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Restless legs syndrome in multiple sclerosis

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Background/aim: There have been conflicting results in the literature regarding the relationship between functional system involvement, the expanded disability status scale (EDSS), and the presence of restless legs syndrome (RLS) in patients with multiple sclerosis (MS).

Materials and methods: Ninety-one patients with MS and 40 patients in a control group (headache, essential tremor, and benign positional paroxysmal vertigo) were studied. The patients underwent a complete neurological examination and Kurtzke functional system scores were calculated. In order to assess the temporal relation between the onset of RLS and MS, a semistructured interview guided by a questionnaire about RLS was applied to all of the patients.

Results: Sixteen (17.6%) of the patients with MS and 1 (2.5%) patient in the control group had RLS. The prevalence of RLS was higher in patients with MS, compared to the control group (P = 0.018). Among the patients with MS, none of them suffered from RLS before the onset of MS, whereas sixteen patients (16%) suffered RLS after the onset of MS. There was no significant relationship between functional system involvement and the presence of RLS.

Conclusion: The prevalence of RLS was higher in MS patients than it was in the control group. No association was found between RLS and functional system involvement in MS patients.

Key words: Multiple sclerosis, restless legs syndrome, EDSS

1. Introduction

Restless legs syndrome (RLS) is a sleep disorder characterized by an urge to move the legs associated with uncomfortable paresthesias. Usually, the symptoms manifest in the evening or at night, when the patients take rest, and are relieved by walking or moving the legs (1). Diagnosis of RLS needs to involve the following clinical features: (a) uncomfortable and unpleasant sensations in the legs, (b) worsening of the symptoms during rest, (c) relief of the symptoms by movement, (d) exacerbation of the sensitive disturbance in the evening or at night (1). The majority of RLS cases are commonly classified as idiopathic and include sporadic and inherited forms. Secondary form of RLS has been associated with iron deficiency, renal failure, pregnancy, antidopaminergic therapy, rheumatoid arthritis, or several neurological disorders, including peripheral neuropathy, spinocerebellar ataxia, essential tremor, Parkinson disease, and myelopathies (2–4). The etiopathogenesis of RLS is unknown, yet there is increasing evidence of dopaminergic neurotransmission dysfunction (5–9).

RLS prevalence has been reported to be 1.2%–15% and 12.12%–65.1% in the general population and in MS patients, respectively (10–30). RLS symptoms appear usually after the onset of MS (18–20,23,26,27). There is no relationship between MS subtypes and the presence of RLS (18,20,22–25,31). There are only three studies that investigated the relationship between functional system involvement and the presence of RLS in MS patients (19,23,25). Two of them showed that there was a significant relationship between some functional system involvement and RLS (19,25). In contrast, Deriu et al. did not find any relationship between the presence of RLS and functional system involvement (23). Some studies suggested that the expanded disability status scale (EDSS) was not related to RLS in MS patients (22,23). However, other studies showed that EDSS score was higher in MS patients with RLS than in those without RLS (18–20,30).

Lesion localization in brain MRI did not show any relationship with the presence of RLS in MS patients in most studies (18–20,22,23). There is only one study showing that MS patients with RLS (MS/RLS+) and patients without RLS (MS/RLS–) had similar cervical cord lesion load, but with less fractional anisotropy in cervical and brain MRI in the latter.

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Because there are conflicting results in the literature, we decided to investigate whether there was a difference among patients with MS and the control group (patients with headache, essential tremor, and benign positional paroxysmal vertigo), in regard to the prevalence of RLS. We also compared the relationship between functional system involvement, EDSS score, and the presence of RLS in MS patients. Moreover, we investigated brain lesion localization in MS/RLS+ and MS/RLS– patients.

2. Materials and methods

A prospective cohort study was conducted at one of Ankara's major teaching hospitals (Ankara University, İbni Sina Hospital, Turkey) from October 2006 to March 2009. Approval was obtained from the research ethics committee in advance. Written informed consent was acquired from all the patients. Participants were chosen solely from among those who visited the outpatient clinic. Ninety-one consecutive patients with a definitive MS diagnosis (67 female, 24 male) and 40 control patients (27 female, 13 male) were recruited. The control group consisted of patients with headache, essential tremor, or benign positional paroxysmal vertigo. The following criteria were evaluated for both study groups: age, sex, MS course, disease duration of MS, other underlying acute or chronic disease, and name and duration of the treatment intake related to MS. Exclusion criteria for the study were anemia, chronic renal failure, hypothyroidism, and diabetes mellitus.

A semistructured interview guided by a RLS questionnaire was applied to all of the patients. The temporal relation between the onset of RLS and MS (before or after the onset of MS, or during relapses) was questioned if RLS was present in the MS group. Patients were interviewed by two neurology specialists who were trained for the questionnaire. Patients were diagnosed with RLS if they fulfilled all four criteria. All of the patients underwent a complete neurological examination. Functional systems were assessed according to Kurtzke functional system scores and EDSS scores (32). Localization of the MS lesions (frontal, parietal, temporal, occipital, mesencephalon, pons, cerebellum, thalamus, caudate nucleus, putamen, globus pallidus, and internal capsule) on MRI was noted. Moreover, the mini-mental state examination (MMSE) was applied to all patients.

2.1. Statistical analysis

Student's t test was used to compare independent quantitative data. A chi-squared test was used to compare independent categorical variables. A P value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 11.5 for Windows.

3. Results

The MS group and the control group had a mean age of 37.6 and 35.4 years, respectively; the difference was not significant (P = 0.23). There were 24 males (26.4%) and 67 females (73.6%) in the MS group and 13 (32.5%) males and 27 (67.5%) females in the control group (P = 0.47). Average disease duration was 8.0 (1–32) years in the MS group. Among the patients with MS, 71 (78%) had relapsing-remitting MS (RRMS), 8 (8.8%) had secondary progressive MS (SPMS), 3 (3.3%) had progressive relapsing MS (PRMS), and 9 (9.9%) had primary progressive MS (PPMS). The median number of attacks was 3 (1–20) and the median EDSS score was 3 (0–9) in the MS group (Table 1).

Sixteen (17.6%) MS patients had RLS and 75 (82.4%) did not. One (2.5%) of the control patients had RLS; the difference was significant (P = 0.018) (Figure). There were no significant differences regarding age, sex, disease duration, the presence of depression, antidepressive or immunomodulatory drugs use, or the presence of median EDSS score between MS/RLS+ and MS/RLS– patients (P > 0.05 for each) (Table 1).

None of the 16 MS/RLS+ patients had RLS before the onset of MS and all of them had RLS after the onset of MS (17.6%). Ten of the 16 MS/RLS+ patients described an increase in RLS symptoms during MS attacks (11%). There was no relationship between functional system involvement and the presence of RLS (P > 0.05 for each) (Table 2).

RLS was found in 15/56 (21.1%) of the patients with RRMS and in 1/2 (33.3%) of those with PRMS (Table 1). There was no RLS+ patient in the SPMS and PPMS groups. Although there was a tendency towards a higher prevalence of RLS in RRMS than in progressive MS, the difference was not statistically significant (P = 0.18).

Ten (11%) MS/RLS+ patients described that their RLS related symptoms appeared or were aggravated during MS attacks, and eight of them underwent brain MRI during the same period. Twenty-one MS/RLS– patients underwent brain MRI during their relapse period. There was no difference in regard to lesion localization among MS/RLS+ and MS/RLS– patients on brain MRI that was acquired during the relapse period (P > 0.05) (Table 3). Only five patients underwent spinal MRI in the MS/RLS– group during their relapse period. Cervical plaques were observed in three MS/RLS– patients.

4. Discussion

Our study showed that the lifetime prevalence of RLS (17.6%) was significantly higher in MS patients than it was in the control group (2.5%). Auger et al. performed the earliest investigation on this topic, and reported that RLS prevalence was 37.5% in 200 patients with MS and 16% in a control group with 100 participants (17). A RLS prevalence

Table 1. Demographic features and presence of other chronic conditions in MS/RLS+ and MS/RLS– patients and the control group.

	MS/RLS+ (16)	MS/RLS– (75)	Total MS (91)	P	Control group (40)
Age (mean)	38.2	37.5	37.6	0.23	35.4
Sex (F/M)	14 / 2	53/22	67/24	0.47	27/17
Disease duration, year, Median (Min–Max)	8.0 (1–32)	8.0 (1–18)	8.0 (1–32)	0.14	
RRMS	15 (93.8%)	56 (74.7%)	71 (78.0%)	0.19	
SPMS	-	8 (10.6%)	8 (8.8%)		
PPMS	-	9 (12.0%)	9 (9.9%)		
PRMS	1 (6.2%)	2 (2.7%)	3 (3.3%)		
Attack number, Median (Min–Max)	4 (1–7)	3 (1–20)	3 (1–20)	0.26	
EDSS, Median (Min–Max)	3 (0–4.5)	3 (0–9)	3 (0–9)	0.80	
MMSE (mean)	28	27	28	0.45	
Immunomodulatory drugs usage (name, dose)				0.84	
-interferon beta - 1a 44 µg	1	9			
-interferon beta - 1a 6 MIU	3	10			
-interferon beta - 1b 22 µg	2	8			
-glatiramer acetate 20 mg	2	5			

EDSS: expanded disability status scale, RRMS: relapsing-remitting MS, SPMS: secondary progressive MS, PRMS: progressive relapsing MS, PPMS: primary progressive MS, MMSE: mini-mental status examination

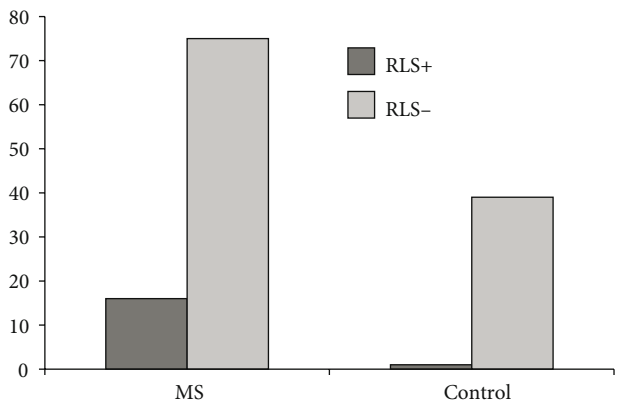

Figure. Prevalence of RLS was higher in MS patients than it was in the control group (P = 0.018).

of 32.5% was reported in 156 MS patients by Manconi et al. (18). In a multicenter case control study by Manconi et al., RLS prevalence was 19% in 864 MS patients and 4.2% in 649 healthy controls (19). Moreira et al. showed that the prevalence of RLS was 27% in 44 MS patients (20). A recent study reported that RLS frequency was 13.3% in 135 MS patients and 9.3% in a control group. In that study Gómez-Choco et al. showed that the prevalence of RLS was similar to that in the general population (22). Deriu et al. reported that RLS prevalence was 14.6% in 202 MS patients and 2.8% in 212 healthy controls (23). Moderate to severe and very severe RLS symptoms were reported in 57.5% of 80 MS patients and 15% of 180 controls by Farogaso et al. (24). Aydar et al. showed that RLS frequency was 27.6% in 98 MS patients and 10.1% in 128 healthy volunteers (25). Liu et al. demonstrated that the prevalence of RLS and severe RLS was 15.5% and 9.9%, respectively, among woman with MS and it was 6.4% and 2.6%, respectively, among women without MS (26). Miri et al. reported that RLS prevalence was 27.8% in 205 MS patients (27). In a recent study by Shaygannejad et al., the prevalence of RLS was 65.1% in MS patients and 12.7% in a control group (30). In agreement with most of the previous reports, we found that the prevalence of RLS was higher in MS patients than in the control group (17,19,23–27,29,30).

Age and sex in MS/RLS+ patients have been reported to be similar to those in MS/RLS– patients in most studies (17,20,22–27). There are other studies showing that the duration of MS did not show any difference between groups, MS/RLS+ patients were older and had higher EDSS scores than MS/RLS– patients (18–20,30). On the other hand, other studies showed that EDSS score in MS/RLS+

Table 2. Functional system involvement in MS/RLS+ and MS/RLS– patients.

		MS/RLS+	MS/RLS–	P
Pyramidal	(+)	3 10.3%	26 89.7%	0.16
	(–)	3 30%	7 70%	
Cerebellar	(+)	3 14.3%	18 85.7%	0.84
	(–)	3 16.7%	15 83.3%	
Brain stem	(+)	1 4.8%	20 95.2%	0.07
	(–)	5 27.8%	13 72.2%	
Sensorial	(+)	6 19.4%	25 80.6%	0.31
	(–)	0 0%	8 100%	
Bowel/bladder	(+)	3 12%	11 88%	0.64
	(–)	3 21.4%	22 78.6%	
Visual	(+)	1 16.7%	5 83.3%	0.66
	(–)	5 15.2%	28 84.8%	

Table 3. Brain MRI in MS/RLS+ and MS/RLS– patients during the relapse period.

		MS/RLS+	MS/RLS–	P
frontal	(+)	7	19	0.63
parietal	(+)	6	16	0.64
temporal	(+)	6	17	0.54
occipital	(+)	6	18	0.42
mesencephalon	(+)	2	5	0.64
pons	(+)	1	3	0.69
bulbus	(+)	1	2	0.63
cerebellum	(+)	4	11	0.61
thalamus	(+)	0	1	0.72
caudate nucleus	(+)	0	2	0.51
putamen and globus pallidus	(+)	0	2	0.51
internal capsule	(+)	0	1	0.72

patients was similar to that in MS/RLS– patients (22,23). Age, sex, disease duration, and EDSS scores in MS/RLS+ patients were similar to those in MS/RLS– patients in our study, compatible with some of the previous studies. We also found that anemia and immunomodulatory drug use did not differ between the MS/RLS+ and MS/RLS– groups. Therefore we concluded that immunomodulatory drug use had no effect on the prevalence of MS.

Moreire et al. reported that 11 of 35 RRMS patients and 1 of 4 PPMS patients had RLS (20). Manconi et al. showed that RLS prevalence was higher in PPMS than it was in other types of MS (19). Farogaso et al. reported that 5 patients presented with SPMS, while 75 patients presented with RRMS (24). There was a significant relationship between the type of MS and RLS, according to Aydar et al. (25). Miri et al. showed that 91.2% of patients (52 patients) had RRMS and 8.8% (5 patients) had PPMS (27). However, Deriu et al. did not find a higher RLS prevalence in PPMS patients (23). In our study, 15 of the 16 MS/RLS+ patients had RRMS and only one of the 16 MS/RLS+ patient had PRMS. We could not find any relationship between PRMS and the presence of RLS.

Only three studies have evaluated functional system involvement and the presence of RLS to date. Manconi et al. showed pyramidal and sensorial functional system scores were higher in MS/RLS+ patients than in MS/RLS– patients (19). Aydar et al. showed that there was a significant relationship between the pyramidal symptoms, intestinal and bladder dysfunction, and RLS (25). In contrast, Deriu et al. did not find any relationship between the presence of RLS and functional system involvement (23). However, in our study we did not find any relationship between functional system involvement and the presence of RLS.

We found that RLS got worse during MS attacks. Previous studies showed that MS/RLS+ patients had brain lesions on MRI similar to those in MS/RLS– patients (19–21,23,28). Aydar et al. reported that the number of lesions on brain MRI was related to RLS (25). In our study, eight MS/RLS+ and 16 MS/RLS– patients underwent brain MRI, which was performed during MS attacks. There was no difference in lesion localization in brain MRI between MS/RLS+ and MS/RLS– patients, which is compatible with previous reports. Therefore, we conclude that neither the presence nor the worsening of RLS is related to lesion localization in the brain.

Although the etiopathogenesis of RLS is still unknown, impairment of dopaminergic transmission and the iron metabolic pathway might be involved. The primary evidence that indicates involvement of primary dopaminergic pathology comes from the effectiveness of dopaminergic agents in treating RLS symptoms (5). It has been suggested that RLS might be caused by a dysfunction of the dorsoposterior hypothalamic dopaminergic A11 cell group (2). However, in a recent study, the A11 region showed no significant difference in brain autopsies of RLS and age-matched control cases (33).

Although extrastriatal as well as striatal brain regions were involved in RLS patients, reduction of the striatal dopaminergic function in RLS has been found in some brain PET studies (6–9). It has been suggested that hypoactive dopaminergic neurotransmission might contribute to the pathophysiology of RLS (9).

MS lesions in the brain may cause dysfunction in dopaminergic pathways, although there is no association between the brain lesion localization and the presence of RLS. Comparing the dopamine levels in MS/RLS+ and MS/RLS– patients may provide a clue.

There are some limitations of our study. First, family history of RLS was not evaluated in the MS or the control group. Although a complete blood count was performed in all of the participants, ferritin level was not measured. Moreover, the number of patients who underwent brain MRI during the relapse period of MS was small.

In conclusion, in contrast to some previous reports, there is no association of RLS with pyramidal or sensory system involvement in MS patients. Moreover, RLS is unrelated to EDSS score or lesions in brain MRI. In most of the cases, RLS was manifested after the onset of MS. Although there is no relationship between MS lesions in brain MRI and the presence of RLS, dopaminergic activity still might be decreased in MS patients. Dopaminergic activity in MS/RLS+ and MS/RLS– patients should be investigated in further studies. Moreover, the study should be replicated with further studies and more patients.

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