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# Optic nerve head, retinal nerve fiber layer and macular thickness analysis in restless legs syndrome

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ABSTRACT

*Purpose:* The human retina contains dopaminergic neurons within the inner retinal layer. Several studies demonstrated dopaminergic neuronal loss in Parkinson's disease (PD) using optical coherence tomography (OCT). Hypothetically, restless legs syndrome (RLS) may have an underlying dopaminergic mechanism and a probable relation to PD is assumed. Therefore, we aimed to analyze retinal morphology in RLS patients.

*Methods:* In this cross-sectional study we used spectral domain OCT to measure the features of various retinal layers such as thicknesses of peripapillary retinal nerve fiber layer (RNFL), macular and foveal layers, ganglion cell complex (GCC), and optic nerve head parameters of 36 patients with idiopathic RLS, together with 36 age and sex-matched controls. Differences in the thicknesses of RNFL, macula, GCC and optic disc parameters are statistically compared between patients and controls.

*Results:* The average peripapillary RNFL thickness, mean macular volume and total retinal thickness were reduced in RLS compared with healthy controls ($p = 0.032$, $p = 0.029$, and $p = 0.026$, respectively). After Bonferroni correction, only the reduction in the inferior inner and outer quadrants of the macula remained significant ($p = 0.0040$, for both). Optic nerve head parameters (cup volume, cup/disc area ratio, rim area and disc area) and GCC thickness showed no significant difference between patients and healthy controls.

*Conclusion:* Our study revealed significant retinal thinning in the macula region in RLS. Our results may support the dopaminergic dysfunction in the pathogenesis of RLS. Prospective longitudinal studies with a larger sample are needed to corroborate our results.



## 1. Introduction

Restless legs syndrome (RLS) is a common neurological disorder characterized by sensorimotor symptoms, an overwhelming urge to move the legs that worsen with rest, relieved by movement, and often occurs in the evening or at night [1,2]. It usually presents as a primary idiopathic disorder. Secondary forms of RLS are associated with several pathological or physiological conditions including iron deficiency, pregnancy, polyneuropathy, uremia, rheumatic disease and venous insufficiency [2]. The most important factors in the pathophysiology are presumed to be dopaminergic dysfunction and impaired iron homeostasis in the brain [3]. As no substantial degeneration of dopaminergic neurons in the substantia nigra could be shown, degeneration or dysfunction of A11 cell group in diencephalon which has dopaminergic projections to the spinal cord is proposed operative in the pathophysiology of RLS [4,5]. Askenasy was the one who first suggested and introduced the theory of impaired striatal dopamine neurotransmission to the spinal circuits that generate RLS/periodic leg movements of sleep (PLM) [6]. RLS can coexist with Parkinson's disease (PD). Hence, a common pathophysiologic mechanism with PD, namely dopaminergic dysfunction is proposed [4,7].

Optical coherence tomography (OCT) is a fast, cost efficient and noninvasive method which generates cross-sectional images of the retina in vivo. It enables the quantitative estimation of peripapillary retinal nerve fiber layer (RNFL) thickness and measures optic nerve head parameters. OCT also allows obtaining high resolution images of the macular RNFL, ganglion cell layer (GCL) and internal

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plexiform layer (IPL) [8].

Vision is a non-motor sensory function affected by PD [9,10]. Dopamine is released by dopaminergic amacrine and interplexiform cells [11,12]. In PD, a possible reduction or dysfunction of dopamine precursor producing retinal cells may lead to thinning of inner retinal layers [13].

Dopaminergic amacrine cells have been described in the inner nuclear and plexiform layers of human retina close to the ganglion cells [14]. While the inner retina comprises the nerve fiber layer, the ganglion cell layer, and the IPL; other layers starting from inner nuclear layer up to and including the retinal pigment epithelium consist the outer retina [15]. The RNFL represents ganglion cell axons and GCL-IPL is composed of ganglion cell bodies, a network of axons and dendrites from ganglion cells, bipolar cells and amacrine cells [16]. Experimental evidence from humans and monkeys showed that D1 and D2 receptors are essential for retinal ganglion cell receptive field organization [17,18]. Dopaminergic amacrine cells control the tuning of foveal ganglion cells via D1 and D2 linked receptors [17,18]. In PD patients, the intraretinal dopaminergic circuitry and final retinal output to the brain are affected [15].

Some data from experimental work imply an underlying dopaminergic mechanism and probable relation to PD for RLS. Therefore, analyzing retinal changes may give insight into the pathophysiology of this disorder. To our knowledge, up to date, no study has been performed investigating structural alterations in the macular and peripapillary RNFL and the optic nerve head (ONH) changes in RLS. Thus, the purpose of the current study was to investigate the possible structural changes of the retina and optic nerve in RLS patients prospectively.

## 2. Materials and methods

**Patients:** We enrolled 36 consecutive patients with idiopathic RLS and 36 age and sex matched healthy control subjects. All patients were neurologically evaluated by one of the authors (AK). RLS was assessed based on the International Restless Leg Syndrome Study Group (IRLSSG) criteria [19]. Participants meeting four RLS diagnostic criteria recommended by the IRLSSG and had restless legs $\geq$5 times a month were considered to have RLS. The severity of RLS symptoms was assessed using the Turkish version of the International RLS scale. Turkish versions of both the four minimal criteria and IRLSSG severity scale were formerly found to be reliable [20]. We excluded RLS mimicking conditions by detailed medication history, neurological examination and nerve conduction studies.

Subjects diagnosed with RLS attending the neurology outpatient clinic and the healthy controls were referred for ophthalmic evaluation in the Ophthalmology Department. A complete neuro-ophthalmologic examination included best-corrected visual acuity (BCVA), eye movements, pupillary evaluation, slit-lamp biomicroscopy of the anterior segment and fundoscopic examinations by using +78 D noncontact lens, Goldmann applanation tonometry, contrast sensitivity (CS), colour vision and OCT examinations. Each eye was considered separately, and only one eye from each subject was randomly included in the study.

Patients with systemic disorders, neurodegenerative diseases, optic neuropathy or active ophthalmologic disorders associated with media opacities that interfered with imaging processes were excluded. Subjects with any retinal disease (like age-related macular degeneration, retinal artery or vein occlusion), glaucoma, a history of ocular trauma, inflammation or history of an intraocular surgery, presence of significant refractive errors (>5 diopters of spherical equivalent refraction or 3 diopters astigmatism) were also excluded from the study. Three patients with diabetes mellitus, one patient with history of cataract surgery, two patients with fort myopia (above 5 diopters refractive error) were excluded. Patients with secondary RLS, two with end-stage renal disease, five with peripheral neuropathy, one pregnant patient and one with a sleep disorder were excluded from the study. Healthy controls were recruited from hospital staff and family members of healthy subjects.

Best-corrected visual acuity (BCVA) was measured with an Early Treatment Diabetic Retinopathy Study (ETDRS) chart as the logarithm of the minimum angle of resolution (logMAR).

**Colour vision:** Colour vision was evaluated using the Ishihara pseudo-isochromatic plates (24 plates, 2001 edition). The Ishihara test was carried out at 66 cm or arm-length. The maximum viewing time was four seconds per plate. Each error made was recorded. The test was performed at artificial daylight simulating natural one with fluorescent illumination.

**Contrast Sensitivity:** CS is performed with Pelli-Robson chart at 1 m distance and expressed as logarithmic CS. The “letter-by-letter” scoring system was used, whereby each letter was scored as 0.05 log units. Testing ended when the patient missed two of three letters in a triplet. Mean chart luminance was 85 cd/m$^2$.

**Optical Coherence Tomography:** All OCT scans were carried out with a spectral domain Cirrus HD-OCT (Model 4000, software version 6.0; Carl Zeiss Meditec, Dublin, CA, USA). Measurements of the peripapillary RNFL, macula, optic disc and GCL were performed by experienced technicians. Patients with a pupil diameter less than 2 mm received topical mydriatic eye drops. Optic Disk Cube 200 $\times$ 200 scan mode was chosen to derive the optic nerve head (ONH) parameters, including the horizontal and vertical cup-to-disk ratios, and peripapillary RNFL thickness. In each series of scans, mean RNFL thickness, quadrant RNFL thickness (superior, inferior, temporal, and nasal), and thickness at the 12-clock hours of 30° RNFL were analyzed. The hour sectors were assigned a number from position C1 to C12 in the clockwise direction for the right eye and in the counter-clockwise direction for the left eye. Further, Macular Cube 512 $\times$ 128 mode was used to determine the central subfield thickness (CST), cube average thickness, and macular cube volume. GCL-IPL thickness was calculated with the macular cube 512 $\times$ 128 analysis protocol. The macular GCL-IPL thickness was measured within a 14.13-mm$^2$ elliptical annulus area centered on the fovea, which has the following dimensions: vertical inner and outer radius of 0.5 and 2.0 mm, respectively, and horizontal inner and outer radius of 0.6 and 2.4 mm, respectively. The average, minimum, and 6-sectoral (superior, superotemporal, superonasal, inferonasal, inferior, and inferotemporal) GCL-IPL thickness values were obtained from this elliptical annulus. Fig. 1 in the Supplemental Material available online shows a macular cube scan representing the macular segmentation of a RLS patient included in the study. Scans with a signal strength less than 7/10, or with an artifact, were excluded from analyses.

**Ethics:** The study protocol was approved by the local ethics committee. All subjects gave written informed consent to participate.

**Statistical Analysis:** All statistical analyses were performed using SPSS 20.0 (IBM, New York, NY, USA). To describe qualitative characteristics, we used frequency index and chi-square test. Gender distribution between groups was analyzed by chi-square test. Also, the continuous data were presented as the mean value with standard deviation (SD). The normality of the distribution for all variables was assessed by the Kolmogorov-Smirnov test. The means in two groups of variables were compared using independent sample *t*-test. To reveal the correlation between the duration and the severity of the disease, Pearson's correlation test was used. A p value less than 0.05 was considered to be significant. Results of statistical significance were also provided after Bonferroni correction, based on the number of the comparisons within each analysis.