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ORIGINAL ARTICLE

Restless leg syndrome and multiple sclerosis: a case-control study in China

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Abstract
Background As a common neurological movement disorder, restless leg syndrome (RLS) is often seen in patients with multiple sclerosis (MS). However, the relationship between RLS and MS is still unclear. This case-control study aimed to measure RLS prevalence and uncover its association with MS, as well as to identify possible associated risk factors.
Methods Six hundred and ninety-five patients were randomly selected from a cohort of patients with MS at the Neurology Department of our hospital, and a group of age- and sex-matched healthy controls (n=603) was enrolled from the general population. Using a face-to-face interview questionnaire, we collected data on RLS incidence in participants with or without MS. We further assessed sleep quality in all the participants.
Results We found there to be a significantly higher prevalence of RLS among patients with MS compared to healthy controls (odds ratio [OR], 3.8; P<0.001). Risk factors such as an older MS age at onset and a longer MS duration were significantly associated with the presence of RLS. Furthermore, patients with both MS and RLS were more likely to suffer from sleep complaints compared to patients with MS without RLS.
Conclusions RLS was significantly associated with MS and was found to have a significant impact on sleep quality, particularly in patients with MS.

Keywords Restless leg syndrome · Multiple sclerosis · Sleep · China

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Introduction

Restless leg syndrome (RLS) is a common neurological movement disorder characterized by a distressing urge to move the legs to stop uncomfortable sensations that are brought on by rest. The symptoms of RLS usually become worse at night or in the evening and improve or disappear with movement [1]. RLS prevalence in the general population has been revealed to be somewhere between 1.57 and 15 % [2, 3], and the prevalence of RLS in Chinese adults has been reported to be 7.2 % [4]. The standardized criteria for the diagnosis of RLS was developed by the International RLS Study Group (IRLSSG) in 1995 (and revised in 2003), and it considers four cardinal features based on patient history [5].

RLS can be idiopathic and secondary. However, the pathophysiology of RLS remains unclear. Previous studies have reported that 50–92 % of patients with idiopathic RLS have a family history of RLS [6], and secondary RLS has been associated with many etiologies, such as pregnancy [7], iron deficiency [8], renal failure [9], and antidopaminergic therapy [10].

Some neurological disorders have also been reported to be associated with RLS, such as peripheral neuropathy [11],

essential tremor [12], myelopathies [13], and Parkinson's disease [14]. Recently, some researchers have studied the relationship between RLS and multiple sclerosis (MS). However, these have produced inconsistent results. For instance, some studies have found a higher frequency of RLS in patients with MS compared to the normal population [15–20], while others have reported there to be a very similar frequency of RLS in patients with MS and controls [21]. Thus, MS has not yet been regarded as a secondary cause of RLS.

Taking into account the disparity in the literature and the huge variability of RLS prevalence among distinct populations, we believe that it is worth verifying the risk of RLS in patients with MS. In this study, we investigated whether patients with MS have a higher RLS frequency than controls and evaluated the characteristics of MS with and without RLS.

Methods

Population

Our study was performed at the Neurology Department of The First Affiliated Hospital of Zhengzhou University between January and December, 2014. A total of 1298 people were enrolled in this study (695 definite MS patients and 603 healthy control subjects), and informed patient consent was obtained for this study. MS had been diagnosed according to the revised 2005 version of the "McDonald criteria" [22] in the outpatient neurology clinic in our hospital, and the control group comprised healthy age- and sex-matched volunteers (teachers and students of Zhengzhou University, and health care personnel). Subjects with the following cases were excluded: neurological disorders other than MS, pregnancy, an RLS-related disease (iron deficiency, renal failure, rheumatoid arthritis, diabetes mellitus, and anemia), taking medication such as clonazepam, dopamine agonists (except for the definite RLS subjects), or antidopaminergic compounds. Subjects that had a history of alcohol or drug abuse were not included in the study. Further exclusion criteria for patients with MS were the following: a recent MS diagnosis (within 6 months from the time of interview), a recent clinical MS relapse (within 3 months from the time of interview), and treatment with any dose of steroids (within 3 months from the time of interview). The MS group was divided into three subgroups according to their clinical course: relapsing-remitting form (RR), secondary progressive form (SP), and primary progressive form (PP).

Procedure

All patients and controls underwent a face-to-face interview to assess the presence of RLS, based on the Chinese version of essential IRLSSG diagnostic criteria [5]. Subjects who fulfilled the IRLSSG criteria and had symptoms at least four times/month were diagnosed as having RLS. A structured questionnaire was also administered during this interview process, and this allowed us to collect the following data: demographics (age, gender), the description of MS (age at onset of MS, MS duration, the mean expanded disability status scale) and RLS (the severity of RLS, the frequency of RLS, family history of RLS), and sleep disorders (insomnia, snoring, and nightmares). The RLS rating scale (IRLS-RS) was also administrated to all participants in order to investigate the severity of RLS.

Sleep quality and excessive daytime sleepiness (EDS) of participants were defined according to the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS), respectively. The score ranges from 0 to 21 in the PSQI, with scores >5 indicating a clinical sleep disturbance. Scores >10 in the ESS were considered to indicate EDS.

Statistical analysis

SPSS (version 17.0) was used for statistical analysis. Logistic regression analysis was applied to identify significant predictive factors for MS. The continuous variables were expressed as mean±SD, and Student's t tests were used to compare means between the two groups. The qualitative variables were expressed as proportions and were compared using the chi-squared test. Unless otherwise stated, $P<0.05$ was set as the level of significance.

Results

RLS prevalence

The data of 695 MS patients (482 women, 213 men, mean age 37.9±8.8 years) and 603 healthy controls (416 women, 187 men, mean age 38.6±9.3 years) were obtained in this study. Age and sex were not significantly different between the two groups. One hundred and seventy-one patients in the MS group and 48 participants in the healthy control group fulfilled RLS diagnostic criteria, resulting in a prevalence of 24.6 % in the MS group and 8.0 % in control group. These demographic results are summarized in Table 1, which also reports that the risk of suffering from RLS was calculated to be over three (odds ratio [OR] 3.8, 95 % confidence interval [CI] 2.7–5.3 for univariate analysis; OR 3.8, 95 % CI 2.7–5.4 for multivariate analysis) times greater for patients with MS than for control subjects.

Comparison of the characteristics of patients with MS and control subjects

Based on their reports of experiencing RLS symptoms, patients with MS were defined as being with RLS (MS/RLS+

Table 1 Baseline of patients with MS and healthy control subjects

			Univariate analysis			Multivariate analysis		
	MS cases	Healthy controls	OR	95 % CI	*P* value	OR	95 % CI	*P* value
N	695	603						
Age (mean±SD)	37.9±8.8	38.6±9.3	1.0	0.9–1.1	0.736	1.0	0.9–1.0	0.521
Sex								
Male	213 (30.6)	187 (31.0)	1.0	/	/	1.0	/	/
Female	482 (69.4)	416 (69.0)	1.0	0.8–1.2	0.887	1.0	0.7–1.2	0.624
RLS, *N* (%)	171 (24.6)	48 (8.0)	3.8	2.7–5.3	<0.001	3.8	2.7–5.4	<0.001

group) or without RLS (MS/RLS− group). Control subjects found to be affected by RLS were classified as control/RLS+, and the remaining subjects were included in the control/RLS− group. As shown in Table 2, no differences were found in the mean age between the MS/RLS+ and MS/RLS− groups. However, patients in MS/RLS+ group were significantly older than those in MS/RLS− group at the onset of MS. MS duration was also found to be longer in MS/RLS+ group compared with MS/RLS− group.

We also compared the three different clinical courses (RR, SP, PP) of MS in patients with or without RLS (Table 2) and found that there was a significant between-group difference. The primary-progressive form (PP) was more prevalent in MS/RLS+ group than in MS/RLS− group, and correspondingly, the relapsing-remitting form (RR) and secondary progressive form (SP) were more prevalent in the MS/RLS− group than in the MS/RLS+ group. Furthermore, there were no differences in the EDSS scores between the two patient groups.

On comparing data from RLS subjects with and without MS, there were no differences in the mean age or the age at RLS onset (Table 2). RLS severity was also investigated using the International RLS Rating Scale (IRLS-RS) score, which was higher in the MS/RLS+ group compared to the con/RLS+ group. The distribution of the frequency of the four levels of RLS severity (mild, moderate, severe, and very severe) was also different between the MS/RLS+ and con/RLS+ group. The prevalence of RLS with a frequency ≥1 time/day was found to be higher in the MS/RLS+ group compared to the con/RLS+ group. RLS family history was also different between the two RLS+ groups.

Comparison of sleep quality between patients with MS and control subjects

Data for sleep-related disorders are showed in Table 3. No differences were found in the sleep latency, in the frequency of nightmares, and sleep apnea between the MS/RLS+ and MS/RLS− groups. However, the total sleep time, snoring, insomnia, PSQI score, and ESS score were all significantly higher in frequency or value in the MS/RLS+ group compared to the MS/RLS− group. As for the RLS subjects with or without MS, total sleep time, PSQI score, and a PSQI frequency of >5 were found to be higher in the MS/RLS+ group than in the con/RLS+ group. There were no between-group differences in the remaining sleep complaints (EDS, insomnia, snoring, nightmare, sleep latency, total sleep time, and self-reported sleep apnea).

Discussion

To our knowledge, this study is the first population-based survey on RLS prevalence of MS patients in the mainland China. The prevalence of RLS in patients with MS (24.6 %) was much higher than in healthy controls (8.0 %), which indicates the risk of developing RLS to be almost 3.8 times higher in patients with MS. This finding was consistent with most previous studies [15–20], with only one exception [21]. Nonetheless, the reasons behind this high RLS prevalence in patients with MS are still unclear. One suggestion has been that, because RLS and MS are both inflammatory-related diseases, there may be connections between disease processes [23]. Manconi et al. have also speculated that this high incidence of RLS in patients with MS might be associated with high disability and damage to the cervical cord [24]. Furthermore, the authors reported that the clinical onset of RLS was later than that of MS, which indicates a causal relationship between their symptoms [24]. Similar results were obtained in our study, with a mean delay of about 4 years. We also found that the proportion of MS/RLS+ patients who experienced RLS before MS diagnosis was 32.7 % and who experienced RLS after MS diagnosis was 67.3 % in this study, which could also support the theory that RLS may be induced, somewhat, by MS.

It is also worth noting that reported RLS prevalence varies widely among different studies, ranging from 13.3 to 65.1 %. There are several possible reasons for these discrepancies. First, the mode of survey methods used was different between studies. Patient-filled questionnaires, interviews, and

Table 2 Demographic and clinical features of patients with MS and healthy control subjects

	MS/RLS+	MS/RLS−	Con/RLS+	Con/RLS−	P^a	P^b
N (%)	171 (24.6)	524 (75.4)	48 (8.0)	555 (92.0)		
Age (mean±SD)	38.1±8.5	38.6±10.3	40.2±8.3	37.4±8.1	0.566	0.130
Sex, *N* (%)						
Female	125 (73.1)	353 (67.4)	36 (75.0)	380 (68.5)	0.160	0.792
Male	46 (26.9)	171 (32.6)	12 (25.0)	175 (31.5)		
MS age at onset (mean±SD)	35.8±8.6	30.6±9.3	–	–	<0.001	
MS duration, years (mean±SD)	13.8±9.4	10.5±12.1	–	–	0.001	
EDSS score (mean±SD)	2.5±2.1	2.4±1.9	–	–	0.561	
MS clinical course, *N* (%)					0.021	
RR patients	137 (80.1)	411 (78.4)	–	–		
SP patients	32 (18.7)	85 (16.2)	–	–		
PP patients	2 (1.2)	28 (5.4)	–	–		
RLS age at onset (mean±SD)	39.7±12.3	–	36.2±15.6	–		0.103
IRLS-RS score	18.2±5.3		14.5±5.8			<0.001
IRLS-RS, *N* (%)						0.038
Mild (0–10)	18 (10.5)	–	9 (18.8)	–		
Moderate (11–20)	36 (21.1)	–	17 (35.4)	–		
Severe (21–30)	79 (46.2)	–	16 (33.3)	–		
Very severe (31–40)	38 (22.2)	–	6 (12.5)	–		
Frequency of RLS, *N* (%)						0.037
1–4 times/month	55 (32.0)	–	24 (50.0)	–		
1–6 times/week	83 (48.3)	–	20 (41.7)	–		
≥1 time/day	34 (19.8)	–	4 (8.3)	–		
RLS family history, *N* (%)		–		–		0.021
Yes	20 (11.7)	–	12 (24.6)	–		
No	151 (88.3)	–	36 (75.4)	–		

[a] MS cases (RLS+) vs. MS cases (RLS−). The continuous variables were compared using Student's *t* tests, and the qualitative variables were calculated using the chi-squared test

[b] MS cases (RLS+) vs. healthy controls (RLS+). The continuous variables were compared using Student's *t* tests, and the qualitative variables were calculated using the chi-squared test

Table 3 Sleep quality assessment in patients with MS and healthy control subjects

	MS/RLS+	MS/RLS−	Con/RLS+	Con/RLS−	P^a	P^b
EDS (%)	42.7	27.6	36.3	13.6	<0.001	0.365
Insomnia (%)	51.3	20.7	41.4	14.3	<0.001	0.230
Snoring (%)	35.6	19.3	32.7	11.2	<0.001	0.764
Nightmare (%)	53.2	44.7	41.2	38.6	0.090	0.053
Sleep latency, min (mean±SD)	28.3±25.2	22.6±23.5	18.6±19.3	8.2±20.8	0.119	0.066
Total sleep time, min (mean±SD)	387.2±76.5	432.4±82.1	337.9±72.3	463.7±75.9	<0.001	<0.001
Sleep apnea (%)	45.6	37.6	41.7	16.3	0.063	0.627
PSQI score (mean±SD)	9.2±5.1	7.5±3.1	7.8±3.3	4.7±3.8	<0.001	0.041
PSQI >5 (%)	84.2	72.7	61.3	26.9	0.002	<0.001
ESS score (mean±SD)	11.8±3.9	7.8±3.4	9.6±3.1	5.2±4.2	<0.001	0.004

[a] MS cases (RLS+) vs. MS cases (RLS−). The continuous variables were compared using Student's *t* tests, and the qualitative variables were calculated using the chi-squared test

[b] MS cases (RLS+) vs. healthy controls (RLS+). The continuous variables were compared using Student's *t* tests, and the qualitative variables were calculated using the chi-squared test

structured interviews were all used for RLS diagnosis, and patient-filled questionnaires tend to result in more false-positive diagnoses. For example, a high false-positive rate of RLS diagnosis was found in MS patients because of the MS-related sensorimotor symptoms. It seems that greater severity of symptoms in MS than in controls may reflect not RLS but some of these other symptoms [25]. Second, the diagnostic threshold of RLS frequency applied in these studies was different. In our own study, we applied a diagnostic threshold of four times with RLS symptoms per month. In an REMS study performed by Manconi et al. [15], the threshold was set as 2 days/week, while Vavrova et al. [26] applied no threshold. Indeed, these authors found that RLS prevalence was found to increase with a more stringent threshold. Third, these studies used different exclusion criteria. Some excluded particular diseases that could lead to the occurrence of RLS or have similar symptoms to RLS. Indeed, the frequency of RLS was found to be higher in studies without such exclusion criteria. Fourth, genetic differences, memory bias, and individual differences in these studies may have also influenced RLS prevalence results.

Some studies have reported higher EDSS scores in MS patients with RLS [15, 24, 27, 28] and have thus suggested that higher EDSS scores might be a risk factor for RLS in these patients. However, we did not replicate this finding, similarly to other studies [16, 21]. Thus, large sample studies will be needed to clarify this point. We found that the MS/RLS+ group displayed more severe RLS symptoms than the con/RLS+, a consistent finding in most of the published studies [15–17]. This indicates that RLS in patients with MS may have a more severe course. We also investigated the MS clinical course between patients with and without RLS. The results showed that the PP form, rather than RR form and SP form, was more frequently found in MS patients without RLS, which indicates that RLS may have an impact on the clinical course of MS. This result was similar to that of Manconi et al. [15]. We also found that a positive family history of RLS was significantly less in the MS group compared to the healthy controls.

Regarding sleep assessments, RLS was found to be significantly associated with a reduced sleep quality in MS patients. The percentage of insomnia, snoring, EDS, as well as the ESS score and PSQI score in MS patients with RLS was higher than patients without RLS. Considering that RLS may reduce sleep quality in the general population [15], it is not difficult to understand that this may extend to patients with MS. More interestingly, the PSQI score in the MS/RLS+ group was higher than in the con/RLS+ group, which may suggest that MS could further influence sleep quality of subjects with RLS symptoms. Some neurological symptoms of MS, such as leg jerks before sleep, may contribute to this. However, this suggestion requires further study.

There are some limitations to our study. First, RLS diagnosis was not confirmed by a sleep specialist. Second, we only investigated certain medications (clonazepam, dopamine agonist, and antidopaminergic compounds) in this study; data from patients using alternative drugs has not been collected. We also failed to make the diagnosis of comorbidities. Third, we did not employ additional diagnostic procedures, such as laboratory tests, to reduce false-positive diagnoses. Fourth, we did not investigate whether treatment of MS led to a bias in the reported prevalence of RLS. Fifth, the limit in subject numbers may mean that these data do not represent all patients with MS in China.

Conclusions

In accordance with most of the existing literature, our data confirm that RLS is significantly associated with MS. Sleep quality was also found to be poorer in MS patients with RLS than in those without. Therefore, we recommend that patients with MS should always be assessed for the presence of RLS.

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Conflicts of interest The authors declare that they have no competing interests.

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