Original article / *Araştırma*

Decreased olfactory bulb volume in patients with restless legs syndrome

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ABSTRACT

Objective: *Restless legs syndrome (RLS) is a chronic progressive movement disorder with a pathophysiology that is still not fully known. In recent years, a growing number of studies have suggested that the disease may be of a neurodegenerative nature. We aimed to measure olfactory bulb volume (OBv) in RLS using cranial magnetic resonance imaging (MRI).* ***Methods:*** *The study included 24 patients (11 males, 13 females) aged 18-60 years who were diagnosed with idiopathic RLS according to the criteria of the Restless Legs Syndrome Study Group (IRLSSG) 2014 and followed up by our neurology clinic, and 26 age-matched controls (12 males, 14 females). In the cranial MRI examination of both groups, the right, left and total OBv values were manually calculated in mm^3.* ***Results:*** *While there was no significant difference between the right and left OBv values of the patient and control groups, the total OBv value of the patient group was found to be significantly lower compared to the control group (p=0.041). There was no significant difference between disease severity and OBv values. It was seen that right, left and total OBv values decreased significantly as the duration of the disease increased (p=0.001, p<0.001, p<0.001).* ***Conclusion:*** *Our study showed that the olfactory system could be involved in RLS and the underlying mechanism of RLS may be related to neurodegeneration and RLS may be a disorder of central origin. However, longitudinal follow-up studies are needed to fully assess whether neurodegeneration will occur.* ***(Anatolian Journal of Psychiatry 2020; 21(5):537-543)***

Keywords: *restless legs syndrome, olfactory bulb volume, sleeping disorders, neurodegeneration, neuroimaging*

Huzursuz bacak sendromu hastalarında azalmış olfactor bulbus volümü

ABSTRACT

Amaç: *Huzursuz bacaklar sendromu (HBS) patofizyolojisi tam olarak bilinmeyen kronik, ilerleyici bir hareket bozukluğudur. Son yıllarda artan sayıdaki çalışmalar hastalığın nörodejeneratif doğada olabileceğini düşündürmüştür. Biz de HBS'de olası nörodejenerasyonu kraniyal manyetik rezonans görüntüleme (MRI) ile olfactor bulbus volümünü (OBV) değerlendirerek araştırmayı amaçladık.* ***Yöntem:*** *Çalışmaya nöroloji kliniğimizde izlenen 18-60 yaşları arasındaki kadın ve erkeklerden oluşan ve Restless Legs Syndrome Study Group (IRLSSG) 2014 tanı ölçütlerine göre idiopatik huzursuz bacak sendromu tanısı konan 24 hasta (11 E, 13 K), ve 18-60 yaşları arasındaki kadın ve erkeklerden oluşan 26 kontrol grubu (12 E, 14 K) alındı. İki grubun kraniyal MRI incelemesinde sağ, sol ve toplam OBV değeri mm^3 cinsinden, manuel olarak hesaplanarak karşılaştırılmıştır.* ***Bulgular:*** *Ölçülen sağ ve sol OBV değerlerinde hasta ve kontrol grupları arasında anlamlı fark saptanmazken, hasta grubunun toplam OBV değeri kontrol grubuyla karşılaştırıldığında anlamlı derecede düşük bulundu (p=0.041). Sağ, sol ve toplam volüm değerleri arasında hastalık şiddetine göre anlamlı fark bulunmadı. Hastalık süresi uzadıkça sağ, sol ve toplam OBv değerlerinin anlamlı olarak azaldığı saptandı (p=0.001, p<0.001, p<0.001).* ***Sonuç:*** *Çalışmamız HBS hastalarında olfaktör sistemin tutulabileceğini, HBS'de altta yatan mekanizmanın nörodejenerasyon olabileceğini ve hastalığın merkezi*

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kökenli bir bozukluk olabileceğini göstermiştir. Nörodejenerasyonun olup olmayacağını tam olarak değerlendirebilmek için uzunlamasına izleme çalışmalarına gerek vardır. ***(Anadolu Psikiyatri Derg 2020; 21(5):537-543)***

Anahtar sözcükler: *Huzursuz bacak sendromu, olfaktor bulbus volümü, uyku bozuklukları, nörodejenerasyon, nörogörüntüleme*

INTRODUCTION

Restless legs syndrome or Willis-Ekbom's Disease is a movement disorder characterized by a strong drive to move the legs due to unpleasant sensations therein. Unpleasant sensations are very subjective, most commonly expressed by patients as tingling, pricking, burning, muscle tension.[1] The term RLS was first used by Karl A. Ekbom in 1945 to describe the sensory symptom and motor discomfort in the extremities that occur especially during rest.[2] RLS, affecting 5-15 percent of the adult population, has increased prevalence with age.[3] In Europe, Turkey has the lowest reported RLS prevalence of 3.19%.[4] The diagnostic criteria for RLS were determined by the International Restless Legs Syndrome Study Group (IRLSSG).[5]

Although the pathophysiology of RLS remains unclear, the dopaminergic system is considered to play a role in the pathogenesis of the disease. Some recent studies have shown that there is a pre- and post-synaptic dopamine receptor abnormality in the basal ganglia, which suggests that RLS is a dysfunction of the central not peripheral nervous system.[6,7]

This syndrome is mostly idiopathic, it also coexists with diseases, such as iron deficiency anemia, pregnancy, renal failure, diabetes mellitus, hypothyroidism, and Parkinson's disease.[8] Antidepressant drugs commonly used in psychiatric practice may also cause this syndrome such as antiepileptics.[9]

The olfactory bulb (bulbus olfactorius) is an extension of the olfactory tract (tractus olfactorius).[10] The olfactory bulb, which has an oval, long and flat neural structure, connects the olfactory tract to the brain. The olfactory bulb and tract are found in the olfactory sulcus (sulcus olfactorius) on the lower surface of the frontal lobe.[11] The olfactory nerve is not a real cranial nerve, but an extension of the telencephalon, which is surrounded by meningeal structures and contains cells (e.g., oligodendrocytes and microglia) specific to the central nervous system.[10] It is thought that olfactory degeneration is associated with structural and/or functional changes in various diseases, including Parkinson's, Alzheimer's, Huntington's and motor neuron diseases.[12]

In many previous studies, MRI examination has been shown to be a reliable method for the measurement of the olfactory bulb volume (OBv).[13,14] Identification of the olfactory system on MRI was first performed by Suzuki et al.,[15] and the standard OBv measurement method for this imaging modality was developed by Yousem et al.[16]

Following the hypotheses that in RLS, neurodegeneration occurs as in idiopathic Parkinson's disease (IPD) and the olfactory system may be involved in addition to the progressive motor and sensorial findings, we conducted this study in order to demonstrate the possible neurodegeneration mechanism by evaluating OBv in patients with RLS.

METHODS

This was a retrospective case study comparing the RLS group and the control group. The patients who were diagnosed with RLS according to the diagnosis criteria of Restless Legs Syndrome Study Group (IRLSSG) 2014 were examined by file archives. Among these patients, patients who underwent cranial MRI imaging for a simple and non-degenerative reasons (tinnitus, vertigo, tension headache, etc.) and whose cranial MRI examination was completely normal were included. These reasons have been confirmed as correct diagnosis. The patient group consisted of 24 participants including 11 males and 13 females. The mean age of the patient group was 41 (range: 23-58). Patients divided into 4 groups as mild (n=4), moderate (n=8), severe (n=7) and very severe (n=5) according to International Restless Legs Syndrome Study Group Rating Scale for Severity of Restless Legs Syndrome.[17] Patients were also divided into three groups according to disease duration. Group 1 (n=7) 0-12 months, group 2 (n=9) 13-60 months and group 3 (n=8) was more than 61 months. The sociodemographic characteristics (age, gender) of both groups were examined. Sociodemographic characteristics were similar for both groups.

Routine blood hemogram, biochemistry and hormonal analyses were performed in all patients.

Excluded from the study were patients with iron deficiency, renal dysfunction, chronic hepatic failure, thyroid dysfunction, vitamin B12 and folic acid deficiency, multiple sclerosis, diabetes mellitus, rheumatic diseases, hypertension, as well as those with a malignant and neurodegenerative disease. Other exclusion criteria were using antidepressants, antiepileptics or antipsychotics for the treatment of dopamine dysregulation and having another sleep disorder, such as parasomnia and insomnia. Patients with a history of trauma and pregnancy were also excluded. The control group was selected from individuals who fulfilled the exclusion criteria and diagnosed as vertigo, tinnitus and tension headache in the neurology outpatient clinic and whose cranial MRI examination was completely normal. The control group consisted of 26 participants including 12 males and 14 females. The mean age of the control group was 39.38 (range: 20-56).

MRI protocol

All cases with normal reports for non-enhanced brain MRI and good MRI quality were included in the study. These MRI were re-evaluated by a radiologist with more than 10 years' experience in conducting brain MRI. All studies were performed using a 1.5 T system (Achieva; Philips Medical Systems, Best, the Netherlands) using a head coil. Contrast material was not utilized. These images were used for volumetric and morphometric measurements. Coronal imagery B-FFE 3D T2 weighted via images (TR 6.5 ms; TE 3.4 ms; FOV 180x180 mm; NSA 2; thickness 1 mm; G.A.P. -0.5mm; slice 75; matrix 308x308 mm).

Image analysis

Bilateral OBv were measured in all participants. The olfactory bulb was observed as a hypointense ovoid structure surrounded by hyperintense cerebrospinal fluidin T2-weighted series. Sections were obtained at a right angle to the cribriform plate. The volume measurements were obtained semi-automatically using multiplanar reformations a View 3D workstation and manual segmentation based on the contour stack principle. OBv was calculated in mm^3 (Figs. 1 and 2). All the measurements were undertaken by an individual who was blinded to the patient diagnoses.

Statistical analysis

Statistical analysis was performed using SPSS version 17.0. The normality of the distribution of the variables was analyzed by histogram graphs and the Kolmogorov-Smirnov test. Descriptive data were presented as mean, standard deviation, median and minimum-maximum values. For the comparative evaluation of the normally distributed (parametrical) variables between the groups, the independent samples t-test was used. The Spearman correlation test was conducted to comparatively analyze the measurement data. P values of below 0.05 were evaluated as statistically significant.

RESULTS

A total of 50 individuals, 24 (48%) male and 26 (52%) female, were included in the study. The mean age was calculated as 40.16±11.00 years in all individuals. The patient group consisted of 13 females and 11 males, and the control group comprised 14 women and 12 men. The mean age was 41.00±11.02 years for the patients group, 39.38±11.14 years for the control group, 39.26±10.45 years for the male population and 40.93±11.59 years for the female population. The sociodemographic data were similar in both groups (Table 1).

Table 1. Group, gender and age of the participants

	Male	Female	Age	p
Patient	11	13	41.00±11.0	
Control	12	14	39.38±11.14	
Age	39.26±10.45	40.93±11.59		0.599
p			0.609	

The measured values were compared by gender. In the male population, the right OBv value was 57.96±17.92 mm^3 (range: 22.00-93.20 mm^3), the left OBv value was 60.34±18.36 mm^3 (range: 36.50-93.00 mm^3) and the total OBv value was 118.30±31.75 mm^3 (range: 81.90-178.00 mm^3). While in the female population, these parameters were measured as 41.99± 22.97 mm^3 (range: 5.80-89.00 mm^3), 45.00± 23.31 mm^3 (range: 6.90-89.00 mm^3) and 86.99± 42.70 mm^3 (range: 21.00-178 mm^3) respectively. The mean right, left and total OBv values were found to be higher in males than females (p=0.009, 0.014 and 0.006, respectively).

Analysis of the results according to the study groups showed that the right, left and total OBv values were 43.20±21.37 mm^3 (range: 5.80-87.39 mm^3), 46.01±20.45 mm^3 (range: 6.90-76.00 mm^3) and 89.21±38.75 mm^3 (range:

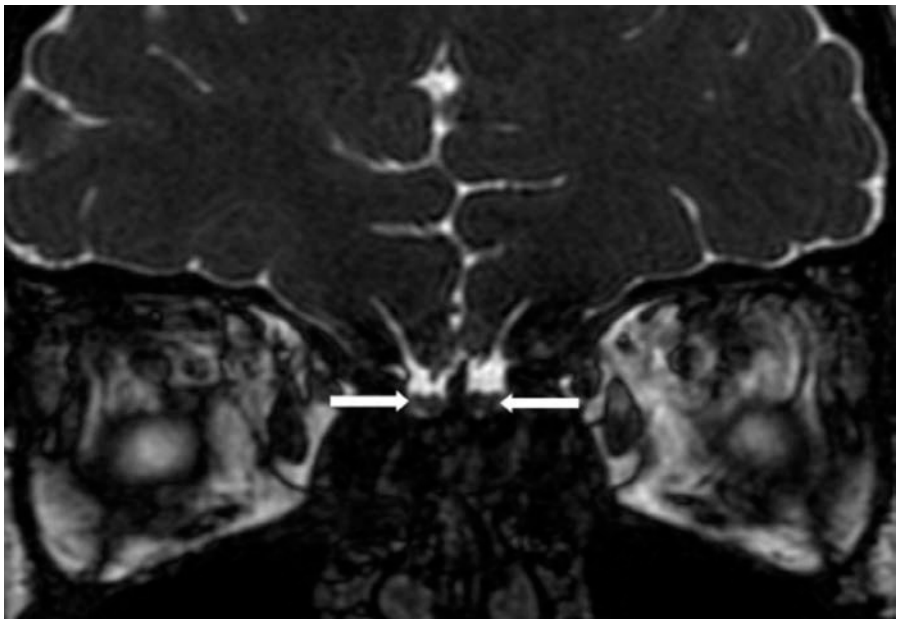

Figure 1. A coronal T2-weighted image showing the right and left olfactory bulb as a hypointense ovoid structure (arrows).

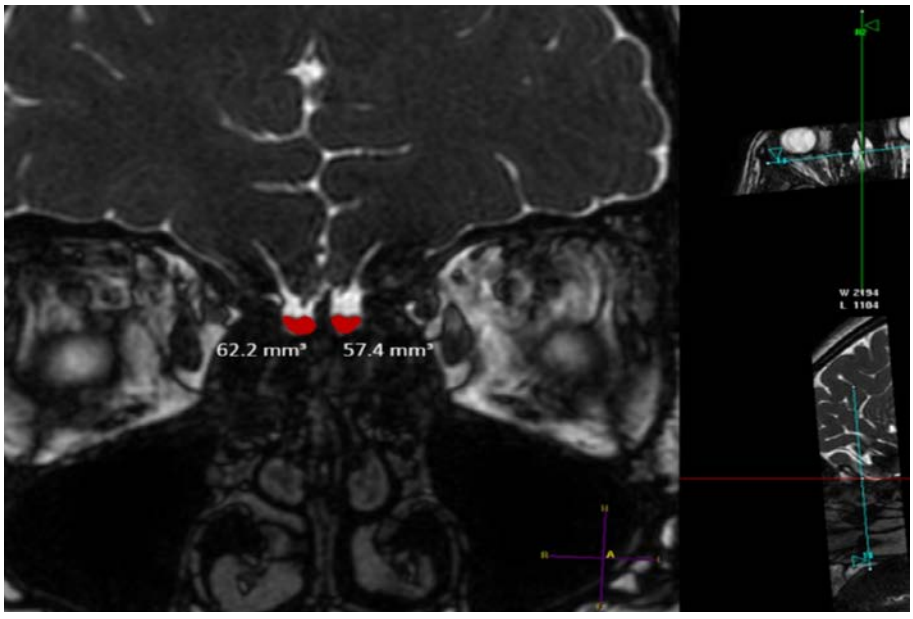

Figure 2. Semi-automatic measurement of the olfactory bulb volume using manual segmentation and multiplanar reformations in the 3D workstation. The olfactory bulb is shown in red on both sides and the volumes are given in mm^3.

21.20-144.10 mm^3) respectively for the patient group and 55.00±21.64 mm^3 (range: 22.00-93.20 mm^3) 57.64±22.95 mm^3 (range: 13.70-93.00 mm^3) and 112.63±40.19 mm^3 (range: 38.30-178.00 mm^3), respectively for the control group. The comparison of the measured parameters between the patient and control groups revealed no significant difference in the right and left OBV values, but the total OBv was significantly lower in the patient group compared to the controls (p=0.041) (Table 2).

When the right, left and total OBv values were compared according to the severity of the dis-

Table 1. Group, gender and age of the participants

	Male	Female	Age	p
Patient	11	13	41.00±11.0	
Control	12	14	39.38±111.14	
Age	39.26±10.45	40.93±11.59		0.599
p				0.609

ease, there was no significant difference between the groups (Table 3). When the right, left and totol OBv values were compared according to the duration of the disease, right, left and total OBv values decreased significantly as the duration of the disease increased (p=0.001, p<0.001, p<0.001). (Table 4)

Table 2. Comparison of measured values between patient and control groups

	Control		Patient		
	Mean±SS	Median	Mean±SS	Median	p*
Age	39.38±11.14	40.00	41.00±11.02	44.50	0.609
ROBv	55.00±21.6	52.55	43.20±21.37	41.30	0.059
LOBv	57.64±22.95	55.50	46.01±20.45	46.15	0.065
TOBv	112.63±40.19	118.40	89.21±38.75	86.95	**0.041**

**: Independent T test*

Table 3. Relationship between measured values and disease severity

	Mild	Moderate	Severe	Very severe	$p^{1,2}$
ROBv	46.07±16.49	50.56±21.39	42.92±24.86	29.50±18.51	0.40
LOBv	53.55±19.36	58.08±17.97	31.91±15.21	40.38±21.77	0.06
TOBv	99.62±34.80	108.65±36.60	74.84±37.74	69.88±39.38	0.22

[1]: ANOVA test; [2]: Tukey test

Table 4. Relationship between measured values and disease duration

	0-12 months	13-60 months	>61 months	$p^{1,2}$
ROBv	61.74±14.46	44.95±18.58	25.00±14.16	**0.001**
LOBv	67.60±7.30	47.74±12.92	25.16±13.04	**<0.001**
TOBv	129.34±8.59	92.70±27.82	50.16±24.81	**<0.001**

[1]: ANOVA test; [2]: Tukey test

DISCUSSION

The pathophysiology of RLS has not yet been fully elucidated. Therefore, effects on the olfactory system may be an indicator of the involvement of central structures, and this may also support the hypothesis that RLS is a central rather than a peripheral disease. Olfactory functions of the central nervous system can play an important role in the management of the pathophysiology of brain disorders.[18] We aimed to measure olfactory bulb volume (OBv) in RLS using cranial magnetic resonance imaging (MRI). In our study, we found that OBV decreased significantly in patients with RLS compared to the control group, and that this was related to the duration of the disease. To the best of our knowledge, this is the first study in the literature that measuring OBv parameter in RLS. In addition, the use of imaging methods in the study and the examination of the olfactory nerve which is the direct extension of the cranium with these imaging methods makes our study one step forward from many previous studies on etio-

pathogenesis. Our results suggest that the olfactory system can be structurally affected in RLS.

In addition, some studies revealing cognitive dysfunction[19] and emotional disorders[20] in RLS patients, and similar clinical characteristics to IPD, has led to the idea that the disease does not merely present with sensorial and motor findings. Our results support the idea that RLS may be a disease of central origin. OBv measurement has previously been used in many psychiatric disorders. In a study conducted on patients with major depressive disorder, OBv was found to be significantly lower compared to the control group and also correlated with the severity of depression.[21] In a different study, it was found that OBV decreased in schizophrenic patients.[22] Central neuromediators play a role in the pathophysiology of these diseases and may show a progressive course. Considering this aspect, the relationship between these diseases and OBv is noteworthy.

MRI is the standard examination method for the evaluation of the olfactory bulbus. MRI-based investigations provide information concerning the status of the olfactory system through the measurement of OBv.[23] However, although OBv measurement is a usable method, it shows a wide variation among individuals. The OBv of men is reported to be larger than that of women. OBv can also change with advanced age.[24] The results of our study were consistent with this information, with the right, left and total OBv values being significantly higher in males than females. The patients and control groups were composed of individuals under the age of 60 years to eliminate the effect of advanced age factor on the volume. There may also be differences between the right and left OBv values of the same individual; therefore, OBv measurements are performed bilaterally.[25] Since OBv is a volumetric value, the right and left OBVs are collected to calculate the total OBV value.[26] We followed a similar path in our study and did not find any significant difference between the right and left OBv values of the patient and control groups, but we noted significantly lower total OBv values in the patient group.

RLS and IPH have similarities in terms of their association with central dopaminergic neurotransmission, good response to dopaminergic therapy, and aggravation by dopamine antagonists. In addition, both diseases have common features, such as increasing prevalence with age, chronic progressive course, and causing significant sleep disorders[27]. Prevalence studies showed a high rate of RLS among patients with IPD, and similarly, it was reported that patients with RLS develop a high rate of IPD over time.[28,29] All these findings show the pathophysiological and clinical similarities between IPD and RLS. Our study supports the idea that a similar form of neurodegeneration and dopamine dysregulation, which is an underlying mechanism in IPD, may also be present in RLS. Furthermore, decrease in OBv values with prolonged duration of disease supports the idea.

There are some limitations in our study. Our study was retrospective. There was a relatively small number of patients, and we could not perform smell function tests. Our study results should be evaluated within this framework.

Ethiopathologic picture of the RLS is still unclear. The findings of our study support the idea that RLS is of a neurodegenerative nature. This study also supports the idea that the disease is a central nervous system disease, not peripheral. Clinicians should be aware of the olfactory deficits and should investigate odor loss in RLS patients. RLS should be kept in mind when low OBv is detected in MRI. This may allow early diagnosis of the disease. We consider that there is a need for multicenter, longitudinal studies with a larger case series in this area. We hope that our study will shed light on subsequent studies seeking degenerative and central causes in the etiopathogenesis of RLS. We also think that future studies will focus on the structural and imaging methods and will be more useful in revealing the etiopathogenesis of RLS.

***Ethical approval**: Ethics committee approval was obtained from Adıyaman University Clinical Researches Ethics Committee (Date: 26.09.2019 Number:6/26).*

***Authors' contributions:** E.A.: Formation topic and hypotheses, collection of cases, literature review, writing manuscript; A.H.B.: re-evaluate the study in the scientific sense, provide the necessary all resources.*

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