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Restless Legs Syndrome in Patients with Behçet's Disease and Multiple Sclerosis: Prevalence, Associated Conditions and Clinical Features

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ABSTRACT

Introduction: To investigate the prevalence and characteristics of Restless Legs Syndrome (RLS) in patients with Behçet's Disease (BD) and Multiple Sclerosis (MS).

Methods: Consecutive patients with BD and MS seen in the outpatient clinic were included in the study. As a control group, volunteer subjects without a known peripheral or central nervous system disorder were included. The BD group was divided into two sub-groups as BD with neurological involvement [Neuro-Behçet's Disease (NBD)] and BD without any neurological involvement (other BD) for further evaluation. Data on demographic characteristics, medical history and family history were collected, and all patients underwent neurological examination. The patients were evaluated for the presence of diagnostic criteria for RLS. The features and severity of RLS were evaluated in patients with RLS using Restless Legs Syndrome Identification Form, and the International Restless Legs Syndrome Study Group (IRLSSG) Rating Scale. The clinical and radiological findings of patients with BD and MS were retrieved from their medical files.

Results: The study included a total of 96 patients with BD (mean age 39.9±11.8; 51 males; 41 patients with NBD) and 97 patients with MS (mean age 34.97±4.1 years; 24 males). There were 100 healthy control subjects (mean age 36.18±11.10 years; 46 males). RLS was more prevalent in MS (22.8%) and NBD (22%) groups compared to the control group (10%; p=0.004 and 0.029, respectively) with a statistically significant difference. The prevalence of RLS was higher in MS patients with less disability. Most severe RLS symptoms were observed in the MS group. The rate of sleep disorders was also higher in MS group. Although stress appeared to be a factor worsening RLS in all groups, its prevalence was higher in the MS group (p=0.011). There was no correlation between the distribution of magnetic resonance imaging lesions and RLS in both MS and NBD groups.

Conclusions: It is well established that RLS can accompany disorders involving the peripheral and central nervous systems such as all types of peripheral neuropathy, myelopathy, and Parkinson's disease. The present study showed that MS and NBD also seem to be a risk factor for RLS, being associated with more severe symptoms.

Keywords: Restless legs syndrome, Behçet's disease, neuro-Behçet's disease, multiple sclerosis

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INTRODUCTION

Restless Legs Syndrome (RLS) is a sensorimotor disorder that is mostly experienced in the evening and nighttime with unpleasant sensations (paresthesia, dysesthesia, etc.), particularly more pronounced in legs, and relieved by movement (1). There is no diagnostic test for the condition, and the diagnosis is based on clinician's assessments of patient's subjective data and the criteria that were developed in 1995 by the International Restless Legs Syndrome Study Group (IRLSSG), and then revised in 2003 and 2012 by the same group (2).

Restless Legs Syndrome is divided into two types depending on its etiology; primary and secondary. Primary (idiopathic RLS, often familial) RLS is characterized with an early onset, usually under 40 years of age. Secondary etiologies include iron deficiency anemia, pregnancy, chronic renal failure-uremia, peripheral neuropathies, multiple sclerosis (MS), some rheumatoid diseases [rheumatoid arthritis, Behçet's Disease/ Neuro-Behçet's disease (BD/NBD), Sjogren syndrome], spinocerebellar ataxia, and thyroid disorders (3–5).

Although the etiology of RLS remains unknown, studies have shown that dopaminergic mechanisms play a role in its pathogenesis. The strongest evidence for dopaminergic pathology is that patients substantially benefit from treatment with dopamine agonists. Also, evidence of a lower rate of ferritin and a higher rate of transferrin in the cerebrospinal fluid of patients with RLS compared to control groups provides support to the hypothesis that iron deficiency leads to the symptoms as a result of the dysfunction of dopaminergic systems (1–3).

It is believed that the disease develops in association with spinal neuronal excitability, particularly in lesions involving the spinal cord, MS, syringomyelia and BD (3, 6). Although it has been found that RLS showed increased excitability of the cortical and central motor pathways and improvement in increased excitability with dopamine agonists and reduced intracortical inhibition at the spinal level, there has been no integrated study combining relevant biochemical parameters, magnetic resonance imaging (MRI) results and clinical course. Based on this information, we aimed to evaluate whether or not there is a difference

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in the incidence and characteristics of RLS between patients diagnosed with BD, NBD, MS and healthy population, and in clinical, biochemical parameters and MRI images between patients diagnosed with RLS and other patients without RLS.

METHODS

The study included consecutive patients who were followed up in our outpatient clinic, and diagnosed with BD according to the 1990 International Criteria for Behçet's Disease (7) and consecutive patients who had a final diagnosis of MS according to the 2005 Mc Donald Criteria for Diagnosis of MS (8). The healthy control group consisted of 100 volunteers, of similar age, without any known medical condition selected from the hospital staff and their families.

Following the approval of local ethics committee (44140529/2014-66) and the informed consent obtained from the participants, their demographic and detailed medical information were collected, and they underwent neurological examination. The occupational groups were divided into two groups depending on the need for active use of legs and/or feet. The workers, teachers, and physicians were considered to have active use of legs while students, housewives, designer, unemployed people, engineers, and civil servants were those who didn't require active use of legs/feet (Table 1). We collected information on conditions that might be associated with secondary RLS such as hypertension, diabetes mellitus (DM), chronic renal failure, thyroid disease, and anemia and current medications. We used RLS Identification Form (2, 9) to diagnose the Restless Legs Syndrome and the IRLSSG Rating Scales to assess the severity of RLS symptoms (10). The questionnaires were completed by the investigators during face to face interviews.

The questions included timely distribution, severity and remission status of complaints, presence of any triggering stress, fatigue, standing, variability when alone or with others, presence of any factors which alleviated RLS symptoms (massage, warm water, medication, movement or other factors), comorbid Periodic Limb Movement Disorder (PLMD), presence of any nocturnal sleep disorder with respect to quality of sleep, difficulty in falling asleep and time to fall asleep**.** Checking levels of vitamin B12, free thyroxine, thyroid stimulating hormone, hemoglobin, hematocrit, ferritin, iron, total iron-binding capacity, magnesium and calcium blood levels in subjects with RLS was planned, but unfortunately only 13 of the patients could be tested, due to the limitations of the social security system. The group with BD were divided into two sub-groups as BD with neurological involvement [Neuro-Behçet's Disease (NBD)] and BD without any neurological involvement (other BD) for further evaluation according to the International Neuro-Behçet's Disease consensus recommendations (11). They were classified as parenchymal (brainstem, hemispheric) and non-parenchymal (sinus vein thrombosis, arterial, neuropsychiatric) based on the type of involvement. We used MRI to assess if there was an involvement of the brainstem, hemispheric involvement (especially basal ganglions and deep structures), spinal (cervical-thoracic) involvement and comorbid RLS. The disease disability was determined using the Neuro-Behçet's Disability Score (NBDS) (12).

The site of the involvement was classified as supratentorial, brainstem and spinal cord in patients with MS. We examined the involvement type by MRI. Supratentorial lesions (based on the distribution criteria in localization) were considered as being <9, or >9. The brainstem and spinal involvement was considered as present or absent regardless of the number of lesions. The functional state of the patients were assessed using the expanded disability status scale (EDSS) (13). The clinical course was classified as clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS) and secondary progressive MS (SPMS) (14).

The statistical analysis was performed using the IBM-SPSS 22.0 (SPSS Inc., IL, USA) software program. Demographic data were assessed by frequency and crosstab analysis, while parametric data were described as median, mean, minimum and maximum values and standard deviation. We used Pearson's correlation test for parametric data, and Spearman's correlation test for non-parametric data to examine the correlation. For intergroup comparisons, we used Chi-square test for categorical variables, and for non-categorical variables; Kruskal-Wallis test to make comparisons among 3 groups with Bonferroni corrections, and Mann-Whitney U test and independent Student's t-test for comparisons between two groups. The statistical significance was set at $p<0.05$ or $p<0.018$.

RESULTS

There were 96 patients with BD (mean age 39.9±11.8 years; 51 males); 41 of those were diagnosed with NBD. There were 97 patients with MS (mean age 35.0±4.1 years; 24 males). MS group had the youngest mean age (p=0.012) (Table 1). With respect to the gender distribution, again the MS group mainly consisted of women (75%) due to the nature of

Table 1. Demographic characteristics and incidence of RLS in the study groups

Parameter	Behçet's Disease	Multiple Sclerosis	Controls
Number of Subjects	Total: 96 NBD: 41 Others: 55	Total: 97 RRMS: 85 SPMS: 12	100
Age, years			
Mean ± SD (min-max)	Total: 39.9±11.8 (23–75) **NBD: 42.2±10.7 (25–67)** Others: 38.3±12.3 (18–75)	Total: 35.0±4.1 (17–62) RRMS: 34.0±8.5 (17–58) SPMS: 42.4±9.3 (30–62)	36.2±11.1 (21–70)
Male/Female	Total: 51/45 NBD: 28/13 Others: 23/32	**Total: 24/73** RRMS: 20/65 SPMS: 4/8	46/54
Occupation type[a], n (%)	Total: 27 (28.1%) NBD: 10 (24.4%) Others: 17 (30.9%)	Total: 20 (20.6%) RRMS: 20 (23.5%) SPMS: 0	**36 (36%)**
Disease duration, months			
Mean ± SD (min-max)	Total: 121.4±107.5 (4–500) **NBD: 152.8±110.8 (12–500)** Others: 98.0±100.0 (4–430)	Total: 101.6±91.1 (1–564) RRMS: 91.8±78.2 (1–432) SPMS: 171.0±140.3 (24–564)	-
Incidence of RLS, n (%)	Total: 15 (15.6%) **NBD: 9 (22%)** Others: 6 (10.9%)	**Total: 22 (22.7%)** RRMS: 20 (23.5%) SPMS: 2 (16.7%)	10 (10%)

[a]Occupations that require active use of legs and/or feet. The parameters written in bold are statistically significant.
RLS, restless legs syndrome; NBD, neuro-Behçet disease; RRMS, relapsing-remitting multiple sclerosis; SPMS, seconder progressive multiple sclerosis; min, minimum; max, maximum; SD, standard deviation.

Table 2. Demographic and clinical characteristics of patients diagnosed with RLS

	Behçet's Disease n=15	Multiple Sclerosis n=22	Controls n=10
Age of onset (years), Mean ± SD (min-max)	28.7±11.33 (18–45)	23.7±10.03 (13–44)	20±6.95 (12–30)
Male/Female	7/8	8/14	6/4
Occupation type* (n)	5	5	4
Family history, (n)	4	4	1
Kinship marriage of parents	10	6	1
Chronic Disease (%)			
Diabetes mellitus	5 (5.2%)	2 (2.1%)	7 (7%)
Iron deficiency anemia, n (%)	9 (9.5%)	18 (18.6%)	5 (5%)
Hypertension, n (%)	16 (16.7%)	5 (5.2%)	7 (7%)
Hypothyroidism, n (%)	2 (2.1%)	5 (5.2%)	9 (9%)
Chronic Renal Failure, n (%)	0	0	0

*Occupations that require active use of legs and/or feet.
n, number of subjects; min, minimum; max, maximum; SD: standard deviation.

the disease (p<0.001) (Table 1). The occupational groups were similar concerning the need for active use of legs/feet between MS and BD groups; the difference was not statistically significant although it was a little bit higher in healthy subjects. RLS had the most common incidence in MS group (22.7%), followed by NBD (22%), and by BD (15.6%) groups (Table 1). The incidence of RLS was significantly higher in MS and NBD groups (9 patients, 22%) compared to the control group (10 subjects, 10%) (p=0.004, 0.029 respectively). In other BD, the incidence of RLS was similar to one in the control group (10.9%). In the course of MS, a majority of the patients had RRMS (85 patients); and of these patients, 20 (23.5%), and 2 out of 12 SPMS patients (16.7%) had RLS. No significant difference was found in the incidence of RLS by the MS type (Table 1).

The demographic and clinical characteristics of the patients with RLS were summarized in Table 2. The onset age of RLS was the latest in BD group; no significant correlation was found between the age, gender, familial history of RLS, kinship between the parents, presence of an occupation that requires use of legs/feet and RLS. The most common comorbid conditions that may be associated with RLS included hypertension, DM, hypothyroidism and iron deficiency anemia. A significant association was found between the iron deficiency anemia and RLS in both MS and BD groups (p=0.008, and p=0.004, respectively). Vitamin B12, free thyroxine, thyroid stimulating hormone, hemoglobin, hematocrit, ferritin, iron, total iron-binding capacity, magnesium and calcium blood levels were normal in 13 subjects with RLS (7 MS, 4 BD, 2 control).

The characteristics of RLS in groups are summarized in Table 3. The factors that were associated with increased severity of RLS symptoms were stress, fatigue and standing for long periods, respectively. The RLS symptoms went into remission intermittently in 42 patients while they were enduring in 5 patients. The RLS symptoms were relieved by moving

Table 3. RLS Characteristics of Groups

	Behçet's disease	Multiple sclerosis	Control
Exacerbating symptoms;			
Stress	11	22	6
Fatigue	8	10	7
Standing	3	3	5
Remission in symptoms	13	19	10
Persistence of symptoms	2	3	-
Alleviating symptoms;			
Movement	14	20	10
Stretching	5	5	1
Warm water	4	2	4
Massage	4	3	3
Rubbing	1	1	-
Swinging	1	1	-
Sleep	1	1	-
Involuntary leg movements during sleep	6	11	0
Onset of sleep;			
5–15 min	4	4	2
15–30 min	2	3	1
>30 min	9	12	3
without any problem	0	3	4
Involvement pattern;			
Arm, symmetrical	4	4	
Arm, asymmetrical	1	1	2–6
Leg, symmetrical	7	20	4
Leg, asymmetrical	4	2	
Severity score	20.7±5.19 (median: 20)	22.18±6.38 (median: 23)	19.8±6.97 (median: 16.5)

RLS, restless legs syndrome.

legs, stretching, bathing in warm water, massage, rubbing, swinging and sleep. The severity score of RLS was the highest in MS group (22.18±6.38), however it didn't reach to a statistical significance (BD group 20.7±5.19, control group 19.8±6.97). The sleep disorder was more common in MS group, who also reported longer time to fall asleep. Although stress was a factor that increased RLS in all groups, the highest rate was seen in MS group (p=0.011).

In NBD group, the type of involvement was parenchymal in 28 (67.5%) patients (3 with RLS), and non-parenchymal in 13 (32.5%) patients (6 with RLS); and RLS was more common in those with non-parenchymal involvement (p=0.024). The mean NBDS was 2.12±1.42 in NBD patients with parenchymal involvement. There was no significant correlation between the NBDS and RLS severity scores.

In MS group, the EDSS score was 0–4 in 76 patients, >4 to 7 in 18 patients and >7 in 3 patients. A majority of the RLS and MS patients had a lower EDSS score (21 patients, 95.5%) of 0–4; one patient had a score >4 to 7. This relationship between the EDSS score and RLS was statistically significant (p=0.031).

Cranial imaging findings showed that in NBD group, 6 patients had supratentorial (other than basal ganglia), 8 (16.3%) had basal ganglia, 19 (38.8%) had a brainstem lesion, and 2 (2.1%) had a spinal lesion. Of those patients with NBD and RLS, 2 (18.2%) had a brainstem lesion, but no supratentorial lesion, 1 (9.1%) had basal ganglia lesion, and 1 (6.7%) had a spinal lesion. Two patients had spinal lesions, one with RLS. The relationship between spinal lesion and RLS was not assessed due to small number of patients. In MS patients, the number of patients with a cranial lesion count of <9 was 32 (33%), of >9 lesions was 65 (67%). Forty-five (46.4%) and 47 (48.5%) patients had brainstem and spinal involvement, respectively. Of those with MS and RLS, 14 (63.6%), 7 (31.8%), and 14 (63.6%) had >9 cranial brainstem and spinal lesions, respectively. No correlation was found between the MRI findings and RLS.

DISCUSSION

The present study examined the incidence of RLS in patients with BD, NBD and MS, and its associated conditions and clinical characteristics. RLS was more common in both MS and NBD groups compared to control group. The incidence of RLS in BD patients without NBD was similar to the control group.

The prevalence of RLS has been reported to vary from 0.013% to 18.3%, which may be associated with the criteria used (1995, 2003, 2012 IRLSGG) and the type of interview (4, 9). In Turkey, the incidence has been reported to range from 3.19% to 9.7% (4, 15, 16). Age and gender are known to be predictive factors of incidence in RLS. While the prevalence of RLS is about 3% in the 30's, it increases up to 20% in those with 80 years of age, and RLS is about twice as high in females than in males (4, 5). The incidence of RLS was 10% in our control group, which was somewhat higher. It may be attributed to the fact that a higher rate of hospital staff was included in the control group which might have resulted in better/over evaluation of their symptoms, resulting in a biased rate.

We found a 15.6% incidence of RLS in BD group. A Turkish study (17) examined 104 patients with BD, and found RLS in 32 (29.4%) patients. A comparison between those with and without RLS showed no significant difference in clinical characteristics. However, the patients were not evaluated for presence of NBD. The present study found that RLS was frequent in patients with NBD, and its incidence was similar to control group in the absence of neurological involvement. From a demographic perspective, the onset age of BD is most commonly the third decade, and it is more common in males, although it can also occur under 30 years of age and above 50 years of age (18). In our 96 patients with BD, 51 were male; the mean age was 39.9±11.8 years; and the duration of disease was 121.4±107.5 months. Among all our groups, BD represented the oldest age group of patients. From another point of view, the duration of disease was longer in patients with BD. It suggests that it might be related with the chronic course of BD, earlier onset and persistence, and prolonged duration of disease.

Idiopathic RLS has an early onset (<45 years), and it is reported to be more common in women since pregnancy aggravates RLS symptoms under 35 years of age (1, 4). The mean age in our control group was 36.2±11.1 years, and 54 of our subjects were female. The mean age and gender distribution of our group was consistent with the onset age and gender of RLS.

The prevalence of RLS in patients with MS has been reported to vary between 13.3% and 65.1% (6, 19). The REMS study group found that prevalence of RLS was 19% in patients with MS, and 4.2% in control subjects; the risk of RLS was 5.4 times greater for patients with MS. It is the largest study on the coexistence of MS and RLS (5). On the other hand, Gomez et al. (20) were found that the incidence of RLS was similar in patients with MS and control subjects. In our patients with MS, the incidence of RLS was 22.8%, which was significantly higher than control subjects (p=0.004). The younger age of MS group might have reduced potential RLS whereas higher rate of females might have increased it; since iron deficiency anemia was most commonly seen in this group, we thought that it might have had a positive impact on the prevalence of RLS. However, the age, gender and iron deficiency anemia in MS group was not correlated with the prevalence of RLS. In other words, MS represented a risk factor on its own regardless of other factors. One of our limitation in this study, the ferritin level was not examined in all of patients and controls whereas low ferritin levels alone without associated anemia is a well-known risk factor for RLS.

Idiopathic RLS is a hereditary disease with an autosomal dominant inheritance pattern. More than 30 genetic loci with suspected susceptibility to RLS have been analyzed, and 6 different genes (*BTBD9, MEIS1, MAP2K5/LBXCOR1, PTPRD, TOX3*) with allelic variants that may convey the risk to develop RLS (16, 21, 22). On the other hand, MS, which is a secondary cause of RLS, also may show genetic susceptibility, and there are familial MS patients known. The presence of common genetic factors that dictate predisposition to MS and RLS has been investigated. A study by Vávrová et al. showed that a single gene polymorphism of *MAP2K5/SCOR1* contributed to the predisposition to RLS (23). From a clinical perspective, the rate of family history in our patients with MS and RLS was not higher compared to both those with individual MS and individual RLS. The association of BD with the HLA B51 gene is already known, but there is no study available on coexistence of RLS and BD. We found kinship of parents in 10 and 6 in patients with BD and MS, respectively compared to 1 subject in control group, which indicates BD's genetic susceptibility in itself, and increased kin marriage consistent with the socioeconomic level. However, analysis of a relationship between kinship and RLS in all patients showed no significant correlation.

Conditions such as DM, HT, hypothyroidism, CRF and anemia are known to play a significant role in the etiology of secondary RLS. Particularly iron deficiency anemia has been reported to result in severe symptoms that may regress with treatment (3). Recently, a prevalence study on patients diagnosed with type 2 DM showed a very high RLS prevalence of 27% (24). However, there are many other studies which do not support this (4). In our patients, only the distribution of iron deficiency anemia was different across patient groups: it was the highest in the MS group with a rate of 18.5% (p=0.008). It has been attributed to the immunomodulatory treatments, the steroid treatment used in relapses, and the immunosuppressive agents in more severe patients. However, there was no significant correlation between RLS and iron deficiency anemia in MS group. The incidence of anemia was 9.5% in patients with BD, which was higher compared to control group (not significantly), and in fact there was a significant correlation between the patients with BD and RLS and the iron deficiency anemia (p=0.004). It is already known that

a patient with BD has a higher use of non-steroidal anti-inflammatory drugs (NSAIDs) for chronic pain and arthralgia. In the long-term, NSAID-induced intestinal inflammation and minor hemorrhages may develop, which, in turn, may result in subclinical iron deficiency. In a study on patients with BD, Ediz et al. evaluated the iron, ferritin, hemoglobin and MCV levels in blood, and found no difference (17).

The coexistence of PLMS and RLS is very common, and reported to occur in 80–89% of patients (1). A study by Uygunoğlu et al. evaluated PMLS in BD by polysomnography (25). They found that there was no significant difference between BD patients and those with brainstem involvement in polysomnography but the mean sleep onset latency was significantly longer in patients with NBD compared to control subjects, and superficial NREM sleep stage was longer ($p<0.005$). Another study by Tascilar et al. found a higher rate of insomnia with 50.9% in patients with BD (26). Similarly, patients had difficulty in falling asleep, and sleep duration was shorter (<5 hours/night). We couldn't perform polysomnography in our patients since we didn't have a laboratory. However, replies to our questions demonstrated that the time to fall asleep was longer in patients with MS and BD, and they had involuntary movements at night.

Fatigue has an impact on daily life activities, aggravating the RLS symptoms. It is a common symptom in patients with MS (27, 28). A study by Aydar et al. reported a fatigue rate of 61.2% in MS (28). As a factor aggravating the RLS, we found a fatigue rate of 45%, 53% and 70% in MS, BD and control groups, respectively.

Typical RLS sensations are felt in both legs, deep muscles and bones. Some patients may describe more superficial sensations in both legs, but predominantly in one leg. Studies have shown that the sensation of restlessness is always felt in the legs, but it can also sometimes affect the arms and trunk (29). In our study, leg involvement was common in patients with MS, being bilaterally symmetrical (20/22), with less, but symmetrical involvement in arms (4/5). The involvement pattern in patients with BD was symmetrical in the arms of 4 patients, and legs of 7 patients (46%) compared to symmetrical involvement in the arms of 2 patients, and legs of 6 patients in the control group.

The REMS study evaluated the relationship between types of MS and RLS, and found that RLS was reported more frequently in PPMS (5). Our patient group included 85 patients with RRMS, and 12 with SPMS, and there was no significant difference in the frequency of RLS by MS type. However, since we didn't have a variety of patients, and almost all of them had RRMS, we were unable to make any comparison in respect to the course of MS and RLS. The REMS study which examined the relationship between the EDSS score and RLS in patients with MS showed a significant correlation. However, a study by Aydar et al. demonstrated no relationship between severity of RLS and EDSS score (28). Based on the distribution of EDSS scores, 28% of our patients had 0–4, and 5.6% had >4–7 with RLS. There was significant relation between the EDSS score and RLS, and interestingly RLS was more common in the group with a lower EDSS score (who were able to walk independently). This result may be attributed to active work life in this group, standing longer hours and experiencing fatigue.

Ediz et al. (17) evaluated the severity of RLS and clinical characteristics of BD, and found similar results with the control group. In our study, the mean severity score of the RLS Scale was 20.7±5.2 (median: 20) in patients with BD, which was slightly higher than the control group (18). No study is available that evaluated the relationship between the severity of impairment and RLS in patients with NBD. In our study, the mean NBDS score was 2.1±1.4 in 26 patients with BD who had parenchymal involvement. However, there was no correlation between the NBDS score and severity of RLS.

A large study by the Italian REMS study group (5) showed that the severity of RLS was significantly higher in patients with MS (MS: 17.5±5.70 vs. control: 14.0±4.71; $p<0.003$). Aydar et al. also showed that the severity of RLS was significantly higher in patients with MS (28). We also had similar results. The MS group had the highest RLS score. Compared to both studies, the severity score was higher in our patients. The higher mean severity score in the BD groups may be attributed to the presence of iron deficiency anemia. Similarly, neurological involvement and medications used may also contribute to the severity of symptoms.

An analysis of MRI findings in patients with NBD revealed that brainstem had the highest involvement (38.8%). In patients with coexistence of NBD and RLS, it was 18.2%, not reaching to a statistical significance. A relationship between myelopathy and RLS has been previously reported (30). In the NBD group, we had 2 patients with spinal involvement, out of which one also had RLS. We were unable to make any comment due to very small number of patients. There is also no study evaluating the relationship between the site and distribution of lesions and RLS in patients with NBD. Therefore, we plan to examine it further in patients with NBD in the absence and presence of RLS by MRI and f-MRI in the future.

A review of the relationship between RLS and MRI lesions in MS showed that Aydar et al. found a significant correlation between the number of lesions in cranial MRI and RLS, but it was not related with contrasting lesions and cervical spinal cord lesions (28). The REMS study analyzed the MRI findings of 594 patients with MS, and found no correlation between the number of supratentorial and infratentorial lesions and RLS (5). Similarly, we found no correlation between the distribution of lesions and RLS. It may be related with the fact that both MRIs were not performed in a single center in a standardized manner, and the MRI images we had were the most recent images, and no review was available for those with RLS.

In conclusion, it is well established that RLS may accompany medical conditions affecting the peripheral and central nervous system, mainly any types of neuropathy, myelopathy and Parkinson's disease. The present study showed that MS and NBD also represent an independent risk factor for RLS, also resulting in more severe course of the symptoms. Many sensational phenomena occur particularly in patients with MS. If the patient is examined more carefully for the presence of RLS, his/her quality of life may be improved through treatment with dopamine agonists. Furthermore, treatment of iron deficiency anemia in both MS and BD groups may contribute to prevent/reduce RLS symptoms.

Ethics Committee Approval: Local ethics committee approved (No. 44140529/2014-66)

Informed Consent: Informed consent was obtained from the participants.

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