Multicenter Case-Control Study on Restless Legs Syndrome in Multiple Sclerosis: the REMS Study

The Italian REMS Study Group
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Study objectives: To verify the existence of a symptomatic form of restless legs syndrome (RLS) secondary to multiple sclerosis (MS) and to identify possible associated risk factors.

Design: Prospective, multicenter, case-control epidemiologic survey.

Settings: Twenty sleep centers certified by the Italian Association of Sleep Medicine.

Patients: Eight hundred and sixty-one patients affected by MS and 649 control subjects.

Interventions: N/A.

Measures and results: Data regarding demographic and clinical factors, presence and severity of RLS, the results of hematologic tests, and visual analysis of cerebrospinal magnetic resonance imaging studies were collected. The prevalence of RLS was 19% in MS and 4.2% in control subjects, with a risk to be affected by RLS of 5.4 (95%confidence interval: 3.56-8.26) times greater for patients with MS than for control subjects. In patients with MS, the following risk factors for RLS were significant: older age; longer MS duration; the primary progressive MS form; higher global, pyramidal, and sensory disability; and the presence of leg jerks before sleep onset. Patients with MS and RLS more often had sleep complaints and a higher intake of hypnotic medications than patients with MS without RLS. RLS associated with MS was more severe than that of control subjects.

Conclusions: RLS is significantly associated with MS, especially in patients with severe pyramidal and sensory disability. These results strengthen the idea that the inflammatory damage correlated with MS may induce a secondary form of RLS. As it does in idiopathic cases, RLS has a significant impact on sleep quality in patients with MS; therefore, it should be always searched for, particularly in the presence of insomnia unresponsive to treatment with common hypnotic drugs.

Keywords: Restless legs syndrome, multiple sclerosis, sleep

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ACCORDING TO THE *INTERNATIONAL CLASSIFICATION OF SLEEP DISORDERS*[1] AND TO THE STANDARD DIAGNOSTIC CRITERIA,[2] RESTLESS LEGS SYNDROME (RLS) is a sleep-related movement disorder characterized by uncomfortable sensations in the legs, which begin or worsen during rest, improve or disappear with movement, and occur or worsen in the evening or at night. Periodic limb movements (PLM), sleep disturbance, and a responsiveness to dopamine-agonist therapy are often associated with RLS.[2] RLS is still underdiagnosed; however, its prevalence in the general population has been estimated to be approximately 5%.[3] The majority of RLS cases are commonly classified as idiopathic and include sporadic and inherited forms.[4] The terms "symptomatic" or "secondary" refer to RLS forms significantly related to physiologic or pathologic conditions, such as iron deficiency,[5] renal failure,[6] pregnancy,[7] antidopaminergic therapy,[8] or rheumatoid arthritis.[9] Although the etiopathogenesis of PLM and RLS is still unknown, several lines of evidence suggest a dopaminergic system dysfunction as the basic mechanism.[10] The neuroanatomic basis of this dysfunction is also unclear, but a hyperexcitability of the spinal locomotor generator, due to an impairment of inhibitory supraspinal descending neurons to the dorsal spinal gray matter, has been postulated.[10,11]

Among the neurologic disorders, peripheral neuropathy,[12] spinocerebellar ataxia,[13] essential tremor,[14] Parkinson disease,[15] and myelopathies[16] are reported to be associated with RLS. A possible causal relationship between multiple sclerosis (MS)

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and RLS has been anecdotally reported.[17-19] More recently, 2 epidemiologic investigations[20,21] reported a prevalence rate of RLS in patients with MS as being higher than 30%, whereas another[22] did not confirm this finding. For this reason, a new controlled and methodologically sound study on a large cohort of subjects is needed.

Research on neurologic symptomatic forms of RLS may help in understanding which nervous centers or pathways play a role in the pathogenesis of RLS. The aim of this study (REstless legs syndrome in Multiple Sclerosis or REMS) was to verify the real existence of a form of RLS secondary to or associated with MS and to identify possible risk factors for RLS, by comparing the prevalence of RLS in MS with the one found in the general population.

METHODS

A prospective, face-to-face multicenter epidemiologic survey of a large group of patients affected by MS and of aged-matched control subjects was carried out. The study was coordinated by the Sleep Medicine Center of the Scientific Institute of San Raffaele (Milan, Italy) and was proposed to 25 Italian sleep centers certified by the Italian Sleep Medicine Association and specializing in the diagnosis and treatment of neurologic disorders. Twenty sleep centers agreed to participate in the study, which started on February 2006 and ended on October of the same year. The study involved centers distributed over the entire Italian territory in the following proportions: 9 centers from northern Italy (Bergamo, Cuneo, Dolo, Genova, Milan [Scientific Institute of San Raffaele], Milan [Niguarda Hospital], Pavia, Torino, and Udine), 7 centers from central Italy (Bologna, Ferrara, Parma, Pescara, Pisa, Roma, and Siena), and 4 from Southern Italy (Bari, Messina, Telese, and Troina). Patients with MS and control subjects were consecutively enrolled by each center over a period of 8 months. According to the standard diagnostic criteria for MS,[23] only patients affected by definite MS and with age ranging between 18 and 65 years were included. Age- and sex-matched control subjects, not affected by MS, enrolled among the spouses or friends of the probands, but not by proband consanguineous, were also consecutively recruited by each center. Exclusion criteria for both patients and controls included the following: neurologic disorders (other than MS for the patient group); specific diseases known to be induced by or related to RLS; pregnancy; previous or current treatment with clonazepam, dopamine agonists (except if used for a definite RLS diagnosis), or antidopaminergic (neuroleptic) compounds; history of alcohol or drug abuse; and a Mini Mental State Examination[24] score lower than 24 at the moment of the evaluation. Further exclusion criteria for patients were recent MS diagnosis (within 6 months from the time of the interview), recent clinical MS relapse (within 3 months from the interview), and treatment with any dose of steroids during the 3 months before the interview. No specific limitations were used regarding chronic MS treatments such as interferon, cyclophosphamide, copolymer, or azatioprine. On the basis of its clinical course, MS was classified as primary progressive, secondary progressive, or relapsing remitting.

In agreement with the epidemiologic rules suggested by the National Institutes of Health in collaboration with members of the International RLS Study Group,[2] all patients and controls underwent a face-to-face interview using a structured questionnaire, which was first proposed by the coordinating center; was then adjusted, taking into account the contribution of each center; and was finally approved for the standard diagnostic interview. The questionnaire covered the following aspects: demographics, medical and drug history, sleep habits, sleep disorders, and a detailed description of RLS symptoms when they were present. One physician, expert in sleep medicine (board certified by the Italian Association of Sleep Medicine), per each center, conducted the interviews. The presence of insomnia and excessive daytime somnolence (EDS) was evaluated by the 2 following questions: *Did you experience insomnia more than two times per week during the last 6 months?* and *Did you experience EDS more than two times per week during the last 6 months?"*

Subjects were considered to be affected by RLS if they met the 4 standard diagnostic criteria[2] and if the frequency of occurrence of RLS symptoms was at least twice per week during the 6 months preceding the interview. Patients and controls who were found affected by RLS underwent the validated self-administered International RLS Rating Scale[25] (10 items, score range between 0 and 40), to measure the severity of their RLS symptoms. The clinical impairment of patients with MS was evaluated by using the Expanded Disability Status Scale (EDSS),[26] assessed during the same day of the interview. A retrospective review of the medical reports assessed if patients and controls had undergone hematologic tests during the 2 months preceding the interview; in such a case, the following parameters were collected: hemoglobin, mean red cells corpuscular volume, creatinine, iron, transferrin, ferritin, vitamin B_{12}, and folate levels.

Magnetic resonance imaging (MRI) data for each patient were also taken into account only if they had been obtained during the 6 months preceding the interview and only if they included a complete brain-spinal scan. MRI analysis was performed by 2 experienced observers, by consensus, who were unaware of the identity of the scans. Brain lesions were identified on proton-density weighted scans and marked on the hard copies. The corresponding T2-weighted images were always used to increase the confidence in lesion identification. After the MRI analysis, each patients was classified as "supratentorial" if no lesions were detected in the brainstem and spinal cord and at least 1 lesion was detected in the brain; as "infratentorial" if no lesions were detected in brain and at least 1 lesion was detected in the brainstem or spinal cord, and as "supra/infratentorial" if at least 1 lesion in the brain and at least 1 lesion in brainstem and spinal cord structures were detected. The Local Ethics Committee of Milan approved the investigation. After receiving a detailed explanation of the protocol, each subject signed a written informed consent to the study.

Subgroups Classification and Statistical Analysis

According to the above-mentioned criteria, patients and controls were classified into 4 subgroups: (1) patients affected by MS without RLS symptoms (MS/RLS−), (2) patients affected by MS and RLS (MS/RLS+), 3) control subjects without RLS (CS/RLS−), (4) control subjects with RLS (CS/RLS+). The sta-

Table 1—Demographic Parameters of the Subjects Included in this Study

Sex	MS subjects			Control subjects		
	No.	Age, y		No.	Age, y	
		Mean	SD		Mean	SD
Men	265	40.5	10.14	218	39.6	10.32
Women	596	41.6	10.87	431	39.9	10.92
Total	861	41.2	10.66	649	39.8	10.71

tistical analysis included descriptive statistics and comparisons between patients with MS and control subjects or between the above subgroups; the χ^2 test and the Student t-test were used, as appropriate. Moreover, binomial logistic regression analysis was used to determine the best predictors of the presence or absence of RLS in patients with MS. Binomial logistic regression is a form of regression that is used when the dependent variable is dichotomous and the independent variables are continuous or nominal; the EDSS variable was excluded because it is not continuous and cannot be considered nominal. The commercially available software STATISTICA (data analysis software system), version 6, StatSoft, Inc. (2001) was used for all statistical tests.

RESULTS

Eight hundred and sixty-one patients affected by MS (596 women, 265 men, mean age 41.2 ± 10.66 years) and 649 age- and sex-matched control subjects (431 women, 218 men, mean age 39.8 ± 10.71 years) were included in the study (Table 1).

The median MS duration at the moment of the visit was 10.4 years (range 1-46 years), and the median EDSS score[26] was 2.7 (range 0.0-8.5, SD 1.7). The number of patients affected by the relapsing-remitting form of MS was 649 (75.43%), 50 patients with MS (5.8%) presented a primary-progressive form, and 162 (18.8%) patients had a secondary-progressive form. Two hundred and eleven (24.5%) patients with MS reported experiencing insomnia during the last 6 months, and 122 patients (14.2%) of the same group were taking daily medication (zolpidem, lorazepam, diazepam, prazepam, alprazolam, trazodone, amytriptiline, citalopram) to improve their sleep at the moment of the interview.

RLS Prevalence

One hundred and sixty-four patients with MS (19.0%) reported experiencing RLS symptoms at least twice per week during the 6 months preceding the interview and were classified as MS/RLS+. Patients with MS who never experienced RLS symptoms (634 patient, 73.6%), and patients who experienced RLS symptoms during the 6 months preceding the interview with a frequency of occurrence lower than twice per week (63 patient, 7.3%), were all included in the MS/RLS– subgroup (697 patient, 81.0%). No patients experienced RLS symptoms only before the considered window of time.

Twenty-seven out of 649 (4.2%) control subjects were found to be affected by RLS and were classified as CS/RLS+, whereas the remaining 622 (95.8%) were included in the CS/RLS–

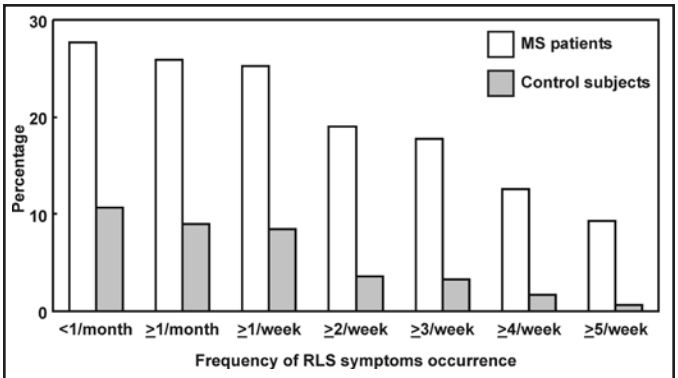

Figure 1—Likelihood of prevalence rate of restless legs syndrome (RLS), in both control subjects and patients with RLS, based on the frequency of RLS symptom occurrence chosen as a threshold for the diagnosis of RLS.

group. The above-mentioned results are summarized in Table 2, which reports the statistical significance ($P < 0.00001$) of the difference in RLS prevalence between MS and control subjects and quantifies the risk to be affected by RLS of 5.4 (95% confidence interval: 3.56-8.26) times greater for patients with MS than for control subjects.

Figure 1 shows the strong dependency of RLS prevalence rate, in both controls and cases groups, on the frequency of RLS symptom occurrence chosen as a threshold for the diagnosis of RLS. Changing the diagnostic threshold from once per month to at least 5 per week, decreased the prevalence of RLS from 27.6% to 9.3% in MS group and from 10.6% to 0.6% in the control subjects.

Figure 2 shows the prevalence of each RLS diagnostic criterion in patients with MS and control subjects classified as RLS negative. These patients lacked at least 1 of the RLS diagnostic criteria or RLS occurred with a frequency lower than twice per week in them. One hundred and fifty patients (21.5%) belonging to the MS/RLS– group and 55 (8.8%) belonging to the control subjects/RLS– group reported an unpleasant limb sensation; this corresponds with the first of the 4 essential diagnostic criteria for RLS. The prevalence of each of the 4 criteria was always reported with a significantly higher prevalence in the MS/RLS– than in the CS/RLS– group.

Considering the whole MS/RLS+ group, in only 22.0% of them were RLS symptoms experienced preceding the clinical onset of MS, whereas, in the remaining cases (78.0%), RLS appeared subsequent to or simultaneously with the clinical MS onset. The average delay between the onset of MS and that of RLS was 5.4 years (SD 11 years).

MS/RLS+ vs MS/RLS–

As shown in Table 3, MS/RLS+ patients were significantly older than MS/RLS– subjects at the moment of the interview or at the clinical onset of MS. MS duration was longer in the MS/RLS+ group, compared with MS/RLS– group. Sleep complaints (longer sleep latency, shorter total sleep time, higher prevalence of insomnia, excessive daytime sleepiness, snoring and leg jerks during pre-sleep rest wakefulness) were reported with a significantly higher frequency in RLS sufferers. Further-

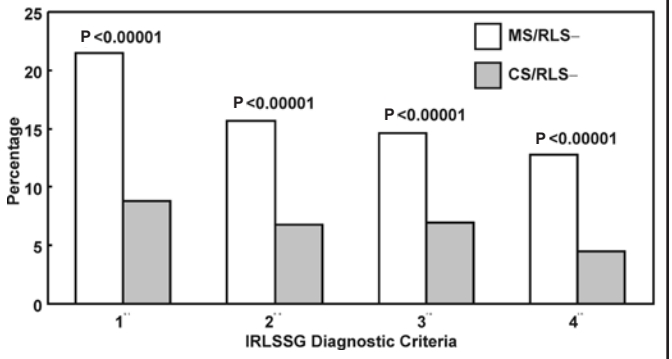

Figure 2—Prevalence of each restless legs syndrome (RLS) diagnostic criterion in patients with multiple sclerosis and control subjects classified as RLS negative (MS/RLS– and CS/RLS–, respectively).

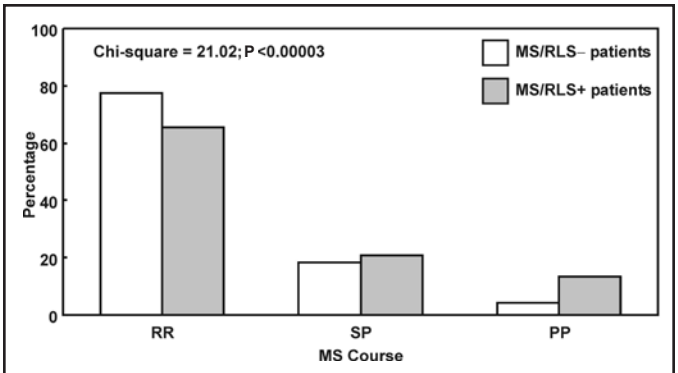

Figure 3—Distribution of the frequency of the 3 clinical courses of multiple sclerosis (MS) in patients with and without RLS. RR refers to relapsing remitting; SP secondary progressive; PP, primary progressive.

Table 2—Comparison Between the Prevalence of RLS in Patients with MS and in Control Subjects. The Odds Ratio of the Risk for RLS of Patients with MS Relative to Control Subjects is also Reported.

	Total no.	RLS– no.	RLS+ no.	RLS		
				Prevalence, %	+95% CI	−95% CI
Patients with MS	861	697	164	19.0	16.6	21.8
Control subjects	649	622	27	4.2	2.9	6
χ^2		74.23, P < 0.00001				
Odds ratio		5.4; 95% CI: 3.56−8.26				

RLS refers to restless legs syndrome; MS, multiple sclerosis; CI, confidence interval.

more, RLS was significantly associated with a higher intake of hypnotics, baclofen, and antidepressants. RLS family history was reported by 13.8% of MS/RLS+ patients and by 3.2% of MS/RLS– subjects.

The distribution of the frequency of the 3 MS clinical courses (Figure 3) was significantly different between patients with and without RLS, mostly because the primary-progressive form was more prevalent and the relapsing-remitting form less prevalent in MS/RLS+ than in RLS– patients.

Significantly higher global values of EDSS were found in MS/RLS+ than in RLS– patients (Figure 4). More interesting, this difference involved only the pyramidal and the sensory EDSS functional systems but not the cerebellar and brainstem ones.

As reported in Table 4, no difference between MS/RLS+ and MS/RLS– were found in the plasma values of the following parameters: hemoglobin, mean corpuscular volume, iron, ferritin, transferrin, creatinine, vitamin B_{12}, and folates.

MRI data were available in 594 patients with MS; the following results were found in patients with MS with and without RLS, respectively: only supratentorial damage in 19.4% and 26.7%, only infratentorial damage in 1.9% and 2.1%, supra and infratentorial pattern in 78.7% and 71.2% ($\chi^2 = 2.56$; NS).

Besides analyzing the differences between MS/RLS+ and RLS– patients, we also utilized binomial logistic regression analysis to determine the percentage of variance in the dependent variable (presence or absence of RLS) explained by a set of independent factors similar to those included in Table 3 but excluding EDSS (which is not a continuous variable and cannot be considered nominal). The results of this analysis confirm that some of the factors already found to be different between these 2 subgroups of patients with MS explain a significant part of the variance of the dependent variable, i.e., the presence of insomnia (partial correlation 0.089, P < 0.0075), EDS (partial correlation 0.074, P < 0.0185), leg jerks before sleep (partial correlation 0.224, P < 0.0001), and RLS family history (partial correlation 0.134, P < 0.0002), which appear to be significant predictors for the presence of RLS in these patients.

MS/RLS+ vs CS/RLS+

As shown in Table 5, when comparing data from RLS subjects with and without MS, no differences were found in the mean age at the visit and at RLS onset, in the mean duration of RLS symptoms, and in the mean sleep latency. Total sleep time was significantly shorter in the MS/RLS+ group than in the CS/RLS+ group. On the basis of the International RLS Rating Scale score, RLS was more severe in the MS/RLS+ than in the CS/RLS+ groups. RLS family history was reported by 13.8% of the patients with MS with RLS and by 22.6% of the control subjects with RLS. Drug therapy was reported by 22.6% of subjects belonging to the MS/RLS+ group and by 14.1% of the CS/RLS+ group.

Figure 5 describes the anatomic distribution of RLS symptoms in RLS subjects with and without MS, showing no significant difference in the frequency of involvement of each body part. A lateralization of RLS symptoms occurrence was significantly more frequently reported by the MS/RLS+ than the CS/RLS+ group.

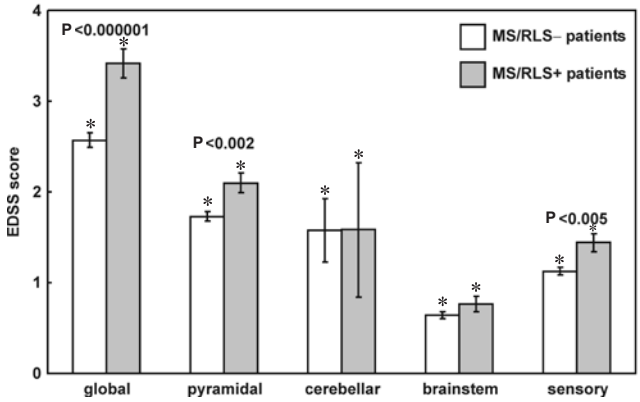

Figure 4—Comparison of Expanded Disability Status Scale (EDSS) scores found in MS/RLS+ and MS/RLS– patients. MS refers to multiple sclerosis; RLS, restless legs syndrome.
*mean ± SD

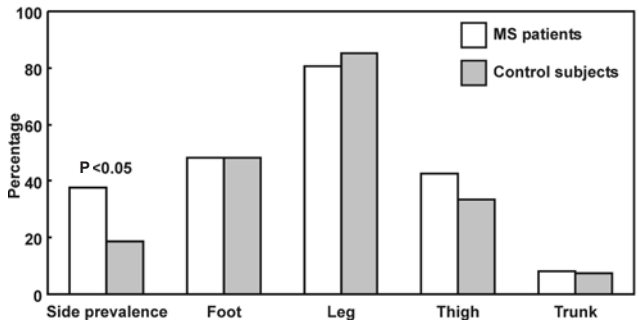

Figure 5—Anatomic distribution of symptoms of restless legs syndrome (RLS) in RLS patients with and without multiple sclerosis (MS).

DISCUSSION

Our results represent solid evidence that the prevalence of RLS is significantly higher in MS than in control subjects. Among patients with MS, RLS is associated with older age, longer MS duration, and more severe disability specifically involving the pyramidal and the sensitive EDSS functional systems. Patients with MS with RLS reported poorer sleep quality and higher drug intake to improve their sleep than did patients with MS without RLS. Iron-storage indicators, as well as plasma levels of creatinine and folate, did not differ between patients with MS with RLS and those without RLS. The severity of RLS symptoms was higher in patients with MS than in control subjects.

Auger et al[20] performed the earliest structured investigation on this topic and found an RLS prevalence of 37.5% in 200 patients with MS and 16% in 100 control subjects. Manconi et al[21] investigated 156 MS subjects and diagnosed RLS in 32.7% of them. Recently, Gòmez-Choco et al found no significant differences in RLS prevalence between 135 patients with MS (13.3%) and 118 control subjects (9.3%).[22] A different methodology may explain the discrepancies in prevalence rates between the present and these previous studies. Although the diagnosis of RLS had been performed by means of the standard criteria in all studies,[2] Auger et al[20] performed their investigation in a French-Canadian population comprising subjects older than ours; they used a self-administered questionnaire and did not specify the frequency of occurrence of RLS needed to define a subject as affected. This methodology may have overestimated the prevalence of RLS, as suggested by the exces-

Table 3—Characteristics of Patients with MS without and with RLS

A. Continuous variables

	MS/RLS− Mean ± SD	MS/RLS+ Mean ± SD	Student t-test t value	P ≤
Age at visit, y	40.2 ± 10.43	45.6 ± 10.60	-5.82	0.000001
Age at MS onset, y	30.3 ± 9.31	34.0 ± 9.55	-3.98	0.00008
MS duration, y	10.1 ± 8.11	12.0 ± 9.37	-2.32	0.02
Sleep latency, min	19.4 ± 25.06	24.7 ± 30.75	-2.32	0.02
Total sleep time, min	425.1 ± 81.03	394.5 ± 86.61	4.28	0.00002

B. Comparison of frequencies, %

	MS/RLS−	MS/RLS+	χ^2	P ≤
Nap	35.9	37.2	0.10	NS
EDS	28.0	43.9	15.77	0.0001
Insomnia	20.5	41.5	31.36	0.00001
Bruxism	11.3	14.6	1.10	NS
Snoring	21.7	33.9	8.34	0.004
Leg jerks before sleep	23.8	56.1	29.78	0.00001
RLS family history	3.2	13.8	27.17	0.00001
Use of medications				
None	86.7	75.0	13.73	0.0002
Hypnotics	9.9	18.3	9.19	0.0024
Antidepressants	2.4	5.5	4.21	0.04
Baclofen	1.0	3.0	4.04	0.045
Other compounds	0.9	1.8	1.20	NS

MS refers to multiple sclerosis; RLS, restless legs syndrome; EDS excessive daytime sleepiness.

Table 4—Comparison of the Results of Hematologic Testing Obtained from Patients with MS without and with RLS

Test	MS/RLS−			MS/RLS+			Student's t-test	
	No.	*mean*	*S.D.*	No.	*mean*	*S.D.*	*t value*	*p*≤
Hemoglobin, g/dL	399	12.72	3.805	80	13.34	1.139	-1.43	NS
MCV, fL	398	85.20	62.157	81	87.00	9.174	-0.26	NS
Iron, µg/dL	260	83.55	33.988	45	77.36	32.284	1.14	NS
Ferritin, ng/mL	224	89.02	98.627	39	68.29	132.034	1.15	NS
Transferrin, g/L	196	185.99	125.751	26	169.78	142.529	0.61	NS
Creatinine, mg/dL	377	0.71	0.251	74	0.75	0.175	-1.37	NS
Vitamin B_{12}, pg/mL	220	420.91	218.536	34	517.70	539.724	-1.86	NS
Folate, ng/mL	220	7.76	34.246	35	8.09	8.238	-0.06	NS

MS refers to multiple sclerosis; RLS, restless legs syndrome; MCV, mean corpuscular volume

Table 5—Characteristics of Patients with MS and RLS and Control Subjects with RLS

A. Continuous variables

	MS/RLS+ Mean ± SD	CS/RLS+ Mean ± SD	Student t-test t value	P ≤
Age at visit, y	45.6 ± 10.60	46.0 ± 10.12	-0.18	NS
Age at RLS onset, y	39.0 ± 11.02	37.6 ± 12.32	0.61	NS
Duration of RLS symptoms, min	38.8 ± 40.86	35.4 ± 40.67	0.41	NS
IRLSRS, score	17.5 ± 5.70	14.0 ± 4.71	2.97	0.003
Sleep latency, min	24.7 ± 30.75	17.4 ± 18.88	1.18	NS
Total sleep time, min	394.5 ± 86.61	342.5 ± 80.71	2.94	0.004

B. Frequencies, %

	MS/RLS+	CS/RLS+	χ^2	P ≤
RLS family history	13.8	22.2	2.17	NS
Use of medication for sleep	22.6	14.1	2.69	NS

MS refers to multiple sclerosis; RLS, restless legs syndrome; CS, control subjects; IRLSSG, International RLS Study Group.

sively high rate (16%) of RLS found in the control subjects. Genetic differences between the French-Canadian and the Italian population may also influence the final prevalence results. Lavigne et al[27] found that RLS symptoms were reported more frequently in French-speaking subjects of eastern Canada than in English-speaking persons of western Canada. Studying a large group of 2036 subjects older than 18 years, Allen et al[28] estimated the prevalence of RLS in the Italian general population as 3.1%; this figure is very similar to our finding in control subjects (4.2%). In agreement with Auger et al,[20] in the present study, RLS symptoms were more severe in patients with MS than in control subjects. The previous study by Manconi et al[21] was a noncontrolled investigation. Furthermore, the diagnostic threshold for the frequency of occurrence of RLS was established as once per week and not twice, as in this investigation. In the study of Gòmez-Choco et al,[22] only "equivocal cases" were scheduled for a second visit with a sleep disorders expert; moreover, the threshold of frequency of symptom occurrence in establishing the RLS diagnosis was not specified. Figure 1 clearly shows the close dependency of the RLS prevalence on the diagnostic threshold chosen and also shows a rate of 26% when subjects who experience symptoms at least once per week are considered as affected by RLS.

As indicated by the high percentage of RLS– patients who reported only some of the essential diagnostic criteria for RLS, in patients with MS, the differential diagnosis between RLS and other sensitive and motor complaints is certainly more difficult than in idiopathic cases. For this reason, a detailed assessment of the 4 essential diagnostic criteria for RLS[2] to avoid false-positive diagnosis was performed. The following findings from this study all provide evidence for a possible symptomatic RLS form, secondary to MS: elevated prevalence of RLS in patients with MS, compared with control subjects; the association of RLS with a higher MS disability and with the most severe MS course; the fact that, in most cases, the clinical onset of RLS followed that of MS, with a mean delay of about 5 years; and the high frequency of asymmetric anatomic distribution of RLS symptoms. On the other hand, some results support the hypothesis that, in at least a small portion of patients with MS—approximately 4% (prevalence of RLS in control subjects)—the nature of RLS may be idiopathic, with a possible genetic contribution. In fact, a positive correlation between RLS and age and female sex was found. Moreover, in a small percentage of patients, RLS preceded the onset of MS and, finally, approximately 14% of MS/RLS+ patients reported the occurrence of RLS symptoms in at least 1 of their first-degree relatives. Another possible confounding factor is represented by the treatment with antidepressants. A few reports suggest that antidepressant use may exacerbate or even trigger RLS symptoms;[29-31] however, it should be considered that, in the present study, although significant, the

difference in antidepressant intake between MS/RLS+ and MS/RLS– subjects was minimal (5.5% vs 2.4%). According to the hematologic findings, considered for the first time in the present study, iron deficiency does not seem to play a significant role in the pathogenesis of this form of RLS. However, it should be taken into account that RLS patients with normal plasma levels of iron-storage indicators might have low cerebrospinal fluid values of the same parameters.[32,33] Moreover, because ferritin is a generic inflammation marker, concurrent inflammatory conditions, which frequently occur in patients with MS, might increase the standard deviation of the mean ferritin value and may influence the final significance between groups.

In patients with MS, RLS symptoms may be the consequence of specific lesions of nervous-system structures or pathways involved in the etiology of RLS. Patients with MS with a higher global EDSS score and a more severe MS course, as compared with patients with a milder MS course, might have more opportunities to develop damage in specific neurologic regions involved in RLS pathogenesis. The dopaminergic hypothalamic-spinal connection descending from the A11 nucleus to the dorsal gray horns might be a possible lesion target in this mechanism. Several lines of evidence suggest that RLS symptoms may be induced by a dysfunction of this pathway that, in turn, would disinhibit lower spinal levels, triggering the typical RLS phenotype.[10,34-36] Neurophysiologic studies have confirmed this hypothesis.[37,38] In particular, the close resemblance between PLM and the Babinski sign has strengthened the theory of a spinal cord hyperexcitability in patients with RLS.[11] In the present study, leg jerks before falling asleep were more frequently reported by patients with MS affected by RLS, and part of this motor activity may be compatible with PLM. It has already been reported in the literature that MS is often associated with PLM, according to the results of polysomnography.[39] Herein, we first established a significant positive relationship between the severity of the motor symptoms and the impairment of the sensory systems in patients with MS and their risk of developing RLS; at the same time, we found no association between the prevalence of RLS and the level of impairment of the cerebellar and brainstem systems. Previous studies have already reported cases of RLS/PLM secondary to lesions that interrupt the descending motor pathways at the spinal cord level due to different etiologies: transverse myelitis,[40] syringomyelia,[41] traumatic transection,[42,43] schwannoma,[44] and postpolio sequelae.[45] Hartmann et al have described a case of unilateral RLS secondary to myelitis due to MS that improved after the administration of levodopa.[43] Moreover, in animal models, the occurrence of limb movements during sleep in rats with experimental spinal injuries has been demonstrated.[46] Although less supported by evidence-based data, the symptoms of RLS have been shown to correlate with impairment of ascending sensory pathways, as a result of a central somatosensory processing dysfunction due to an abnormal peripheral afferent input.[47] In the pathogenesis of this RLS form, a possible role of damage in gray matter nuclei, in glial tissue, or in peripheral fibers because of Wallerian degeneration, which have been all demonstrated to occur in MS,[48-50] cannot be excluded.

We found no significant association between RLS and a particular MRI lesion pattern; this may due to the low sensitivity of our MRI analysis approach. A more detailed MRI study, with the assessment of the lesional load score and the use of the mean diffusion and fractional anisotropy analysis, are needed to better correlate possible anatomic lesions and RLS. Ferini-Strambi et al have found that patients with MS and PLM had higher MRI lesion loads in infratentorial regions, compared with patients with MS without PLM.[39]

Findings regarding insomnia complaints, total sleep time, sleep latency, and legs jerks demonstrate that RLS is significantly associated with a reduced sleep quality and a greater intake of hypnotics and antidepressant medications in patients with MS. Because RLS is usually unresponsive to treatment with benzodiazepines and because symptoms sometimes worsen with the use of some antidepressant drugs, an early recognition of RLS in patients with MS may avoid ineffective drug treatment in favor of a more successful therapy, such as a low evening dose of dopamine agonists. Indeed, sleep disturbances in these patients may also be related to their particularly high level of clinical impairment.

In conclusion, the present epidemiologic findings support the existence of a symptomatic form of RLS secondary to MS. Therefore, to avoid erroneous diagnosis of primary insomnia and the subsequent ineffective and the potentially deleterious effect of medication, we recommend that patients with MS always be assessed for the presence of RLS symptoms, especially those patients who report sleep difficulties or have high motor or sensory disabilities.

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