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Do you have restless leg syndrome? I understood from your eyes

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Abstract

Purpose According to many studies in the literature, there is a strong association between restless leg syndrome and dopaminergic dysfunction. Dopamine is also the major catecholamine in the retina and is also a possible transmitter of the amacrine and interplexiform cells. The aim of this study is to investigate the possible association between RLS and retinal thickness.

Methods In this study, we included 33 patients who were diagnosed with idiopathic RLS according to the "International RLS Study Group" criteria and 31 healthy subjects. All the patients and controls underwent routine ophthalmologic examination and had spectral-domain optical coherence tomography (OCT) performed. We compared the retinal thickness of the patients and control subjects.

Results In the RLS group, foveal thickness was thinner then controls. Also, only inferior, superior, and temporal quadrant retina nerve fiber layer (RNFL) thickness were significantly thinner in the RLS group. The parafoveal ganglion cell complex (GCC) in the superior temporal, inferior temporal, inferior nasal quadrant, and perifoveal superior nasal thickness was also significantly thinner in the patient group. Pearson correlation analyses showed that there were statistically significant negative correlations between disease duration and macular GCC and RNFL thickness. Negative correlations were also detected between parafoveal superior, temporal, inferior and nasal macular thickness, parafoveal superior nasal, inferior temporal GCC thickness, and perifoveal superior nasal GCC thickness and disease duration.

Conclusion According to our results; most retinal layers are thinner in RLS patients, so it can be considered that OCT has a predictive value for progression of RLS.

Keywords Restless leg syndrome · OCT · Retinal thickness

Introduction

Restless leg syndrome (RLS) is a common disease which occurs in the lower extremities, defined by an urgency to move the legs, usually combined with uncomfortable or unpleasant sensations, especially at night and when resting [1]. Most of the time, patients cannot clearly describe this abnormal sensorineural feeling [2]. As a result of this abnormal feeling, the patient wants to move his/her legs compulsively. Symptoms begin at rest and decrease with movement, and the occurrence of the above features not solely accounted for as symptoms primary to another medical or a behavioral condition is the other diagnostic criterion for RLS [3]. The prevalence of RLS is 10–15%, and it is well known in the literature that RLS is an important cause of insomnia and other sleep disorders like periodic leg movement (PLM) [4].

The pathophysiology of RLS is not known clearly. An autopsy study found that, in RLS patients, dopamine 2 receptor levels are significantly decreased in the putamen and also tyrosine hydroxylase levels are increased in the substantia nigra [5]. Dopaminergic dysfunction is supported by other studies; in a SPECT study post-synaptic D2 receptor density and affinities were decreased in this population [6]. Similarly, a PET study showed that absorption of dopamine in the nucleus caudatus and putamen is decreased compared with healthy subjects [7]. There are other findings which support dopaminergic dysfunction in RLS; for example, dopamine agonists improve the symptoms of RLS and dopamine antagonists worsen the symptoms [8].

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Dopamine is the major catecholamine in the retina and is also a possible transmitter of the amacrine and interplexiform cells. Dopamine is used by the retinal neurons so it is very important for pigment epithelial functions. Both dopamine synthase and dopamine catabolizing enzymes exist in the retina, and biochemical and pharmacological studies show that dopamine receptors which exist in the retina are same as dopamine receptors which exist in the brain [9–11].

Optical coherence tomography (OCT) is a non-invasive method which shows the intensity of infrared light in the ~ 800 nm wavelength reflected back from the biological tissue layers and the reflection delay time. OCT provides two- or three-dimensional high-resolution axial images (8–15 μm). It allows examination of the retina nerve fiber layer (RNFL), retina layer, and retina pigment epithelia, in addition to optic disc and macula [12].

Retinal nerve fiber layer thickness is a very important indicator of some syndromes; it shows axonal degeneration in the neuronal retinal layer in the early period of illness. In diseases with degeneration of dopaminergic neurons like idiopathic Parkinson's disease (IPD), the RNFL thickness of the IPD population is significantly decreased compared with controls in some studies. According to this result, the authors claimed that this could be an early indicator of IPD [13, 14].

To our knowledge, there is only one study about the possible association of RLS and RNFL thickness. The aim of this study is to investigate the possible association between RLS and RNFL thickness.

Material and method

Study design

Our study was completed at Trakya University medical faculty, departments of neurology and ophthalmology between January 7, 2016, and January 1, 2016. The local ethics committee approved the study and all participants signed the informed consent form. During the study period, Helsinki declaration criteria were applied.

Study population

In this study, we included 33 patients who were diagnosed as having idiopathic RLS with clinical interview by a neurologist, according to the "updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria" [2]. Among these 33 subjects, 20 of them were using medications for RLS (18 of them dopa agonist pramipexole, 2 of them pregabalin) but not using any other medications (like antidepressant, antihypertensive, antidiabetic). The IRLSSG severity scale questionnaires were completed for patients who had all symptoms of this syndrome. The questionnaire included ten questions. The response to each item provided a total score of 0–40. Based on this questionnaire and severity of the disease, the patients were divided into four groups of mild (0–10), moderate (11–20), severe (21–30), and very severe (31–40) RLS. The severity of RLS symptoms was assessed using the Turkish version of the International RLS scale [15]. Turkish versions of both the four minimal criteria and IRLSSG severity scale were found to be reliable in previous studies [16]. These consecutive patients were followed up in our clinic and had RLS for at least 1 year. The 34 controls who were completely healthy, had no systemic, neurological, or ophthalmological diseases or surgery, used no medications, and were similar to the patient group in terms of age and gender were chosen from volunteer hospital staff or patient's healthy relatives. After a detailed neurological and ophthalmological examination, the patient's symptom duration, drug use and other sociodemographic data were noted. All participants also had blood glucose levels, complete blood count, renal and hepatic function tests, ferritin levels and thyroid function tests performed and evaluated with appropriate methods.

The exclusion criteria were having comorbid diseases which can cause RLS or be confused with RLS like diabetes mellitus, polyneuropathy, lumbosacral radiculopathy, iron-deficiency anemia, or thyroid dysfunctions (hypo- or hyperthyroid). Also, patients who had ophthalmological problems like glaucoma, retinopathy or retinal surgical history, or macular degeneration were excluded from the study. All patients underwent full ophthalmological examination including best-corrected visual acuity, intraocular pressure measurement (NT-4000 Auto Non-Contact Tonometer, Nidek, Japan), biomicroscopic anterior segment, and fundus examination. In addition to routine ophthalmologic examination, spectral domain OCT (RS-3000 Lite, Nidek, Japan) was performed.

Retinal imaging

Macular thickness, ganglion cell complex (GCC) thickness, and peripapillary RNFL thickness were measured using OCT. Parameters for the statistical analysis of the macular thickness were evaluated in the following areas: central 1 mm of the macular area (fovea), 1–3 mm of the parafoveal macular area (superior, inferior, nasal, temporal quadrants), and 3–6 mm of the perifoveal macular area (superior, inferior, nasal, temporal quadrants). Parameters for the statistical analysis of the GCC thickness were evaluated in the following areas: 1–3 mm of the parafoveal macular area (superior nasal, superior temporal, inferior nasal, inferior temporal quadrants) and 3–6 mm of the perifoveal macular area (superior nasal, superior temporal, inferior nasal, inferior temporal quadrants). The disk map protocol was used to evaluate peripapillary RNFL. The peripapillary area was evaluated in the following areas: superior, nasal, inferior, and temporal quadrants.

Statistical analysis

The "SPSS (Statistical Package for Social Sciences) 15.0 for Windows" program was used for statistical analysis in this study. The chi-squared test was used to compare the qualitative data, including symptoms and results of the physical examination. Prior to performing calculations on the non-qualitative data, the Kolmogorov Smirnov test was used to determine the conformity of the data with normal distribution. The nonparametric "Mann-Whitney U" and "Kruskal-Wallis" tests were used, while the parametric "Student *t* test" and "unilateral variance analysis" (ANOVA) tests were also used. Pearson correlation analyses were completed for disease duration and severity. The results are presented as mean ± standard deviation for numeric values and as "*n*" and "%" for the qualitative values. Values of $p < 0.05$ were accepted as significant.

Results

There were 62 patient eyes (female 42, male 20) and 68 control eyes (female 36, male 32) included in the study. Thirteen of the 33 patients were not using any medication for RLS due to different reasons: 5 of them were not using medication due to various side effects, 8 of them were newly diagnosed patients (these patients had RLS symptoms for at least 1 year). Twenty patients were using different medications; 18 of them were using dopa agonists (pramipexole) and 2 of them were using pregabalin. Average ages of RLS and control group were 56.09 ± 10.9 and 55.29 ± 11.2 years, respectively. There were no significant differences between groups in terms of age and gender ($p = 0.5$, $p = 0.1$, respectively). The average duration of RLS was 4.9 ± 3.3 years, and the average IRLS severity scale score was 23.8 ± 7.0 (Table 1).

The foveal thickness was 230.40 ± 23.538 μm in the RLS group and 264.47 ± 17.711 μm in the control group; the difference between the two groups was statistically significant ($p = 0.023$).

Only inferior, superior, and temporal quadrant RNFL thickness were significantly thinner in the RLS group ($p = 0.005$, $p = 0.005$, $p = 0.017$ respectively). Retinal measurements for patients and controls are shown in Table 2. The parafoveal GCC in the superior temporal, inferior temporal, inferior nasal quadrant, and perifoveal superior nasal thickness were significantly thinner in the patient group ($p = 0.004$, $p = 0.044$, $p = 0.033$, $p = 0.050$, respectively).

Pearson correlation analyses showed that there were statistically significant negative correlations between disease duration and macular, GCC and RNFL thickness. There were negative correlations between parafoveal superior, temporal, inferior and nasal macular thickness, parafoveal superior nasal, inferior temporal GCC thickness and perifoveal superior nasal GCC thickness (Table 3).

Additionally, there was a significant negative correlation between disease severity and OCT parameters. There were negative correlations between parafoveal superior temporal, superior nasal and superior, inferior temporal GCC thickness and disease severity. Interestingly, foveal thicknesses were similar in both RLS subjects who used medication and who did not use medication ($p = 0.109$).

Discussion

In our study, we identified significant thinning of the foveal thickness, of the parafoveal GCC in superior temporal, inferior temporal, and inferior nasal areas, and of the RNFL in the inferior and temporal quadrants in the RLS patient group. There were negative correlations between parafoveal superior, temporal, inferior and nasal macular thickness, parafoveal superior nasal, inferior temporal GCC thickness and perifoveal superior nasal GCC thickness and disease duration identified. When assessed according to disease severity, as the disease severity increased, there was a reduction identified in the thickness of parafoveal superior temporal GCC thickness and perifoveal superior nasal, superior temporal and inferior temporal GCC thickness.

Table 1 Socio-demographic data of patient and control groups

	RLS group ($n = 33$)		Control group ($n = 34$)	*p*
Age	56.09 ± 10.9		55.29 ± 11.2	0.5
Gender (f/m)	23/10		24/10	0.1
RLS duration	4.9 ± 3.3			
IRLS score	23.8 ± 7.0			
RLS medications	$n = 20$ Pramipexole ($n = 18$) Pregabalin ($n = 2$)	$n = 13$ No medication		0.11
Foveal thickness	230.40 ± 23.538 μm		264.47 ± 17.711 μm	0.02

RLS restless leg syndrome, *IRLS* International Restless Legs Syndrome Rating Scale, *f* female, *m* male, *μm* micrometers

Table 2 Comparisons of retinal layers between restless leg syndrome patients and controls

	Patients ($n = 62$ eyes)	Control ($n = 68$ eyes)	p value
Central macular area	230.40 ± 23.538	264.47 ± 17.111	*0.023*
Parafoveal macular area			
Temporal	325.65 ± 19.881	325.46 ± 12.897	0.189
Nasal	340.97 ± 18.268	337.75 ± 12.782	0.243
Superior	300.76 ± 13.371	299.29 ± 15.097	0.822
Inferior	333.97 ± 22.447	335.69 ± 13.431	0.592
Perifoveal macular area			
Temporal	284.27 ± 28.549	285.21 ± 13.721	0.810
Nasal	312.24 ± 15.886	311.87 ± 13.087	0.883
Superior	300.76 ± 13.371	299.29 ± 15.097	0.561
Inferior	292.63 ± 19.002	288.16 ± 12.931	0.117
Parafoveal GCC			
Superior nasal	115.61 ± 9.935	117.25 ± 7.774	0.295
Inferior nasal	114.13 ± 12.621	118.04 ± 7.718	*0.033*
Superior temporal	107.42 ± 11.493	112.26 ± 7.206	*0.004*
Inferior temporal	109.42 ± 11.688	113.09 ± 8.838	*0.044*
Perifoveal GCC			
Superior nasal	110.31 ± 8.676	113.12 ± 7.703	*0.050*
Inferior nasal	110.19 ± 9.924	112.26 ± 8.748	0.208
Superior temporal	90.89 ± 9.430	92.62 ± 6.622	0.225
Inferior temporal	110.19 ± 9.924	112.26 ± 8.748	0.210
Retinal nerve fiber			
Temporal	65.03 ± 14.906	70.46 ± 10.361	*0.017*
Nasal	78.47 ± 19.348	78.88 ± 10.502	0.878
Superior	133.20 ± 21.486	135.84 ± 16.544	0.450
Inferior	125.28 ± 25.683	136.85 ± 19.901	*0.005*

GCC ganglion cell complex

To our knowledge, there is only one study on this topic in recent times [17]. This study compared 36 RLS patients with 36 healthy controls and assessed the thickness of the optic nerve head, RNFL, and macula. The authors identified statistically significant thinning of the RNFL in the inferior temporal quadrant in the RLS patient group, while they reported there was no difference between the two groups in terms of GCC. Furthermore, the authors detected thinning of the foveal thickness. However, the difference was not significant statistically. In our study in addition to thinning of the RNFL in the inferior temporal quadrant, we identified thinning of the GCC in some quadrants correlated with the disease severity and duration. We also detected significant thinning of the foveal thickness. Koskderelioglu et al. study did not evaluate the association between dopaminergic drug use and foveal thickness, but in our research, there was no association between dopaminergic drug use and foveal thickness. Although our sample size is small, it can be speculated from our results that dopaminergic medication use does not impact the foveal thickness in RLS patients. This may be explained by the fact that dopaminergic medications do not impact the pathogenesis of RLS, they may only be suppressing symptoms but there is still a level of speculation.

Though the pathophysiology of RLS is not fully known, many studies have focused on dopamine and iron metabolism. In an autopsy study accepted as showing the dopamine disruption in RLS directly in humans for the first time, there was a clear reduction identified in dopamine 2 receptors in the putamen of RLS cases [5]. In addition to dopamine metabolism disruption in the basal ganglion, it is considered that there may be disruption of the spinal neuron functions in RLS. In these patients, the increased cord excitability and the resulting increased flexor reflex activity have been shown clinically [18]. In short, it is considered that RLS occurs due to disrupted functions of the dopaminergic neurons in the basal ganglion changing sensorimotor activity in the spinal cord. As dopamine is one of the major catecholamines in the retina and with the determination that the dopaminergic receptors in the retina and brain are the same, retinal studies related to Parkinson disease (PD) which includes dopamine dysfunction in the pathophysiology have come to the forefront.

Table 3 Correlations between disease duration, disease severity and OCT parameters

Correlations	*p*	*r*
Disease severity GGC3mmST	0.03	0.28
Disease severity GGC6mmSN	0.02	0.33
Disease severity GGC6mmST	0.03	0.27
Disease severity GGC6mmİT	0.03	0.27
Disease duration RT3mmS	0.01	0.33
Disease duration RT3mmT	0.0001	0.55
Disease duration RT3mmİ	0.008	0.33
Disease duration RT3mmN	0.0001	0.55
Disease duration GGC3mmSN	0.02	0.28
Disease duration GGC3mmİT	0.07	0.23
Disease duration GGC6mmSN	0.013	0.32

Disease severity measured by "International Restless Legs Syndrome Rating Scale"

GGC3mmST parafoveal ganglion cell complex superior temporal, *GGC6mmSN* perifoveal ganglion cell complex superior nasal, *GGC6mmST* perifoveal ganglion cell complex superior temporal, *GGC6mmİT* perifoveal ganglion cell complex inferior temporal, *RT3mmS* parafoveal retinal thickness superior, *RT3mmT* parafoveal retinal thickness temporal, *RT3mmİ* parafoveal retinal thickness inferior, *RT3mmN* parafoveal retinal thickness nasal, *GGC3mmSN* parafoveal ganglion cell complex superior nasal, *GGC3mmİT* parafoveal ganglion cell complex inferior temporal, *GGC6mmSN* perifoveal ganglion cell complex superior nasal

First, Inzelberg et al. [19] revealed there was thinning of the inferiotemporal RNFL in PD. Another study of PD patients without visual interaction found the mean inferior and temporal RNFL thickness was significantly lower in patients compared to control subjects [20]. A meta-analysis study of 13 studies reported that there was a significant thinning especially in the temporal quadrant RNFL in PD [21]. When these results are assessed with other studies on the topic [19, 20, 22, 23], it is considered that RNFL is affected more by PD and other neurodegenerative diseases in accordance with involvement of the papillomacular bundle of the temporal fibers especially. Dopaminergic dysfunction is a common problem in both RLS and PD pathophysiology, so it can be considered that in RLS patients retinal findings may be similar to PD retinal findings although still controversial for RLS and Parkinson's disease, in our study of RLS patients significant thinning was identified for RNFL in the inferior and temporal quadrants, as in PD.

In PD apart from the RNFL, the macula was assessed and different results were obtained. A study by Mailankody et al. [24] reported a significant reduction in the central macular thickness in PD and they identified a negative correlation with disease severity. Another study including 101 PD patients identified that the macular volume was lower compared to a control group [13]. Similarly, Bittersohl et al. [14] identified significant thinning of the central macular area in PD. In our study, in accordance with the literature, there was a significant degree of thinning identified in the central macular (fovea) thickness in the RLS cases compared to the control group. Additionally, there were negative correlations identified between parafoveal superior, temporal, and inferior and nasal macular thickness with the disease duration.

Amacrine cells releasing the major catecholamine in the retina of dopamine are defined as inner nuclear and plexiform cells adjacent to ganglion cells [25]. When the retina of vertebrates is stimulated by light, dopamine is released by amacrine cells to allow a neural adaptation to light. Ganglion cells and axons that synapse with these amacrine and bipolar cells comprise the optic nerve. The synaptic structuring of the changes in the receptive fields of ganglion cells and the degree of their susceptibility to dopaminergic degeneration is not known in detail

[26, 27]. A previous study of PD demonstrated reductions in the macular RNFL, the ganglion cell layer (GCL), the inner plexiform layer (IPL), the inner nuclear layer, and the outer plexiform layer, but only the GCL predicted axonal damage in PD patients. Additionally, in the same study the GCL thickness displayed an inverse correlation with disease duration and severity [28]. A review study of the use of OCT for neurodegenerative diseases stated that these changes in the inner retinal area may be a strong biomarker for diagnosis and progression of PD [29]. In our study, the parafoveal GCC in the superior temporal, inferior temporal, and inferior nasal quadrant thickness were significantly thinner in the patient group. Again, a negative correlation was determined between the thickness of the GCC cell layer and the disease duration and severity.

In conclusion; in the recent period the use of OCT to monitor progression and prognosis of neurodegenerative diseases like PD has become a focus. There has been limited research into the retinal changes in RLS, known to be related to dopamine metabolism. In our study, we showed the presence of some retinal changes in RLS patients and that these are correlated with the duration and severity of disease. Analysis of the macular thickness and retinal nerve fiber layer with OCT can be beneficial in follow-up of RLS progression.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers' bureaus, membership, employment, consultancies, stock ownership, or other equity interest, and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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