Evaluation of Optical Coherence Tomography Results and Cognitive Functions in Patients with Restless Legs Syndrome

Ali Zeynal Abidin TAK¹ , Mustafa ÇELİK² , Aysun KALENDEROĞLU² , Sadullah SAĞLAM³ , Yaşar ALTUN⁴ ,
Emre GEDİK¹

¹Adiyaman University School of Medicine, Department of Neurology, Adiyaman, Turkey

²Adiyaman University School of Medicine, Department of Psychiatry, Adiyaman, Turkey

³Free neurologist, Adiyaman, Turkey

⁴Adiyaman University Training and Research Hospital, Department of Neurology, Adiyaman, Turkey

ABSTRACT

Introduction: The aim of this study was to evaluate whether retinal neural network was impaired and cognitive functions were disturbed in restless legs syndrome (RLS) considering the hypothesis that there may be a dysfunction in dopaminergic pathways in RLS like in Parkinson's disease. Therefore, we evaluated retinal neural network with optical coherence tomography (OCT) and presence of cognitive impairment with Montreal Cognitive Assessment (MOCA).

Methods: OCT evaluations were performed for 30 RLS patients and 30 healthy controls. Ganglion cell complex was segmented to retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and inner plexiform layer (IPL) automatically by the device, and recorded. Additionally, all the patients and the controls were evaluated using MOCA.

Results: No statistically significant difference was detected between RLS and controls in RNFL, GCL, IPL, and choroidal thicknesses. However,

total MOCA score and all of its subscale scores were significantly lower in the RLS patients compared with the controls. No significant correlation was detected between OCT and MOCA parameters.

Conclusion: No degeneration was detected in retinal neurons (RNFL, GCL, and IPL) of RLS patients. However, impairments were seen in MOCA total and subscale scores of these patients. On the other hand, no significant correlation was detected between MOCA scores and RNFL, GCL, or IPL thicknesses. These findings suggest decrease in cognitive functions of RLS patients probably due to dopaminergic dysfunction regardless of anatomical neural degeneration. Longitudinal follow-up studies are warranted to evaluate whether neuronal degeneration will develop.

Keywords: Restless legs syndrome, optic coherence tomography, cognition

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INTRODUCTION

Restless leg syndrome (RLS) is a chronic, progressive movement disorder, also known as Willis-Ekbom disease, characterized by the urge or need to move the legs, characterized by abnormal sensations (1). It is seen with a frequency ranging from 0.25% to 15.3% in studies conducted using international diagnostic criteria, it is more common in women and its frequency increases with age (2). International Restless Legs Syndrome Study Group (IRLSSG 2014) international diagnostic criteria for HSB have been established, and all four essential criteria are required for a definitive diagnosis (3). RLS can be seen alone or in combination with certain diseases such as peripheral polynoropathy, diabetes mellitus, renal failure, Parkinson's disease, or the use of certain drugs such as antiepileptics and antidepressants (4). Today, dopaminergic system has been shown to play an important role in the pathophysiology of RLS (5). Dopaminergic activity increases in the morning and decreases in the early hours. This fluctuation is thought to be similar to the daily rhythm in RLS, and dopaminergic activity decreasing at night is thought to cause symptoms (5, 6). In addition, it has been shown that Parkinson's disease and RLS can be seen together and there are studies suggesting that dopaminergic

dysfunction is common in the common etiopathogenesis (7). In retinal physiology, the main neurotransmitter of the photoreceptors responsible for vision was glutamate, and neurotransmitters such as serotonin, dopamine, GABA, glycine, acetylcholine and taurine were detected in amakrin cells. However, their functions are not fully understood (8). In particular, dopamine is known to play a role in retinal function, but it is not clear how dopaminergic deficiency may affect the retina. For example; In Parkinson's disease, the first evidence of dopaminergic deficiency has been the demonstration of decreased tyrosine hydroxylase immunoreactivity in dopaminergic cells in the retina (9). Furthermore, dopamine is one of the most important neurotransmitters that play a role in many symptomatology such as impaired cognitive functions (10). On the other hand, there are studies indicating that chronic and partial sleep disorder seen in RLS may affect prefrontal brain functions and decrease cognitive functions (11).

Optical coherence tomography (OCT); It has become a noninvasive, rapid method for measuring optic nerve head parameters such as retinal nerve

fiber layer (RNFL), macular layer (MT) and volume (MV) and Ganglion cell complex (GCC) in recent years (12). In recent years, OCT has been used as a possible diagnostic tool in the investigation of many neurodegenerative diseases with progressive, diffuse brain involvement (13). Demonstration of myelin loss in the retina with OCT has been evidence in favor of degeneration (14). Thus, retinal layer degeneration has become an important anatomical structure that we can follow.

In this study; Based on the hypothesis that RLS may be impaired in dopaminergic pathways, as in Parkinson's disease, we planned to evaluate whether retinal neural network is affected in RLS and whether these patients have impaired cognitive areas. Therefore, we aimed to determine the retinal nerve structure with OCT in patients with RLS and whether there is cognitive impairment with the Montreal Cognitive Assessment (MOCA) scale.

METHODS

This is a prospective case study comparing the patient group with restless leg syndrome and the control group. Thirty patients (16 males, 14 females) who were diagnosed as primary restless legs syndrome according to IRLSSG 2014 diagnostic criteria (3) consisted of women and men aged 18–55 years followed by our outpatient clinic (16 M, 14 F) was included in the study. Socio-demographic characteristics (age, gender, marital status, etc.) of both groups were analyzed. Routine biochemistry examinations of all patients were performed. The patients and control groups who had secondary restless leg syndrome such as iron deficiency, renal dysfunction, diabetes mellitus, multiple sclerosis, rheumatologic diseases, hypertension, any metabolic disease, epilepsy, stroke and malignant disease were not included in the study. In addition, cases with additional psychiatric disorders were excluded from the study. MOBID scale was applied to the case and control groups. MOCA; It has been developed as a rapid screening test for mild cognitive impairment

and evaluates various cognitive functions such as attention, executive functions, memory, language, visual structuring skills, abstract thinking, calculation and orientation (15). It was adapted to Turkish and validity and reliability studies were conducted (16). MOCA-scale memory tasks, close memory recall, learning five words (2 times) and recalling after 5 minutes (5 points); tasks related to visual-spatial functions, clock drawing evaluation (3 points) and three-dimensional cube (1 point); tasks associated with executive functions, combining consecutive digit and letter arrays (such as 1-A, 2-B, 3-C) adapted from the tracing test-B form (1 point); verbal fluency (1 point) and two abstract thinking tasks (2 points), attention, concentration and working memory tasks, sequential subtraction (3 points), and forward and backward (1 point), language-related tasks, pictures of three little-known animals (lion, rhino, camel) definition (3 points), repetition of two difficult sentences to pronounce (2 points) and finally awareness of place and time (6 points). The lowest score in the test is 0 points and the highest score is 30 points. MOCA total and sub-parameter scores of patients and controls were compared. MOCA was accepted as a cut-off value of less than 21 points for cognitive impairment (16). Ophthalmologic examinations were performed in the ophthalmology clinic of both cases and control groups; best corrected visual acuity (BCVA), intraocular pressure, slit-lamp biomicroscopy, and dilated eye examination were completed. Patients with normal ocular findings and control group were included in the study. OCT was performed by the eye clinic of our hospital in both groups. Choroidal thickness measurements and mean values were performed by the same physician. In addition, the sub-parameters of the retinal nerve fiber layer (RNFL) layer, ganglion cell layer (GHT) and inner plexiform layer (IPT) were measured and recorded by segmentation of the ganglion cell complex. The study was approved by the ethics committee of our university. Signed consent was obtained from both groups regarding their participation in the study.

Figure 1. Retinal nerve fiber layer (RNFL) measurement. A) The appearance of the optic nerve. B) Cross-sectional view of RNFL. C) Segmentation of RNFL. D) RNFL thickness map.

Figure 2. Segmentation of the ganglion cell complex: Retinal nerve fiber layer (RNFL), ganglion cell layer (GCL) and inner plexiform layer (IPL).

OCT

By calculating the reflection delay time and intensity of infrared light at a wavelength of ~ 800 nm, which is directed back to the tissues and reflected back from the different tissue layers, it allows the cross-sectional images of the tissues and their pathologies to be obtained by a method similar to B-scan ultrasound but with much better resolution (17). Heidelberg Engineering Announces 85,000 Hz OCT2 Next Generation SPECTRALIS OCT Module was used to record the measurements of RNFL, choroidal structure of the right and left eye from three regions and their mean, GHT and IPT structures. The RNFL layer is composed of temporal (T) and nasal (N) main segments. These are considered as superior quadrant (TS, NS) and inferior (TI, NI) quadrants. Separate layers for both eyes were measured and analyzed. As a result, a total of 12 sites were analyzed from six sites (N, NS, NI, T, TS, TI) in the right and left eyes, and the RNFL mean of both eyes (Right mean and left mean) was also compared (Figure 1). Ganglion cells in the retina consist of three layers; Retinal nerve fiber layer (RNFL) consisting of ganglion cell axons, ganglion cell layer (GHT) consisting of the bodies of ganglion cells, inner-plexiform layer (IPT) of dendrites of ganglion cells (Figure 2). All three layers together are called ganglion cell complex (GCC) (18). The other structure we compare with OCT is choroidal thickness. The subfoveal choroidal thickness was measured by the OCT software by manually measuring the distance from the outer border of the retinal pigment epithelium to the choroid-sclera border of a line perpendicular to this border. Measurements were performed at three different points from the fovea and fovea to nasal and temporal distances up to 1500 µm at 500 µm intervals (Figure 3). In our study, we measured the thickness of the choroidal structure from three different regions and averaged and looked for differences between the two groups.

Statistical Method

Mean, percentage distribution and frequency analysis were used as qualitative statistics. Fisher's exact chi-square analysis and Pearson chi-square test were used to compare the numbers. Kolmogorov-Smirnov test was used for normal distribution of values. Mann-Whitney U test was used for non-normal distribution ($p < 0.05$). Mann-Whitney U test

Figure 3. Choroidal thickness measurement by spectral optical coherence tomography. A subfoveal perpendicular line was drawn to the choroid-sclera junction on the outer edge of the retinal pigment epithelium. Two more lines were drawn from the nasal and temporal sides at 500 micrometer intervals from this line. The mean of these three measurements was accepted as choroidal thickness.

and Kruskal-Wallis variance analysis were used for nonparametric values. Spearman rank correlation analysis was used to correlate nonparametric values. A p value of < 0.05 was accepted for statistical significance. SPSS 21.0 program was used for statistical analysis of the data (Version 21.0, Microsoft Co., Chicago, IL, USA).

RESULT

Thirty patients with restless legs syndrome (RLS) and 30 control groups participated in our study. Sociodemographic datas were similar in both groups. The mean age of the patients with RLS was 37.40 ± 10.15 and 16 of them were male (53.3%) and 14 of them were female (46.7%). The mean age of the control group was 35.73 ± 9.36 , and 16 were male (53.3%) and 14 were female (46.7%). The mean education level of the RLS group was 10.78 ± 4.77 years and the mean education level of the control group was 11.86 ± 3.80 years. RNFL, GHT, IPT and choroidal thicknesses between the patients with RLS and control group are shown in Table 1, and no

Table 1. OCT Parameters of Patient and Control Group with RLS

OCT Parameters	Group	Number (N)	Mean±SD	P value
RNFL				
TS Right	Patient	30	144.40±19.42	p=0.717
	Control	30	142.80±14.15	
T Right	Patient	30	70.86±14.07	p=0.774
	Control	30	71.73±8.59	
Ti Right	Patient	30	144.73±23.55	p=0.711
	Control	30	146.70±16.73	
NS Right	Patient	30	111.96±19.83	p=0.290
	Control	30	117.16±17.81	
N Right	Patient	30	83.03±12.92	p=0.619
	Control	30	84.73±13.36	
Ni Right	Patient	30	125.60±18.39	p=0.663
	Control	30	123.10±25.31	
Right Mean	Patient	30	105.30±7.39	p=0.531
	Control	30	103.83±10.39	
TS Left	Patient	30	138.36±21.24	p=0.555
	Control	30	141.20±15.19	
T Left	Patient	30	69.50±13.13	p=0.700
	Control	30	70.60±8.33	
Ti Left	Patient	30	144.13±25.23	p=0.895
	Control	30	143.36±19.03	
NS Left	Patient	30	120.30±18.14	p=0.130
	Control	30	127.83±19.76	
N Left	Patient	30	78.16±77.13	p=0.734
	Control	30	77.13±13.48	
Ni Left	Patient	30	123.23±17.83	p=0.554
	Control	30	127.06±30.41	
Left Mean	Patient	30	101.60±9.64	p=0.255
	Control	30	104.13±7.23	
GCL				
GCL Right	Patient	30	1.15±0.08	p=0.235
	Control	30	1.17±0.07	
GCL Left	Patient	30	1.14±0.09	p=0.193
	Control	30	1.17±0.07	
IPL				
IPL Right	Patient	30	0.93±0.06	p=0.639
	Control	30	0.94±0.05	
IPL Left	Patient	30	0.93±0.06	p=0.387
	Control	30	0.94±0.06	
CHOROID				
Choroid Right	Patient	30	353.86±66.92	p=0.672
	Control	30	362.88±94.90	
Choroid Left	Patient	30	361.18±72.64	p=0.764
	Control	30	367.64±92.06	

GCL, ganglion cell layer; RLS, restless leg syndrome; IPT, inner plexiform layer; RNFL, retinal nerve fiber layer; T, temporal; TI, temporal inferior; TS, temporal superior; N, nasal; NI, nasal inferior; NS, nasal superior; OCT, optical coherence tomography; SD, standard deviation.

Table 2. MOCA Score Comparison of Patient and Control Groups

MOCA Sub Parameters	Group	Number (N)	Mean±SD	P value
Naming	Patient	30	2.83±0.37	p=0.00
	Control	30	2.96±0.18	
Abstract Thinking	Patient	30	1.46±0.73	p=0.000
	Control	30	1.86±0.34	
Recall	Patient	30	3.16±1.20	p=0.057
	Control	30	3.76±0.67	
Tendency	Patient	30	5.83±0.46	p=0.000
	Control	30	6.00±0.00	
Visuospatial functions	Patient	30	3.86±1.07	p=0.000
	Control	30	4.46±0.34	
Attention	Patient	30	4.96±1.44	p=0.019
	Control	30	5.36±0.80	
Language	Patient	30	2.00±0.94	p=0.002
	Control	30	2.7±0.43	
Total	Patient	30	24.13±4.21	p=0.000
	Control	30	27.60±1.83	

MOCA, Montreal Cognitive Assessment; Average, average; SD, standard deviation.

Table 3. Correlation of OCT parameters with total score of MOCA.

		RNFL mean left	RNFL mean right	GCL right	GCL left	IPL right	IPT left
MOCA Total	r	-0.44	-0.165	-0.196	-0.227	-0.75	-0.223
	p	0.740	0.207	0.134	0.082	0.569	0.086

GCL, ganglion cell layer; IPL, inner plexiform layer; MOCA, Montreal Cognitive Assessment; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer.

statistically significant difference was found between the two groups ($p > 0.05$). However, it was found that the total score and sub-parameters of the MOBID scale applied to the patient and control groups were significantly decreased compared to the control group ($p < 0.05$) (Table 2). When we look at the correlation between MOBID scale and Right RNFL, Left RNFL, Right GCL, Left GCL, Right IPL and Left IPL in the patient group, respectively; $r = -0.044$ $p = 0.740$, $r = -0.165$ $p = 0.207$, $r = 0.196$ $p = 0.134$, $r = 0.227$ $p = 0.082$, $r = 0.075$ $p = 0.569$, $r = 0.223$ $p = 0.086$ and no significant relationship could be detected. ($p > 0.005$) (Table 3).

DISCUSSION

Although many hypotheses have been mentioned in RSL such as dopaminergic hyperstimulation, iron deficiency, and densification of dopamine receptors in the tubero-infundibular area, its pathophysiology is not yet clear (19). In recent clinical and neuroimaging studies, both presynaptic and postsynaptic abnormalities have been shown in dopamine receptors of the basal ganglia (20). These findings suggest that RLS is not a peripheral disorder but a pathology of the central nervous system (CNS) (8). The presence of similar system disorders in both Parkinson's disease and patients with HBS and the fact that patients respond to dopaminergic agents led to the mention of common pathophysiology (19). In human retina and ganglion cells, dopamine plays a role as modulator (21). Therefore, OCT has been used frequently in recent years to show possible retinal degeneration in neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease and multiple sclerosis (22). In studies on OCT in Parkinson's disease, there are studies showing that the RSLT layer and some sub-segments have significant thinning, and there is also a correlation with the severity of the disease (23). The studies on OCT in patients with RLS are insufficient and to our knowledge, there is only one study and In this study; it was showed

significant thinning in RNSLT and total retinal layer compared to controls, but no significant difference was found in ganglion cell complex (RNSLT + GHT + IPT) compared to controls (24). Unlike this study, in our study; No significant difference was found in RSLT layer and lower segments compared to controls ($p > 0.005$) (Table 1). Thinning of the RSLT layer in the retina is caused by axonal degeneration. However, it is possible to detect RSLT damage by eye examination and photographs after 50% ganglion cell damage (25). Therefore, longitudinal follow-up studies are needed to determine whether axonal degeneration will develop. The other finding in our study was obtained by examining the thickness of the lower segments creating ganglion cell complex separately. As a result, there was no significant difference between ganglion cell layer (GCL) forming the retinal nerve cell body and control group of inner plexiform layer thicknesses formed by dendrites (IPL) ($p > 0.005$) ($p > 0.005$) (Table 1). In addition, there was no significant difference in choroidal thickness in both eyes compared to the control group ($p > 0.05$). Choroidal thickness; may vary between race and gender. In the study conducted in our country, choroidal thickness was found to be 291.3 ± 53.1 μm in men and 252.7 ± 40.9 μm in women (26). In other words, it shows that there is no eye disease (glaucoma, refraction defects, etc.) disrupting systemic (hypertension, etc.) or retinal blood flow in our patients. There was no degeneration of retinal nerve cells in patients with RLS. In a similar study conducted earlier, these layers were measured as ganglion cell complexes and not separately, and no significant thinning was detected in this study (24). Considering the hypothesis of dopamine dysfunction and the effect of dopamine on cognitive functions in patients with RLS; MOCA scale was applied to the patient and control groups in order to evaluate whether these patients had impaired cognitive functions. According to this; MOCA sub-parameters and total MOCA scores were found to be significantly decreased compared to the control group ($p < 0.005$) (Table 2). There are many conflicting studies on cognitive functions in patients with RLS. Some studies have detected cognitive impairment in patients with RLS (27, 28), while others have found no difference compared to controls (29). It was thought that these different results between studies might be caused by confounding factors such as gender, age, education, diseases such as hypertension, diabetes, and exercise (30). On the other hand, dopamine dysfunction hypothesis was supported by the recent studies showing improvement in cognitive functions in patients receiving treatment with dopaminergic agents (30). One of the findings of our study was that the scores of MOCA scale decreased with age and another finding was the thinning of GHT values with age.

As a result; In our study, no degeneration of retinal neurons (RNFL, GCL, IPL) could be detected in patients with RLS. However, it was observed that the total score and sub-parameters of the MOCA scale were impaired. On the other hand, there was no significant correlation between Montreal Cognitive Rating Scale and RNFL, GCL and IPL. These findings suggest that cognitive functions may decrease in patients with RLS due to dopamine dysfunction, independent of anatomical nerve degeneration. However, longitudinal follow-up studies are also needed to assess the presence of nerve degeneration.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Adiyaman (date: 25.05.2016, no. 2016/4-10).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Author Contributions: Concept –AZAT; Design – MÇ; Supervision –SS, YA; Materials – EG; Data Collection and/or Processing – AZAT, EG; Analysis and/or Interpretation – AK; Literature Search – AZAT, AK; Writing Manuscript – AZAT; Critical Review – YA.

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