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Original Article

Clinical and radiological characteristics of restless legs syndrome following acute lacunar infarction

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ABSTRACT

Background: Recent studies have suggested that cerebral ischemic infarction may contribute to the development of restless legs syndrome (RLS). This study analyzed the clinical and radiological profiles of RLS with onset after acute lacunar infarction.

Methods: In this retrospective study we enrolled 244 consecutive patients with acute lacunar infarction between January 2012 and June 2014. RLS was identified and evaluated based on the International RLS Rating Scale (IRLS-RS). Individual sleep quality was assessed using the Epworth Sleepiness Scale (ESS). Psychological state was also assessed using the Hamilton Depression Scale (HDS) and the Hamilton Anxiety Scale (HAS).

Results: The incidence of RLS in patients with lacunar infarction was 5.33%. Our participant group consisted of nine males and four females. Three patients had symptoms in bilateral limbs, and 10 patients had symptoms only contralateral to the cerebral infarction. The infarctions were localized to the pons, centrum semiovale, thalamus, putamen, medulla, and occipital lobe. Contralateral paralysis was found in 13 patients, and contralateral sensory deficit in seven patients. The average IRLS-RS, ESS, HDS, HAS scores were 19.07 ± 8.70, 4.69 ± 5.82, 4.38 ± 4.68, and 3.85 ± 4.76, respectively. Nine patients had diabetes mellitus. After administration of dopaminergic drugs, patients' RLS significantly improved.

Conclusions: The incidence of RLS after acute lacunar infarction was 5.33%. Pons, centrum semiovale, and basal ganglia were the common locations of responsible lesions. Compared to idiopathic RLS, symptoms of RLS after acute lacunar infarction appeared more unilateral and more likely involved the arm. Moreover, diabetes mellitus may be a risk factor for RLS in stroke patients.

1. Background

Restless legs syndrome (RLS), also known as Willis-Ekbom syndrome, is a distinct neurological sensorimotor disorder characterized by an urge to move the limbs, often associated with unpleasant sensations in limbs such as pulling, crawling, tingling or pain [1]. In the majority cases, these sensations are felt in the legs, and (less often) in the arms. Symptoms usually occur or worsen

Abbreviations: RLS, Restless legs syndrome; IRLS-RS, International RLS Rating Scale; ESS, Epworth Sleepiness Scale; HDS, Hamilton Depression Scale; HAS, Hamilton Anxiety Scale; MRI, Magnetic resonance imaging; DWI, diffusion-weighted imaging; IRLSSG, International Restless Legs Syndrome Study Group; EEG, Electroencephalogram; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; SD, standard deviation; OR, Odds ratio; CI, confidence interval.

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when the person lies down or sits for prolonged periods, particularly during the night; and can be partially or completely relieved after walking [1–3]. Furthermore, RLS can adversely impact the individual's sleep, leading to reduced sleep time, daytime fatigue, and reduced concentration; thus, in severe cases, RLS may result in depression and anxiety [4–6].

The exact etiopathogenesis of RLS has yet to be fully elucidated. Clinical evidence has shown that RLS can be associated with other conditions including systemic iron deficiency, uremia, pregnancy, Parkinson's disease, multiple sclerosis, and cerebrovascular disease. Several studies have found an association between cerebral ischemia and RLS; both with lacunar infarction (1.5 cm in diameter or less) and large-vessel infarction [6–8]. The clinical and radiological characteristics of RLS following acute lacunar infarction have not been well documented. Chandan et al., reported a stroke cohort, the prevalence of RLS secondary to acute stroke was 10% [9]. It was found that RLS was much more likely to occur in patients with subcortical stroke [10]. While in our reports and other studies, RLS was also observed to occur with stroke in other locations, such as pons [6,11].

In this study, we investigated the incidence and clinical–radiographic profiles of patients, whose RLS symptom occurred after an acute cerebral lacunar infarction. Furthermore, we investigated the potential risk factors as well as the possible neurological pathways involved in RLS.

2. Methods

This study was approved by the Ethics Committee of Capital Medical University affiliated Beijing Friendship Hospital, China. All enrolled patients agreed to participate the study and completed the informed consent.

2.1. Patients

This is a retrospective study. Between January 2013 and June 2014, Inpatients in the department of neurology, Capital Medical University affiliated Beijing Friendship Hospital, China, who were diagnosed of acute cerebral lacunar infarction, were given questionnaire surveys from July to October 2014, and then followed-up until May, 2017. All patients diagnosed with acute lacunar infarction [12], were enrolled with the criteria as follows: (1) the clinical features meet the criteria of cerebral infarction; (2) brain magnetic resonance imaging (MRI) examination was done within one week since the onset; (3) diffusion-weighted imaging (DWI) showed an acute lacunar infarction; (4) the diameter of the lesion was no more than 1.5 cm. Patients were excluded if: (1) they had a stroke in the past six months; (2) the diameter of the infarction lesion was more than 1.5 cm; (3) they had features like aphasia or cognitive impairment rendering them unable to cooperate in the investigation; (4) the patient was diagnosed RLS before this stroke attack; (5) the clinical or radiological data were incomplete; (6) patients had severe iron deficiency, severe obstructive apnea syndrome, pregnancy, or renal failure; and (7) patients refused to join the investigation or were lost in follow-up (this proportion was limited to no more than 5% of the total cohort).

Clinical manifestation of RLS of the patients was comprehensively evaluated. The diagnosis of RLS was made according to the criteria established by the International RLS Study Group (IRLSSG) in 2014 [13]: (1) An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs; (2) the urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting; (3) the urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; (4) the urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day; (5) the occurrences of the above features is not solely accounted for as symptoms primary to another medical or behavioral condition (eg, myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

The presence of medical conditions producing symptoms mimicking RLS as below were excluded: current treatment with antidepressant (tricyclic antidepressants, serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, mirtazapine) or other drugs (lithium, dopamine antagonists) potentially influencing the occurrence of sleep-related movement disorders and severe motor deficit, psychiatric disorders [13].

According to the diagnosis of RLS, the cohort was divided into two groups: the RLS group and non-RLS group.

2.2. Laboratory and radiological examinations

Physical examinations including blood pressure and neurological symptoms and signs, were recorded. Brain MRI was performed using 3.0T double gradient magnetic resonance image of General Electric Corporation. The result of brain MRI of all patients, especially the location of ischemic infarction lesions were documented. Electroencephalogram (EEG) examination was performed using EEG-1200 made by Japanese Nihon Kohden Corporation, and the result of EEG was documented. The result of laboratory examination as below was recorded, such as serum glucose, hemoglobin, electrolytes such as serum sodium (Na^+), serum potassium (K^+), serum phosphorus (P), serum cholesterol (CHOL), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine transaminase (ALT), aspartate transaminase (AST), urea nitrogen (BUN), creatinine (Cr), and serum homocysteine (HCY).

2.3. Clinical evaluation, treatment and follow-up

The questionnaire of RLS in this study was designed according to Cambridge–Hopkins RLS questionnaire [14], and the severity of RLS was assessed according to the International RLS Study Group (IRLSSG) Rating Scale [13]. The neurological function of each enrolled patient was assessed using the National Institutes of Health Stroke Scale (NIHSS), and modified Rankin Scale (mRS). Sleep quality was assessed using Epworth Sleepiness Scale (ESS). Emotional and psychological state was assessed using Hamilton Depression Scale (HDS) and Hamilton Anxiety Scale (HAS) [15].

Patient suspected of having RLS were visited by senior neurologist whose specialty was RLS and movement disorders, with a face-to-face visit in the outpatient facility. Treatment using Levodopa or the dopamine agonist, piribedil, was given to patients once the diagnosis was made [16,17].

2.4. Statistical analysis

Data was statistically analyzed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). The normality of the distribution was statistically analyzed using the Kolmogorov–Smirnov test. Enumeration data was presented as percentages and was analyzed by Chi-square test. Quantitative data with a normal distribution was presented as 'mean ± standard deviation (SD)' and was compared using student-t test or corrective t test; quantitative data without a normal distribution were presented as 'median ± interquartile range' and were compared by Kruskal–Wallis test. Multivariate logistic regression was used to evaluate potential risk factors associated with RLS. Five

covariates (gender, age, DM, eGFR and serum phosphorus) were included in the model as confounding factors, and backward method was used to selection other covariates, including Odds ratio (OR) with 95% confidence interval (CI) was indicated. Probability (p) values ≤ 0.05 were considered significant.

3. Results

3.1. Demographic characteristics

A total of 244 patients (173 men and 71 women, mean age = 65.00 ± 19.00 years) with cerebral infarction were include in this study, one patient had a history of PLMS (periodic limb movement in sleep, PLMS), one patient's mother had RLS but he did not have symptoms. There were 90/244 (36.88%) patients had DM (Diabetes Mellitus), 185/244 (75.82%) patients had hypertension, 102/244 (41.8%) patients had homocysteinemia. Among the 244 patients, 13 (5.33%) patients (nine male and four female) were diagnosed RLS. Their symptoms of restless legs syndrome occur at the day of or one to two days after the onset of stroke. The mean age of these 13 patients was 59.77 ± 8.11 years. The incidence of RLS in male and female patients were 5.20% and 5.63%, respectively, ($p = 0.56$, chi-squared test).

3.2. Functional evaluation

At admission, the clinical stroke features were: mild to moderate paralysis in all 13 patients, sensory deficit in seven patients, and mild ataxia in five patients. The mean NIHSS score of all 13 patients with RLS was 3.46 ± 1.51, and the mean mRS score was 1.77 ± 1.17. The onset of RLS presented at almost the same time of ischemic infarction. According to the IRLSSG, the severity of RLS in the 13 patients was classified into four groups: mild (score = 0–10) in three cases, moderate (score = 11–20) in four cases, severe (score = 21–30) in four cases, and extremely severe (score ≥30) in two cases. The average IRLSSG score was 19.07 ± 8.70. The ESS score of these 13 patients was 0–17, average 4.69 ± 5.82,; HDS score was 0–13, average 4.38 ± 4.68, and the HAS score was 0–12, average 3.85 ± 4.76.

3.3. Laboratory data

The physical and laboratory examinations and statistical results are summarized in Table 1. Nine out of 13 (69.23%) RLS patients had concomitant diabetes mellitus, and the incidence of diabetes mellitus in the RLS group was significantly higher than that in the non-RLS group (81/231, 35.06%, $p = 0.019$). Moreover, the incidence of homocysteinemia in RLS and non-RLS group was three out of 13 (23.07%) vs. 100/231 (43.29%), there was significant difference between groups (p = 0.019). There was no significant difference between groups in other laboratory data. Seven out of 13 patients in RLS group underwent EEG, with no significant abnormalities found.

3.4. Clinical-radiographic data

Among these 13 patients with lacunar infarction-related RLS, 10 had symptoms in unilateral limbs contralateral to the cerebral ischemic lesion (five in the legs, one in the arm, and four in both upper and lower limbs). Moreover, three had symptoms in bilateral limbs (two in both legs, and one in the contralateral arm and both legs) (Table 2).

Five patients had multiple lacunar infarcts. The locations of lacunar infarction included pons (n = 4), centrum semiovale or corona radiata (n = 5), basal ganglia (n = 6), including thalamus (n = 6), and putamen (n = 2), medulla oblongata (n = 1), and occipital lobe (n = 1). On DWI, these lesions appeared hyperintensity (Fig. 1). The detailed clinicoradiological data of the 13 patients in the RLS group is presented in Table 2. The location-related incidences of RLS in patients with acute lacunar infarction are summarized in Fig. 2.

3.5. Follow-up data

When we administered the questionnaire survey at follow up (six − 20 months after the onset of stroke) the neurological deficits of 13 patients were almost completely resolved, with a mean NIHSS score of 0.23 ± 0.44 and a mean mRS score of 0.23 ± 0.60. One patients RLS symptoms of resolved spontaneously three months after the onset; three patients did not initiate drug treatment because their RLS was mild; and the other nine patients started dopaminergic therapy (Madopa 125–250 mg/day or piribedil 50–100 mg/day). Their RLS symptoms of RLS were significantly relieved after treatment. The mean IRLSSG score before and after treatment among the nine patients was 24.13 ± 7.04 vs 9.63 ± 5.93 (p < 0.0001, paired t-test).

At final follow-up at May 2017, after a mean follow-up period of 36 months (30–53 months), RLS symptoms resolved in two

Table 1
The physical and laboratory examinations and the statistical results.

Characteristics	RLS group (n = 13)	Non-RLS group (n = 231)	*P* value
Gender (male/total)	69%	71%	0.554
Age (years)	59.77 ± 8.11	64.89 ± 11.76	0.138
Hypertension	69.23%	76.19%	0.812
Diabetes	69.23%	35.06%	0.031*
Homocysteinemia	23.07%	43.29%	0.151
Hemoglobin (g/l)	138.69 ± 9.24	137.01 ± 16.50	0.553
Triglyceride (mmol/l)	2.58 ± 2.66	1.56 ± 0.96	0.577
Cholesterol (mmol/l)	4.54 ± 0.79	4.62 ± 1.04	0.777
High-density lipoprotein cholesterol (mmol/l)	1.07 ± 0.20	1.00 ± 0.32	0.558
Low-density lipoprotein cholesterol (mmol/l)	2.49 ± 0.61	2.63 ± 0.69	0.483
Glucose (mmol/l)	6.82 ± 3.25	5.35 ± 2.07	0.853
Creatinine (umol/l)	75.93 ± 11.71	79.00 ± 19.00	0.369
Blood urea nitrogen (mmol/l)	5.02 ± 1.26	4.82 ± 1.68	0.748
Calcium (mmol/l)	2.20 ± 0.11	2.28 ± 0.12	0.416
Phosphorus (mmol/l)	1.19 ± 0.16	1.09 ± 0.23	0.976
Sodium (mmol/l)	142.47 ± 2.64	142.74 ± 2.84	0.416
Chlorine (mmol/l)	102.92 ± 3.45	103.55 ± 2.99	0.468
Potassium (mmol/l)	3.95 ± 0.38	3.98 ± 0.38	0.800
Glomerular filtration rate (ml/min/1.73 m^2)	112.56 ± 22.34	103.69 ± 21.67	0.153

*$P < 0.05$.

Table 2
The detailed clinicoradiological data of the 13 patients in the RLS group.

Age/sex (at Onset)	Location of infarction	Involved limbs of RLS	Paralysis	Sensory deficits	IRLSSG score (O/F)	Treatment (mg/d)	Familial history of RLS	Prestoke history of RLS/PLMS	Risk factors
50/M	Thalamus	CL/A	CL, A	N	8/8	None	N	N	DM
51/M	Pons	CL/L	CL, AL	N	9/9	None	N	N	DM
64/M	Corona Radiata, Thalamus, Putamen	CL/L	CL, AL	N	10/6	LD (100)	N	N	HT
59/M	Medulla	CL/L	CL/AL	CHD	11/6	LD (100)	N	N	N
59/M	Corona Radiata	CL/L	CL/L	N	32/14	P (50)	N	N	DM
59/M	Pons	CL/L	CL/L	CHD	14/14	None	Y	N	DM, HT
63/F	Corona Radiata, Thalamus	CL/AL	CL/L	CHD	14/0	None	N	PLM	DM, HT
67/F	Occipital lobe	CL/AL	CL/AL	CHD	20/0	LD (100–200)	N	N	HT
58/M	Thalamus	CL/AL	CL/AL	CHD	22/11	P (50)	N	N	DM, HT
57/M	Pons, Corona Radiata	CL/AL	CL/L	N	22/20	P (50)	N	N	DM, HT
78/F	Pons	BL/L	CL/AL	CHD	25/9	P (50)	N	N	DM, HT
65/F	Corona Radiata, Thalamus	BL/L	CL/AL	N	29/10	P (50)	N	N	DM, HT
47/M	Corona Radiata, Thalamus, Putamen	CL/A; BL/L	CL/AL	CHD	32/20	P (50–100)	N	N	HT

M, male; *F*, female; CL, contralateral; A, arm; L, leg; AL, arm and leg; BL, bilateral; LD, levodopa; P, piribedil; *CHD*, contralateral sensory deficits; PLMS, periodical limb movements; DM, diabetes mellitus; HT, hypertension.

patients (IRLSSG score 0), significantly improved in six patients (IRLSSG < 10), and moderately improved in five patients (IRLSSG 11–20). No patients experienced symptoms which either still severe or extremely severe. The final mean IRLSSG score of 13 patients was 8.77 ± 5.51, ie, significantly lower than that of the onset ($p \leq 0.0001$, paired t test).

4. Discussion

4.1. Etiology and demography

The etiopathogenetic mechanism and pathophysiology of RLS is incompletely understood. Genetic risk factors have been identified. The prevalence of RLS in the general population has been reported to range from 5% to 10% in Caucasians, while 1–3% in Asian populations, and may increase with age and be ethnic dependent [18]. Previous studies have suggested that the dopaminergic system dysfunction may contribute to the occurrence and development of RLS [19,20]. However, neuroimaging studies have not demonstrated any neurodegenerative changes of dopaminergic neurons in the extrapyramidal system [21]. Reduced brain iron stores are also strongly implicated [15].

Based on previous reports in the literature, RLS may result in cardiovascular and cerebrovascular diseases, as well as hypertension. Furthermore, patients with RLS and/or PLMS often has poor sleep quantity and quality, which may disturb the balance of sympathetic and parasympathetic nervous system, and increase the risk of hypertension and cardiovascular disease and stroke [22–24]. The reverse may also be true, especially in stoke [9,10,25]. Chandan reported the prevalence of RLS secondary to acute stroke was 10% [9]. Gupta et al., reported 10.11% out of 346 acute stroke patients fulfilled IRLSSG diagnostic criteria for RLS [10]. Lee et al.,

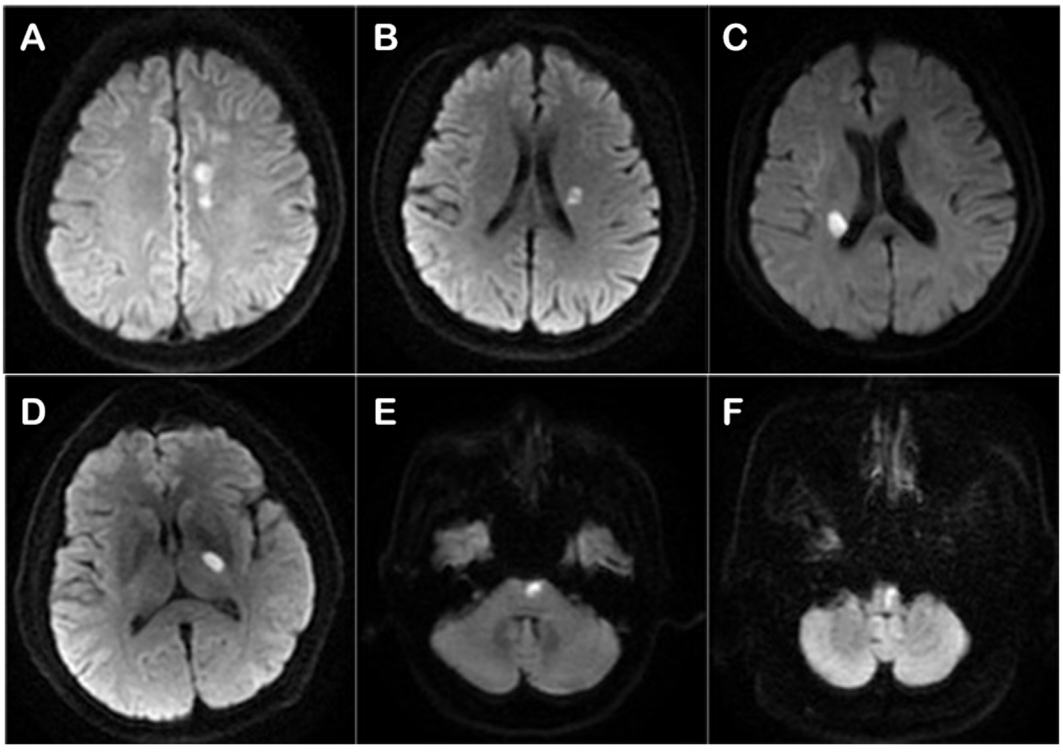

Fig. 1. Radiological profiles of patients with lacunar infarction-related RLS. Magnetic resonance diffusion-weighted imaging showed high signal intensity in the corona radiate/centrum semiovale (A and B), basal ganglia (C and D) and pons (E and F).

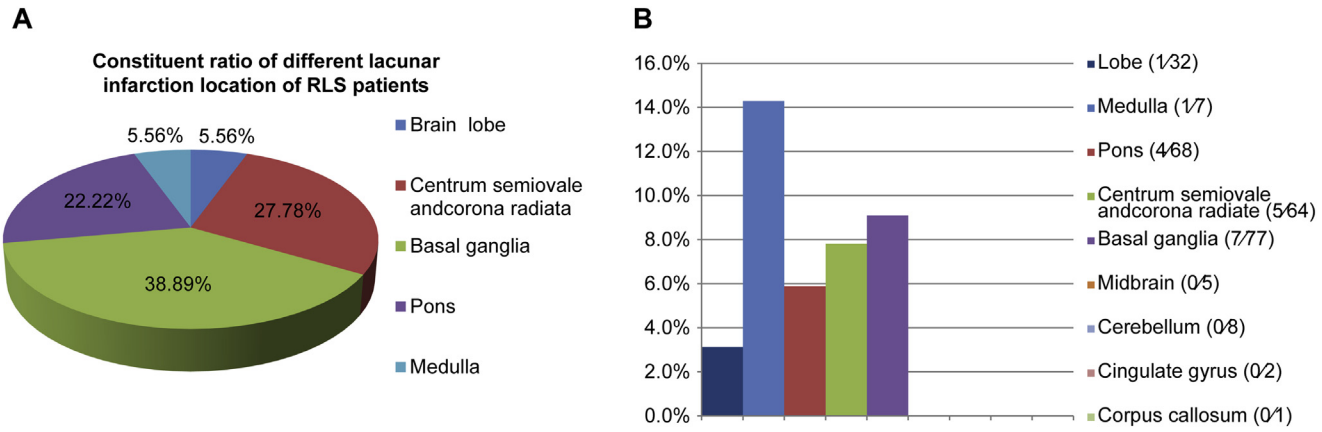

Fig. 2. The association between RLS and infarction locations (A) The pie chart showing the constituent ratios of different lacunar infarction location of in the RLS group (B) The histogram showing the incidence of RLS inpatients with infarctions in variable locations.

studied a cohort involving 137 patients with acute infarction, and reported an incidence of stroke-related RLS of 12.4% [26]. Buratti and colleagues collected 66 patients with lacunar infarction, found that 11% had isolated RLS, 44% had isolated PLM (periodic limb movement), and 12% had RLS and PLM [27]. In our current study, we found the incidence of RLS secondary to lacunar infarction was only 5.33%, much lower than that of others [9,25,26]. There are several explanations for this. First, the infarction lesion of the patients enrolled in this study was lacunar, in which the diameter was no more than 15 mm (ie, small and limited), while the lesion of the patients enrolled in other studies varied, from lacunar lesion to large vessel stroke. Second, patients with long histories of RLS were enrolled in other studies, yet were excluded from our cohort. The literature reports a female predominance in idiopathic RLS [27]. In Lee's study, stroke-related RLS was more common in female than in male; nevertheless, no statistical difference was observed [26]. Our larger sample investigation showed the incidence of stroke related RLS between sex was 5.63% (female) and 5.20% (male) respectively, with no significant difference between genders. The definitive prevalence of stroke related RLS still needs further large-scale and multi-center researches.

4.2. Clinical and radiological considerations

The reported stroke locations in patients with stroke related RLS included basal ganglia, pons, internal capsule, thalamus, and cortex [26]. Gupta et al., found that 82.8% cases were located in subcortical area, including basal ganglia, corana radiate and centrum semiovale [10]. In these 13 cases of lacunar infarction related RLS, there were 66.78% lesions located in subcortical area (basal ganglia 38.89%, corana radiate and centrum semiovale 27.78%), which was similar to the previous findings. Researchers found that DAT bindings and D2 receptor bindings reduced in caudate and putamen regions using PET or SPECT study [28,29], Which was speculated to be the basis of subcortical lesion related RLS.

In addition to the subcortical lesions, there was 22.22% lesions located in brainstem in the current 13 RLS patients. Ruppert et al., conducted a prospective study and found that three out of 30 (10%) of brainstem infarction patients developed RLS [7]. The involved brainstem structures consisted of anteromedial pons, anteromedial and anterolateral pons, and anteromedial medulla oblongata. In our study, five out of 81 patients (6.17%) with brainstem lacunar infarction had RLS, four in pons and one in medulla oblongata. Similar to Ruppert's report, the involved area of brainstem was in the anterior part, including anteromedial pons, anteromedial and anterolateral pons, and anteromedial medulla oblongata. There is evidence that RLS may be related to abnormal dopaminergic transmission in the A11 cell group. Qu and Ondo and colleagues verified the hypothesis of A11 pathway on animal model [30], which projecting from the A11 cell groups in hypothalamic parafascicular nucleus to interomediolateral column of spinal cord (diencephalicspinal tract). The location of A11 cell groups is close to the hypothalamic suprachiasmatic nucleus that regulates the circadian clock, which could explain the phenomenon that the RLS symptoms are usually nocturnal with the prominent leg involvement [31].

The unpleasant sensation of RLS is most commonly in the legs, may also involve the arms and even trunk, usually after years of leg involvement. Idiopathic RLS is usually bilateral, but often asymmetric. In the study conducted by Lee et al., five out of 17 patients (29.4%) with infarction-related RLS had ipsilateral leg involvement, whereas 12 patients had bilateral leg involvement [26]. Gupta et al., reported more proportion of unilateral involvement and asymmetrical RLS, which was also ipsilateral to the stroke lesion [10]. In our study, the result was much different from Lee's study as well as Gupta's, most of the patients (10 out of 13, 76.9%) had unilateral symptoms of RLS in the limbs contralateral to the lesion, while only three patients (23.1%) had symptoms in bilateral limbs. Shukla et al., studied 195 cases of RLS in order to investigate the difference between unilateral and bilateral RLS; in that study they found unilateral RLS was much common in secondary RLS, and patients may have had coexisting neuropathy or radiculopathy, as well as stroke [32]. One hypothesis for this phenomenon is the abnormalities in iron–dopamine metabolism, which may occur more focally in the neuraxis in these unilateral RLS patients, resulting in symptoms sparing limbs of one side [32]. Notably, in this study, we also found that the unilateral RLS symptoms often occurred concurrently with the limb paralysis, instead of hemisensory deficits, suggesting that the pathway of RLS might accompany with the motor tract from cortical to spinal cord. This is the reason why we studied RLS in patients of lacunar infarction. Because lacunar lesion is much small and limited, the study could draw out the pathway of RLS more accurately. In the future studies, functional radiological methods may be employed in this area.

4.3. Dopaminergic treatment

In the current study, we successfully treated the infarction-related RLS patients with dopaminergic drugs, levodopa or

piribedil. In clinics, dopaminergic drugs include dopamine agonists, such as pramipexole and ropinirole, and levodopa are recommended for the treatment of RLS with a significant efficacy. While piribedil, also a dopamine agonist, was not recommended in the guideline, due to the lack of clinical trials [16,20]. The reason we treated patients with piribedil was that it is the only dopamine agonist we could use in our hospital at that period. And the results showed an efficacy for the treatment of stoke-related RLS.

4.4. Association between RLS and sleep or psychological disturbances

As RLS generally occurs at rest during the night, it can cause a variety of sleep disorders and negatively affect the sleep quality [4,5]. The decline of sleep quality may lead to fatigue in the daytime, sleepiness, cognitive dysfunction, irritability, anxiety, and depressed mood. In our study, we evaluated the sleep quality of patients with infarction-related RLS, before and after dopaminergic treatment, and found that the RLS adversely impacted the quality of individual sleep and daily life before treatment, with the relief of RLS, the anxiety and depression scale showed improvement too.

4.5. Potential risk factors for RLS in stroke patients

In the current study, we noted the proportion of diabetic patients in the RLS group is significantly larger than that in the non-RLS group, indicating diabetes may be a potential risk factor for RLS in stroke patients. Cuellar et al., found that the incidence of RLS reached up to 44.6% in patients with 2-type diabetes [31], although this very high number has not been replicated. This association between RLS and diabetes may be due to peripheral nerve injury, lack of neurotrophic factors, oxidative stress and immune dysfunctions of diabetes. Relevant studies also suggested that diabetes accompanied with inflammation, neuroendocrinal or metabolic changes, and activation of the sympathetic nervous system might induce or aggravate RLS [33]. The exact mechanism of infarction-related RLS still needs further investigation.

4.6. Study limitations

This study of lacunar infarction related RLS is a retrospective study, the diagnosis of RLS in some patients was made by the recall of the patients and/or their caregivers, which lead to the bias. Besides, we did not follow up the patients without RLS, this may influence the analysis for risk factors. Due to the limitation of conditions, patients did not have polysomnographic monitoring, and thus the incidence of periodical limb movement remained unclear.

5. Conclusion

RLS secondary to acute lacunar infarction is a relatively uncommon condition, the incidence of infarction related RLS is 5.33%. Basal ganglia, centrum semiovale, and pons, are the most locations of responsible lesions. Finally, diabetes may be a risk factor for RLS in stroke patients.

Ethics approval and consent to participate

Informed consent was obtained from all individual participants. This study was approved and consented by Beijing Friendship Hospital Ethics Committee (NO. 2016-P2-052-01).

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None.

Authors' contributions

Tuo HZ designed the experiment. Tian ZL performed the experiment. Tian ZL processed all the data and wrote the paper. The revision of the article mainly completed by Tuo HZ and Ondo W. Ma XY, Cui YN, Xue Y, Che JJ, Xu CL, Chen K, Zhang YB, Zhang LY, Bi HY, Le WD participated in the revision of the article.

Consent for publication

Not applicable.

Availability of data and materials

The original data is uploaded with the manuscript.

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All enrolled patients verbally agreed to participate in the survey and answered questions on the phone with relevant questions. All patients suffering from restless legs syndrome were followed by regular outpatient visits.

Conflict of interest

None declared.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.06.004.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.sleep.2018.06.004.

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