üzerindeki etkisini açıklığa kavuşturmak için ek geniş kapsamlı araştırmalara ihtiyaç vardır.

Anahtar Kelimeler: Akromegali, optik koherens tomografi, retinal tabakalar, retinal sinir lif tabakası, gangliyon hücre tabakası

Introduction

Acromegaly is a rare, long-term endocrine condition characterised by excessive secretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), resulting in considerable health complications and increased risk of mortality (1). Acromegaly is nearly always caused by pituitary adenoma, most of which are macroadenomas. The disease's clinical features result from excessively increased GH and IGF-1 secretion. Chronic exposure to excessive GH and IGF-1 leads to increased cellular proliferation, organomegaly, and disturbances in metabolism. Excessive production of GH and IGF-1 in acromegaly also negatively affects the eye and ocular system. The ocular manifestations of acromegaly encompass increased corneal thickness, elevated intraocular pressure, retinal pigmentary degeneration, and visual field (VF) defects resulting from chiasmal compression by a pituitary adenoma (2-5).

Spectral-domain optical coherence tomography (SD-OCT) is a noninvasive imaging technique that captures multiple scans across the retina, producing high-resolution quantitative maps of retinal thickness. Ultrahight axial image resolution of SD-OCT provides quantitative measurement of retinal layers. In this way, instead of measuring the entire retinal thickness, individual measurements of retinal layers can be evaluated in different clinical situations.

Limited research has focused on assessing retinal layer thickness in individuals with acromegaly. This current study utilised SD-OCT to examine the thickness of seven distinct retinal layers among patients diagnosed with acromegaly.

Materials and Methods

This cross-sectional comparative study included 23 patients diagnosed with acromegaly and 18 age- and gender-matched healthy control subjects. The collected data encompassed patients' demographic details, treatment modalities received (surgical and medical therapy including somatostatin agonists and radiotherapy), disease activity status (remission versus non-remission), findings from the most recent pituitary magnetic resonance imaging (MRI), and IGF-1 levels measured during the ophthalmological evaluation. Disease remission was defined as age-adjusted normalisation of IGF-1 levels based on the most recent consensus criteria (6). Exclusion criteria included individuals with chronic ocular conditions (e.g., glaucoma, uveitis, conjunctivitis), significant lens opacities, optic disc anomalies, a history of ocular surgery or laser treatment, and systemic diseases such as diabetes mellitus, hypertension, hypothyroidism, hyperthyroidism, chronic renal failure, hepatic failure, or pregnancy.

Informed written consent was obtained from all participants before the study. The research complied with the principles of the Declaration of Helsinki and was approved by the Ankara Yıldırım Beyazıt University Clinical Research Ethics Committee (date: 28.01.2015, decision no.: 2015-30).

SD-OCT is a non-invasive imaging modality that leverages the principles of low-coherence interferometry to generate high-resolution, cross-sectional visualisations of tissue microstructures. By employing near-infrared light, the technology measures the echo time delay and intensity of backscattered light to construct images with an axial resolution in micrometres. This approach enables the acquisition of volumetric data through sequential cross-sectional imaging, which is subsequently processed to create two-dimensional and three-dimensional reconstructions. In the present study, SD-OCT was utilised to capture detailed anatomical images of the retina. This technique provides a thickness map of the following seven different retinal layers via automatic segmentation: retinal nerve fibre layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer

(INL), outer plexiform layer (OPL), outer nuclear layer (ONL), retinal pigment epithelium (RPE).

The SD-OCT scans were performed with the Heidelberg Eye Explorer (version 6) with spectral mapping software. The retinal layers from each OCT scan were measured (Figure 1). The measurements are derived from the central, inner, and outer ring subfields as outlined by the early treatment diabetic retinopathy study report (7). In this study, we focused specifically on the central subfield measurements (Figure 1).

Statistical Analysis

All participants underwent a comprehensive ophthalmological evaluation conducted by a single ophthalmologist blinded to the case status. The assessment included detailed examinations such as VF testing, auto-refraction, and OCT. Data from both eyes of patients and controls were included in the analysis.

The analysis of data was conducted using SPSS software, version 25.0. Descriptive statistics were expressed as mean ± standard deviation for variables following a normal distribution, while for non-normally distributed variables, median values were reported. Categorical variables were examined using chi-square and Fisher's exact tests, whereas continuous variables were evaluated with Student's t-test and the Mann-Whitney U test. A p-value below 0.05 was regarded as statistically significant.

Results

The study comprised 23 individuals diagnosed with acromegaly (16 women and 7 men) and 18 healthy control participants (11 women and 7 men). A total of 46 eyes from the acromegaly group and 36 eyes from the control group were evaluated. The median age of the acromegaly group was 42 years (range: 27-60), similar to the control group (p=0.072). Comprehensive patient data were documented during the ophthalmological evaluation. None of the patients exhibited VF defects. Among the acromegaly patients, 16 had undergone transsphenoidal adenomectomy, while seven had not. Eleven had received medical therapy, and five had undergone CyberKnife radiotherapy in addition to surgery. The median IGF-1 level in the acromegaly group was 353.5 (99-1454) ng/mL. Disease activity assessments revealed that 17 patients had active disease, while six were in remission. MRI findings showed that four patients had microadenomas, 11 had macroadenomas, and 8 had no residual adenomas.

The acromegaly group exhibited lower median RNFL values compared to the control group [12 µm (7-25) vs. 13 µm (9-17); p=0.028]. In terms of median GCL thickness, the patient group had a measurement of 13 µm (8-55), while the control group measured 17.5 µm (11-34) (p=0.031). The IPL measurement demonstrated a reduction in the patient group compared to the control group [19 µm (14-45) vs. 22 µm (15-34); p=0.026]. Likewise, the RPE measurements were decreased in the patient group compared to the control group [17 µm (12-21) vs. 18 µm (15-23), respectively; p=0.005]. There were no significant differences in the values of INL, OPL, and ONL between the two groups (p>0.05) (Table 1).

We assessed whether retinal thickness varied based on disease activity within the patient group. Subgroup analysis revealed that INL thickness was significantly greater in patients with non-remission, with a median value of 19 µm (range: 9-50), compared to 15 µm (range: 12-29) in the remission group (p=0.022). No significant differences were observed for the RNFL, GCL, IPL, OPL, ONL, or RPE in this subgroup analysis (p>0.05) (Table 2).

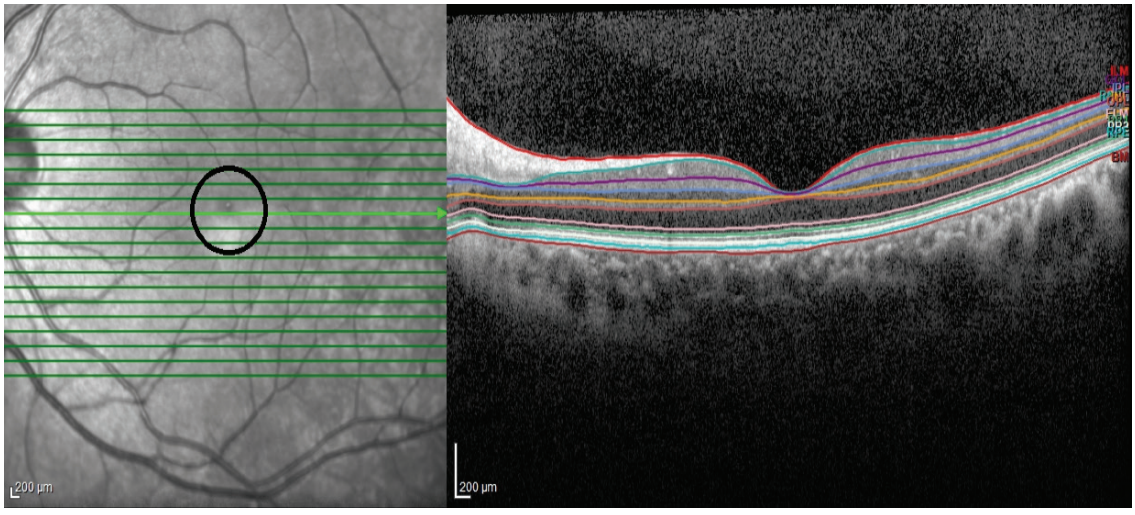

Figure 1: A segmented view of the retinal layers created using the Heidelberg Spectralis automatic segmentation analysis programme. The area within the circle is the central area

Table 1: Comparison of retinal layers in patients with acromegaly and control group

Layers (µm)	Acromegaly patients (n=46 eyes) median (min-max)	Controls (n=36 eyes) median (min-max)	p-value
RNFL	12 (7-25)	13 (9-17)	**0.028**
GCL	13 (8-55)	17.5 (11-34)	**0.031**
IPL	19 (14-45)	22 (15-34)	**0.026**
INL	18 (9-50)	19 (10-29)	0.322
OPL	23 (15-43)	23 (15-35)	0.552
ONL	90 (45-107)	87.5 (59-100)	0.974
RPE	17 (12-21)	18 (15-23)	**0.005**

Bold value: p<0.05
RNFL: Retinal nerve fibre layer, GCL: Ganglion cell layer, IPL: Inner plexiform layer, INL: Inner nuclear layer, OPL: Outer plexiform layer, ONL: Outer nuclear layer, RPE: Retinal pigment epithelium, min-max: Minimum-maximum

Table 2: Retinal layer comparison based on disease remission status in acromegaly patients

Layers (µm)	Non-remission patients (n=34 eyes) median (min-max)	Remission patients (n=12 eyes) median (min-max)	p-value
RNFL	12 (7-25)	11 (7-15)	0.093
GCL	14 (8-55)	11.5 (9-21)	0.112
IPL	20 (14-45)	16.5 (15-24)	0.063
INL	19 (9-50)	15 (12-29)	**0.022**
OPL	25 (17-43)	22.5 (15-26)	0.093
ONL	89 (45-105)	95.5 (72-107)	0.063
RPE	17 (12-21)	16.5 (14-21)	0.745

Bold value: p<0.05
RNFL: Retinal nerve fibre layer, GCL: Ganglion cell layer, IPL: Inner plexiform layer, INL: Inner nuclear layer, OPL: Outer plexiform layer, ONL: Outer nuclear layer, RPE: Retinal pigment epithelium, min-max: Minimum-maximum

When patients were stratified into three groups based on adenoma size (macroadenoma, microadenoma, and no residual adenoma) as determined by MRI during the ophthalmologic assessment, no statistically significant differences were observed across the retinal layers, including the RNFL, GCL, IPL, INL, OPL, ONL, and RPE, with corresponding p-values of 0.28, 0.35, 0.35, 0.55, 0.70, 0.20, and 0.07.

Discussion

Our findings demonstrated that RNFL, GCL, IPL, and RPE thickness were reduced in the acromegaly group compared to the healthy control group. Furthermore, retinal layers were generally thicker in the non-remission group compared to the remission group, with INL being the only layer showing a statistically significant increase in thickness.

GH-secreting pituitary adenomas are very rare and usually present with macroadenoma due to their insidious and slow course. Therefore, chiasma compressions might be seen frequently in acromegaly. Current data on ocular disease and acromegaly are controversial. A few previous studies evaluating retinal thickness in patients with pituitary adenomas have shown that the RNLF was thinner, especially in patients with chiasma compression (8-10). In a recent extensive study, Akay et al. (11) observed that the average RNFL measurements were lower in individuals with acromegaly than healthy controls. Similarly, Şahin et al. (12) reported a reduction in RNFL and IPL thickness in nearly all quadrants in acromegaly patients. These findings were attributed to a greater prevalence of macroadenomas, which are known to compress the optic tracts and optic nerve. In contrast to this attribution, Cennamo et al. (3) reported that RNFL and the ganglion cell complex, comprising the RNFL, GCL, and IPL, were thinner in patients with macroadenoma, even in the absence of optic nerve compression. In the study above, seven patients with macroadenoma had GH-secreting adenomas, six had prolactin-secreting adenomas, six presented with adrenocorticotropic hormone-secreting adenomas, and three had nonfunctional adenomas. In another study, Yazgan et al. (13) reported that RNFL thicknesses were higher in patients with acromegaly than in healthy controls. The authors attributed this surprise result to the fact that most patients were without VF defects. The authors also consider that the direct neuroprotective effects of GH on neurosensory retinal layers might increase retinal volume. In addition, many previous studies have shown no difference between acromegaly and control groups regarding RNFL value (14,15).

Our patients' absence of VF defects suggests that factors other than compression may play a more prominent role in influencing retinal layer thickness in growth hormone-secreting adenomas. Akay et al. (11) reported reduced capillary networks and microvascular atrophy in patients with acromegaly, accompanied by thinner retinal RNFL values compared to controls. This suggests that decreased retinal vascularity may contribute to thinner retinal layers. In the literature, researchers generally focused on the effects of acromegaly on the cornea. In many studies, central corneal thickness (CCT) values were higher in patients with acromegaly than in healthy controls (16,17). Bramsen et al. (17) reported that CCT and intraocular pressure were higher in patients with acromegaly than those with pituitary adenomas, which did not produce GH. These studies indirectly support the IGF-1 effect, which may clarify our study's thicker layers of non-remission patients.

Study Limitations

This study has several limitations. Firstly, the sample size was small, reflecting the acromegaly's rarity, which limits our findings' generalisability. Secondly, the variability in treatment modalities among patients may have influenced retinal layer measurements, introducing potential confounding effects.

Conclusion

In conclusion, our findings suggest that retinal layers were affected in patients with acromegaly, although the precise underlying mechanisms remain unclear. Compared to healthy controls, we observed a reduction in the thickness of retinal layers such as RNFL, GCL, IPL, and RPE in patients with acromegaly. Despite the absence of optic nerve compression in our patients, the thinning of retinal layers implies that factors such as vascular impairment may contribute to these changes. Notably, these layers were thicker in patients with active disease than those in remission, supporting the IGF-1 hormone effect on layers. This study is particularly noteworthy as it is the first to comprehensively evaluate all seven retinal layers in patients with acromegaly. However, given the limited data available in the literature, further extensive studies are warranted to explore these retinal changes and the potential impact of IGF-1 on retinal layers.

Ethics

Ethics Committee Approval: The research complied with the principles of the Declaration of Helsinki and was approved by the Ankara Yıldırım Beyazıt University Clinical Research Ethics Committee (date: 28.01.2015, decision no.: 2015-30).

Informed Consent: Informed written consent was obtained from all participants before the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.E.E.T., N.U., Concept: N.U., Design: B.E.Ö., Ç.K., Data Collection and/or Processing: B.E.Ö., İ.E.E.T., N.U., Analysis and/or Interpretation: B.E.Ö., Ç.K., R.E., B.Ç., Literature Search: B.E.Ö., Ç.K., R.E., B.Ç., Writing: B.E.Ö.

Conflict of Interest: There is no potential conflict of interest to declare.

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