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Original Article

Ocular morphological changes in patients with restless legs syndrome analyzed by optical coherence tomography

Can Kocasarac [a,*], Yavuz Yigit [b], Lynn Marie Trotti [c], Sehnaz Basaran [d]

[a] Department of Ophthalmology, Derince Training and Research Hospital, Kocaeli, Turkey
[b] Department of Emergency Medicine, Derince Training and Research Hospital, Kocaeli, Turkey
[c] Department of Neurology, Emory University, Atlanta, USA
[d] Department of Neurology, Derince Training and Research Hospital, Kocaeli, Turkey

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ABSTRACT

Background: Two leading hypotheses for restless legs syndrome (RLS) pathophysiology are dopaminergic dysfunction and sympathetic overactivity. Ocular changes occur with both dopaminergic and sympathetic pathologies, and thus may provide unique insights into the pathophysiology of RLS.
Methods: Thirty-five patients with RLS and 35 healthy individuals were enrolled in the study. Peripapillary retinal nerve fiber layer (RNFL), macular, and choroidal thicknesses were measured by optical coherence tomography (OCT).
Results: There were no statistically significant differences between the two groups regarding RNFL and macular thicknesses. The subfoveal, temporal and nasal choroidal thicknesses were significantly thinner in patients with RLS compared with normal subjects ($p < 0.05$).
Conclusion: Thinning of the choroid is linked to sympathetic overactivity. Our results provide further evidence for sympathetic overactivity in the pathogenesis of RLS.

1. Introduction

Restless legs syndrome (RLS) is a common neurological sensorimotor disorder characterized by an irresistible urge to move the legs, often with uncomfortable sensations in the legs. Symptoms appear at night or during rest and are relieved by satisfying the urge (ie, moving the legs [1]). Frequently, patients also have motor symptoms such as repetitive leg movements, referred to as periodic limb movements [2]. Untreated RLS may lead to insomnia and fatigue [1].

RLS is generally considered to be a central nervous system disorder, but its pathophysiology is not completely understood. Contributions from genetics and iron deficiency are both well-established [3]. Dopaminergic function has long been implicated in the pathophysiology of RLS. There is a marked improvement in RLS symptoms with drugs that stimulate the dopamine system, and RLS-like symptoms are produced with drugs that block the dopamine system. Based in part on these observations, RLS was long suspected to reflect a state of dopamine deficiency [4]. However, more recent work has suggested regional increases in dopamine more consistent with a state of impaired regulation of dopamine than deficiency per se [5]. Alterations in sympathetic nervous system function are also implicated in RLS pathophysiology, with evidence for sympathetic overactivity [6,7]. Sympathetic overactivity associated with RLS is manifested by an increased pulse rate and blood pressure [6]. It is also found that RLS patients have a tendency toward hypertension during cardiovascular function tests [7].

Optical coherence tomography (OCT) is a relatively new instrument for in vivo observation of ocular tissue thickness. It is a fast, non-invasive optical interferometric method for generating cross-sectional images of the retina that enables quantitative assessment of the thickness of the retinal nerve fiber layer (RNFL) and the macula. With a relatively new technique, EDI-OCT, it also enables measuring the thickness of the choroid. OCT is considered a useful tool for the diagnosis and follow-up of neurodegenerative pathologies like multiple sclerosis [8], migraine [9], Parkinson's disease [10], and Alzheimer's disease [11].

It is now understood that specific changes in ocular structure are seen in association with both dopaminergic and sympathetic nervous system pathologies. In particular, the thickness of the macula and RNFL are reduced in hypodopaminergic states, and the thickness of the choroid is reduced in the presence of sympathetic overactivity [12–18]. Therefore, in this study, we aimed to

* Corresponding author. Derince Egitim ve Arastirma Hastanesi, Goz Hastaliklari Anabilim Dali, Kocaeli, Turkey..
E-mail address: ckocasarac@gmail.com (C. Kocasarac).

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investigate ocular morphological changes in RLS patients to provide further assessment of dopaminergic and sympathetic dysfunction in this disorder.

2. Methods

Between June 2016 and December 2017, 35 consecutive patients with idiopathic RLS and 35 age and sex-matched healthy control subjects were included in our prospective study consecutively. Patients with RLS were evaluated by the same neurologist (SB) and diagnosed using the four essential criteria developed by the International RLS study group. The patients were free of any other neurological disorders; no patients had peripheral neuropathy on examination and mimics of RLS, such as leg cramps and positional discomfort, were excluded. Healthy controls were recruited from the neurology department and were free from RLS and other neurologic diseases. One patient in the RLS group had hypertension; none of the participants had a history of cardiac disease or stroke. All participants underwent a complete ophthalmic examination, including manifest refraction, best corrected visual acuity measurement, axial length measurement, Goldmann applanation tonometry, slit-lamp biomicroscopy of the anterior segment and a detailed fundus examination. Participants were excluded if they had refractive errors of more than ±4 diopters; axial length of more than 25 mm; cataract or media opacity rendering obtainment of reliable retinal and choroidal images impossible; a history of retinal photocoagulation or any other treatment for diabetic retinopathy; previous ocular surgery; the presence of retinal pathology such as glaucoma or age-related macular degeneration; smoking history; and uncontrolled hypertension (>150/95 mmHg) or other systemic complications, as these factors may influence OCT measurements. OCT measurement of all patients was performed using the same OCT device, the Heidelberg Spectralis SD-OCT (870 nm) device (Heidelberg Engineering, Heidelberg, Germany). Participants with a pupil diameter less than 2 mm received topical mydriatic eye drops. Measurements of the peripapillary RNFL, macula, and choroid were performed by the same person (CK). RNFL thickness was measured around the optic nerve head. The Spectralis OCT software, Heidelberg Explorer (HEE, version 5.3; Heidelberg Engineering Co., Heidelberg, Germany), was used for the automatic segmentation of the RNFL (temporal, nasal, inferonasal, superotemporal, superonasal, inferotemporal) and for the calculation of RNFL thickness. Macular thickness was reported in a modified Early Treatment of Diabetic Retinopathy Study macular map with the central foveal subfield which is 1 mm in diameter and the inner and outer subfields having diameters of 3 mm and 6 mm, respectively. Outer subfields were divided into four zones designated as superior, nasal, inferior, and temporal. The numerical values were recorded for each of the nine zones. Enhanced depth imaging (EDI) OCT imaging was performed using a method described previously [19]. A single 30-degree horizontal line scan (approximately 8.9 mm) captures 1536 A-scans per B-scan with 40 averaged B-scans per image, using the automatic averaging and eye tracking features. Measurements were performed perpendicularly from the outer part of the hyper-reflective line (retinal pigment epithelial layer) to the line corresponding to the choroidal-scleral junction, perpendicularly. Choroidal thickness (CT) measurements were recorded under the fovea and at 1500 μm from the foveal center in the nasal and temporal sides. Measurements were performed in the morning between 9 and 11 AM to avoid diurnal variations.

Informed consent was obtained from every participant, and the study was performed according to the declaration of Helsinki. Approval of the Clinical Trials Ethics Committee of Kocaeli University was granted. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) for Windows, version 20.0 (Chicago, IL, USA). Data are expressed as a mean ± standard deviation for continuous variables and as a percent for categorical variables. Normality of distribution was examined by the Kolmogorov–Smirnov test. The Chi-square test was used to see the difference in the frequency of categorical variables in the two groups. The Student's t-test was applied to see the difference in mean in the two groups, with correction for unequal variance when necessary. Results of statistical significance were also provided after Bonferroni correction, based on the number of the comparisons within each analysis. To evaluate whether ocular measures were associated with duration of RLS symptoms, correlations were evaluated using the Pearson correlation coefficient. A p-value less than 0.05 was considered significant.

Table 1
Characteristics of patients.

VARIABLES	RLS (N:35)	CONTROL (N:35)	P VALUE
Age (Years)	46.02 ± 8.05	44.25 ± 7.26	0.337
Gender (M/F)	23/12	18/17	0.225
BCVA	0.81 ± 0.03	0.79 ± 0.02	0.135
Refractive error (DIOPTRE)	0.80 ± 0.03	0.78 ± 0.03	0.061
Axial length (MM)	23.91 ± 0.08	23.92 ± 0.07	0.500
IOP (MMHG)	15.01 ± 0.26	15.00 ± 0.20	0.811
Duration of disease (Years)	5.85 ± 3.93	–	–

3. Results

Thirty-five patients with a diagnosis of RLS and 35 healthy controls were included in our study. Table 1 shows the characteristics of RLS patients and normal subjects. In comparisons between patient and control groups, no significant difference in age, sex ratio, axial length, intraocular pressure, and diopter was found.

RNFL and macular thickness measurements evaluated in the study are shown in Tables 2 and 3. There were no statistically significant differences between the two groups regarding RNFL and macular thickness values.

Table 4 shows the average CT in each location for the two groups. The subfoveal ($p = 0.002$), temporal ($p < 0.001$) and nasal ($p = 0.005$) CT were noted to be thinner in patients with RLS compared with normal subjects. After Bonferroni correction ($p < 0.016$, three comparisons), these differences remained significant. There was no statistically significant correlation between the duration of RLS and CT (Table 5).

We include representative OCT images with RNFL finding, macular map, and CT measurement from one of the RLS subjects in our study (Figs. 1–3).

4. Discussion

This study aimed to analyze the retina, choroid and peripapillary RNFL of patients with RLS for morphological changes consistent with dopaminergic or sympathetic nervous system pathology.

Table 2
Mean ± SD values of RNFL thickness.

Variables	RLS (N:35)	Control (N:35)	p Value
RNFL average	99.22 ± 7.53	100.57 ± 6.17	0.417
RNFL temporal superior	147.54 ± 10.14	149.68 ± 7.27	0.313
RNFL nasal superior	117.11 ± 13.94	122.80 ± 16.92	0.130
RNFL nasal	71.80 ± 13.00	74.94 ± 12.25	0.302
RNFL nasal inferior	105.74 ± 15.03	106.20 ± 17.93	0.908
RNFL temporal inferior	144.80 ± 14.54	147.91 ± 14.05	0.366
RNFL temporal	68.25 ± 6.50	71.08 ± 6.71	0.078

Statistically significant at $p < 0.05$ level. There were no statistically significant differences for RNFL parameters after Bonferroni correction ($p < 0.007$, seven comparisons).

Table 3
Mean ± SD values of macular thickness.

Variables	RLS (N:35)	Control (N:35)	p Value
Macula center	272.05 ± 16.21	276.02 ± 10.36	0.227
Superior inner	356.20 ± 15.02	358.60 ± 14.74	0.502
Temporal inner	343.71 ± 15.94	348.20 ± 10.95	0.175
Inferior inner	342.42 ± 12.78	345.40 ± 9.93	0.282
Nasal inner	348.45 ± 12.67	349.22 ± 7.74	0.760
Superior outer	301.25 ± 7.18	302.05 ± 7.13	0.642
Temporal outer	296.40 ± 10.69	300.68 ± 8.07	0.063
Inferior outer	291.20 ± 5.96	292.57 ± 6.56	0.364
Nasal outer	308.54 ± 13.93	313.77 ± 12.54	0.104

There were no statistically significant differences for macular thickness values after Bonferroni correction ($p < 0.005$, nine comparisons).

Table 4
Mean ± SD values of CT.

Variables	RLS (N:35)	Control (N:35)	p Value
Foveal CT	293.17 ± 39.85	321.91 ± 33.55	0.002
Nasal CT	259.77 ± 65.02	293.05 ± 14.36	0.005
Temporal CT	285.45 ± 55.76	337.20 ± 29.76	<0.001

After Bonferroni correction, there were still significant differences between the subfoveal, temporal and nasal rates of RLS and control groups ($p < 0.016$, three comparisons).

Table 5
Correlation between the duration of RLS and CT.

	RLS duration	
	Correlation coefficient	p-Value
Foveal CT	−0.080	0.649
Nasal CT	−0.151	0.388
Temporal CT	−0.313	0.067

In recent articles, sympathetic overactivity is strongly linked to the pathophysiology of RLS [6,20]. Several large epidemiologic studies have demonstrated that RLS is associated with prevalent cardiovascular disease (CVD) and laboratory studies have shown the accompanying periodic limb movements of sleep to be associated with increases in pulse rate and blood pressure [6,21,22]. Clemens et al., forwarded the hypothesis that the clinical aspects of RLS and the association between RLS and CVD, including hypertension, rests on the dopaminergic A11 neurons in the dorsoposterior hypothalamic region [23]. The authors speculated that a low level of dopaminergic availability, either caused by functional or anatomic aberrations, may result in the disinhibition of somatosensory and sympathetic pathways. The other theory generated by Clemens and Rye and elaborated by Walters and Rye is that a loss of dopaminergic effect at the spinal cord level in RLS leads to enhanced serotonergic drive with resultant increased sympathetic output, vasoconstriction, hypertension, CVD, and stroke [6,23].

Retinal blood flow might change due to autoregulatory mechanisms, but for variations in choroidal blood flow to occur, there is a need for the involvement of autonomic nerves. The choroid has a rich autonomic nerve supply where sympathetic nerves originate in the superior cervical sympathetic ganglion. Steinle JJ investigated regional regulation of choroidal blood flow by autonomic innervation in the rat and reported that sympathetic stimulation decreased flux in all regions in the choroid [24]. Dadaci et al., studied healthy pregnant women and reported a significant decrease in CT in the third trimester due to vasoconstriction related to the increased adrenoreceptor activity and higher a1-adrenoreceptor concentration in this period [18]. Xin et al., evaluated choroidal thickness in adults with obstructive sleep apnea-hypopnea syndrome (OSAS) and reported that a sympathetic nervous system regulation disorder exists in OSAS patients because of alternating hypoxia and arousal, which is followed by changes in the structure of the normal choroid [16]. Celikay et al., reported CT decreased after hemodialysis in patients with end-stage renal disease and suggested that sympathetic activation triggered by blood volume depletion to prevent hypotension might cause choroidal vascular and nonvascular smooth muscle constriction, which leads to a decrease in CT [17]. To our knowledge, this is the first study investigating CT in RLS patients. We found significant thinning of the choroid which supports the hypothesis of sympathetic overactivity in RLS patients. CT was found to be thinner as the duration of the disease increases, but it did not reach statistical significance. This result may be due to the relatively small sample size.

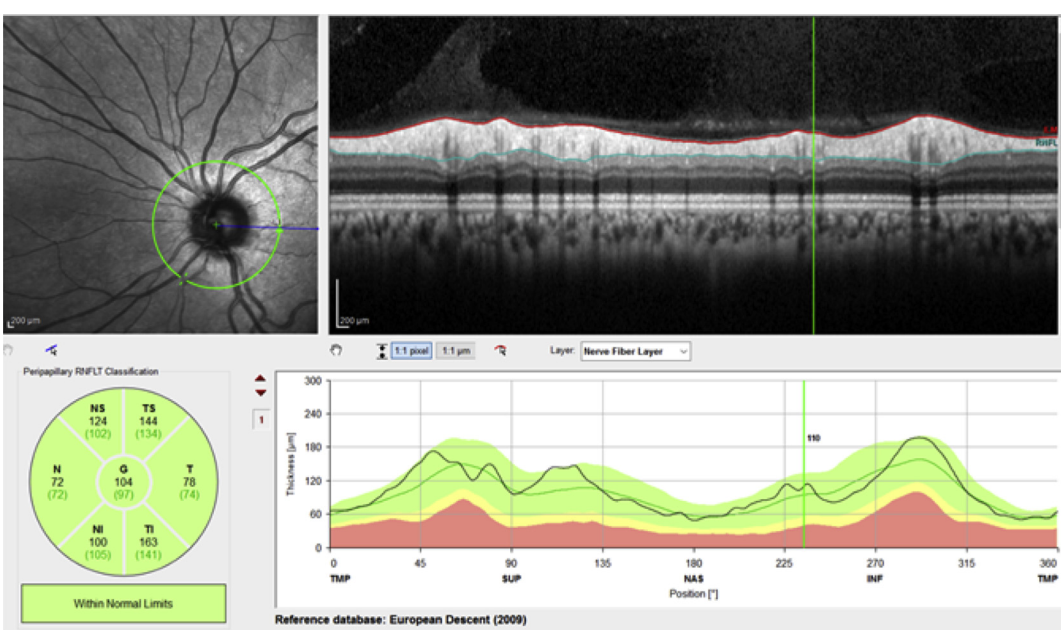

Fig. 1. RNFL thickness measurement. Abbreviations G, Average thickness; TS, Temporal Superior; T, Temporal; TI, Temporal Inferior; NI, Nasal Inferior; N, Nasal; NS, Nasal Superior.

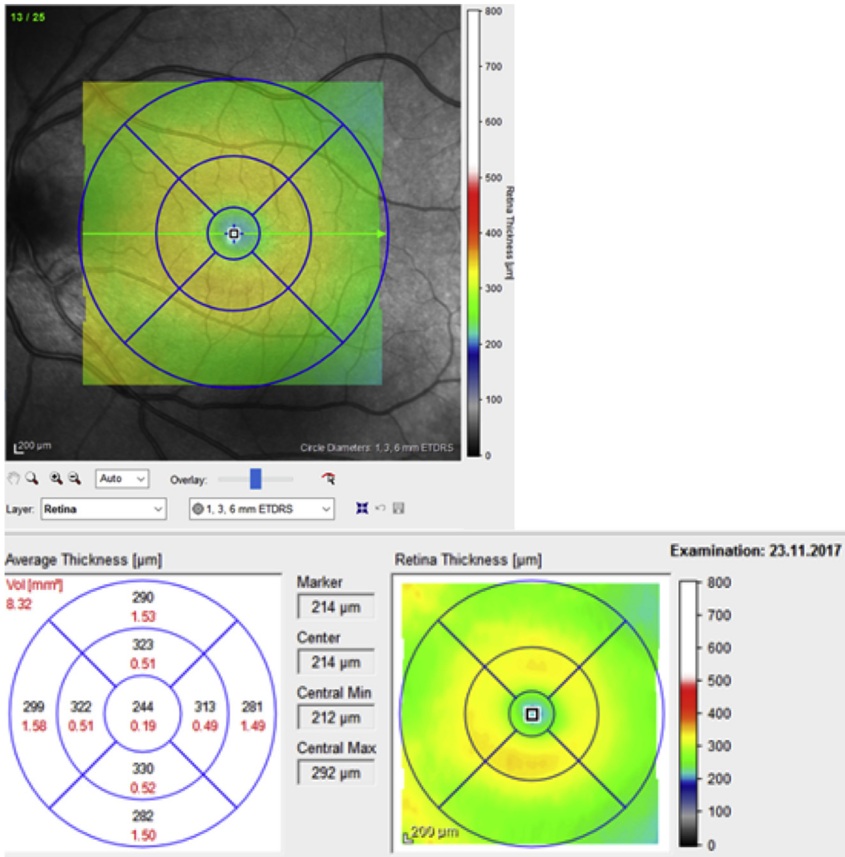

Fig. 2. Macular thickness measurement.

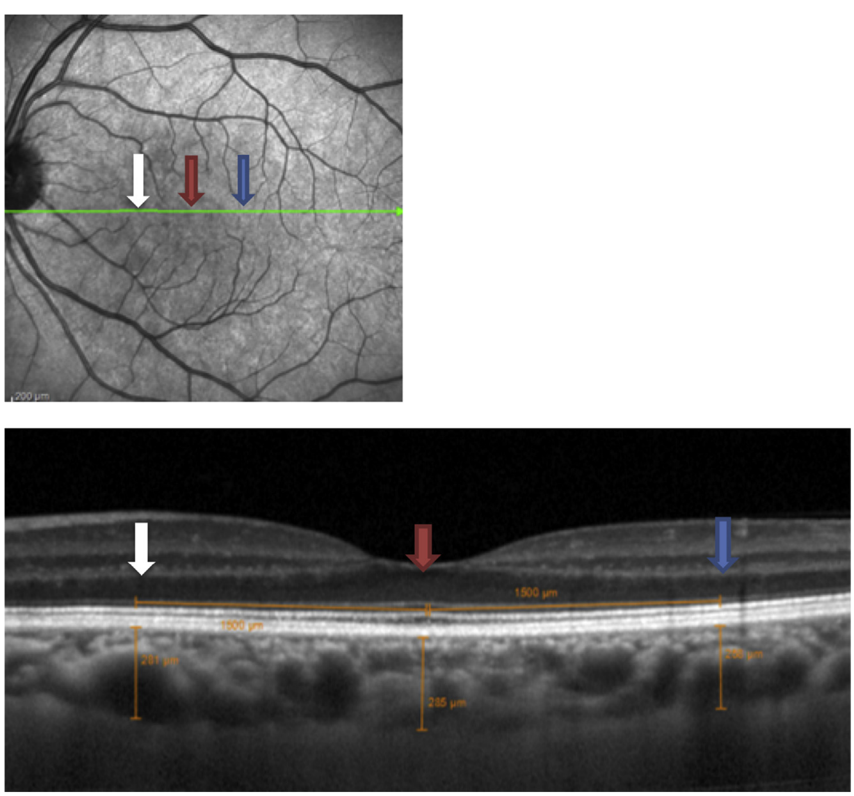

Fig. 3. Choroidal thickness measurement. Choroidal thickness of the macula was measured at the foveal center (red arrow), 1.5 mm temporal to the foveal center (blue arrow), and 1.5 mm nasal to the foveal center (white arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Unlike the observed changes in choroidal thickness, we did not find differences in RNFL or macular thicknesses between RLS patients and controls. This lack of difference is in contrast with the work of Koskderelioglu et al., who reported significant retinal thinning in the macula region of RLS patients in a similarly-sized study (36 RLS patients and 36 healthy controls) [25]. Although the methodology was similar between these two studies, relatively small sample sizes in both might account for this discrepancy. RNFL and macular thickness have been extensively studied in the context of Parkinson's disease, and thinning of these regions is generally thought to reflect a hypodopaminergic state [10,12,13,15] Our lack of association between RNFL and macular thicknesses and RLS diagnosis may underscore that the dopaminergic dysfunction is different in RLS and PD.

Our study had some limitations. Due to resource constraints, we were not able to measure periodic limb movements of sleep in RLS patients. Periodic limb movements are themselves associated with sympathetic hyperactivity and so should be included in further studies of CT and RLS [26]. The other limitation is that there is a possibility of measurement errors of CT due to manual measurements. Nonetheless, recent studies found high repeatability, high interobserver correlation and intervisit reproducibility in CT measurements [27,28] Furthermore, one limitation of our study is the small sample size. However, we had strict inclusion criteria to eliminate confounding factors. Despite these limitations, we have shown that choroidal thickness is significantly reduced in RLS patients compared to controls, providing further evidence for sympathetic overactivity in this disorder. Subfoveal, nasal, and temporal CT may be useful data in understanding the pathogenesis of RLS, and with future longitudinal studies with larger patient groups, it might be used for the diagnosis and follow-up of patients with RLS.

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Conflict of interest

The authors declare that they have no conflict of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.01.024.

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