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Original Article

Restless legs syndrome secondary to pontine infarction: Clinical analysis of five cases

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Abstract

Objective: Pontine infarction is a common type of stroke in the cerebral deep structures, resulting from occlusion of small penetrating arteries, may manifest as hemi-paralysis, hemi-sensory deficit, ataxia, vertigo, and bulbar dysfunction, but patients presenting with restless legs syndrome (RLS) are extremely rare. Herein, we reported five cases with RLS as a major manifestation of pontine infarction.

Methods: Five cases of pontine infarction related RLS were collected from July 2013 to February 2016. The diagnosis of RLS was made according to criteria established by the International RLS Study Group (IRLSSG) in 2003. Neurological functions were assessed according to the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS). Severity of RLS was based on the International RLS Rating Scale (IRLS-RS). Sleep quality was assessed by Epworth Rating Scale (ERS), and individual emotional and psychological states were assessed by Hamilton Depression Scale (HDS) and Hamilton Anxiety Scale (HAS).

Results: The laboratory data at the onset including hemoglobin, serum concentration of homocysteine, blood urea nitrogen (BUN), creatinine, electrolytes, and thyroid hormones were normal. The electroencephalogram (EEG), lower-extremity somatosensory evoked potential (SEP), and nerve conduction velocity (NCV) in four limbs were normal. The average period of follow-up was 34.60 ± 12.76 months. The MRI examination showed acute or subacute pontine infarction lesions, 3 cases in the rostral inner side, 1 case in the rostral lateral and inner side, and 1 case in rostral lateral side. The neurological deficits included weakness in 4 cases, contralateral sensory deficit in 1 case, and ataxia in 2 cases. All 5 patients presented with symptom of RLS at or soon after the onset of infarction and 4 patients experienced uncomfortable sensations in the paralyzed limbs contralateral to the ischemic lesion. Their

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neurological deficits improved significantly 2 weeks later, but the symptoms of RLS did not resolve. Among them, 3/5 patients were treated with dopaminergic drugs. At the end of the follow-up, RLS symptom eventually resolved in 3 patients but persisted in two. The IRLS-RS, NIHSS and mRS scores were significantly lower at the onset than those at the last follow-up ($P = 0.035$, 0.024 and 0.049, respectively). However, there was no significant difference in the ERS, HDS and HAS scores ($P = 0.477$, 0.226 and 0.778, respectively).

Conclusion: RLS can be an onset manifestation of pontine infarction, clinicians should be aware of this potential symptom. RLS usually occurs in the paralyzed limbs contralateral to the infarction lesion. The pathogenesis still needs further investigation.

Keywords: Restless legs syndrome; Pontine infarction; Clinical features

Introduction

Restless legs syndrome (RLS) refers to an urge to move the leg that typically worsens at night and improves with movement. This disorder is reported with a prevalence varying from 4% to 29% in the general population, and approximately 70% of all RLS are primary idiopathic forms.[1] According to the literature, the causes of the remaining RLS include renal failure, depression, pregnancy, iron deficiency, migraine, Parkinson's disease, and stroke.[2–5]

Pontine infarction is a common type of stroke in the cerebral deep structures, resulting from occlusion of small penetrating arteries, may manifest as hemiparalysis, hemi-sensory deficit, ataxia, vertigo, and bulbar symptoms, but patients presenting with RLS are extremely rare. Herein, we reported five cases with restless legs syndrome as the main manifestation of pontine infarction.

Materials and methods

Patients

This study was approved by the Ethics Committee of Beijing Friendship Hospital. Five patients with a diagnosis of pontine infarction were enrolled from July 2013 till February 2016. The inclusion criteria included: (1) Magnetic resonance imaging (MRI) completed within 1 week after symptom onset; (2) acute infarction confirmed by diffusion-weighted imaging (DWI); and (3) the infarction was located in pons. The exclusion criteria included: (1) a previous ischemic stroke history; (2) acute infarction in other area of the brain; (3) patients with aphasia, cognitive impairment, or psychiatric diseases who cannot explain his/her symptom exactly; (4) incomplete clinical or radiological data; or (5) loss to follow-up.

The diagnosis of RLS was made according to criteria established by the International RLS Study Group (IRLSSG) in 2003.[6] The criteria include: (1) an urge to move the legs, which is usually accompanied by uncomfortable and unpleasant sensations in the legs; (2) the urge to move, and/or the unpleasant sensations, begin or worsen during rest or inactivity such as lying down or sitting; (3) the urge to move and/or unpleasant sensations are partially or completely relieved by movement, such as walking or stretching, at least as long as the activities are continued; and (4) the urge to move and/or unpleasant sensations are worse in the evening or night than during the daytime.

Informed consent was obtained from all individual participants.

Laboratory and radiological examinations

Physical and laboratory examinations included blood pressure, serum glucose level, hemoglobin, liver and kidney functions, thyroxine, electrolytes, and serum homocysteine. Electroencephalogram (EEG), lower-extremity somatosensory evoked potential (SEP), and nerve conduction velocity (NCV) in four limbs were performed, and the relevant results were collected. Brain MRI and DWI using a General Electric 3.0T double gradient magnetic resonance image were performed in all patients. The locations of ischemic infarction lesions were documented.

Clinical evaluation and follow-up

Neurological functions were assessed according to the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS). Severity of RLS was based on the International RLS Rating Scale (IRLS-RS). Additionally, individual sleep quality was assessed by Epworth Rating Scale (ERS), and individual emotional and psychological states were assessed by Hamilton Depression Scale (HDS) and Hamilton Anxiety Scale (HAS). Follow-up data for all

patients with RLS were obtained during individual office visits or telephone interviews.

Statistical analysis

SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The normality of the distribution was assessed using the Kolmogorov−Smirnov test. Quantitative data with a normal distribution were presented as "mean ± standard deviation (SD)" and compared by Student-*t* test, or for non-parametric data using the Wilcoxon test; Probability (*P*) values < 0.05 were considered significant.

Results

All the 5 cases (3 males and 2 females), aged 61.0 ± 10.1 years (range, 51−78 years), were collected from July 2013 till February 2016, at Beijing Friendship Hospital, including 4 hospitalized and 1 outpatient. The follow-up period was 12−42 months with an average of 34.60 ± 12.76 months. Four patients had hypertension, 2 had diabetes mellitus and all 5 patients denied any history of RLS or the family history of RLS. They also denied the history of anemia, final renal failure, sleep apnea syndrome, Parkinson's disease, essential tremor, or demyelinating disease.

Among the 5 patients, 2 patients had hemi-paralysis only, 1 had hemi-paralysis accompanied by ataxia, 1 had hemi-paralysis accompanied by ataxia and hemi-sensory deficit, and 1 manifested as onset of pain in one leg in the night, forcing her to walk around. The average hemoglobin at onset was 131.40 ± 6.47 g/L, creatinine 79.32 ± 12.83 μmol/L, blood urea nitrogen 5.41 ± 1.17 mmol/L, serum phosphor 1.24 ± 0.15 mmol/L, serum glucose 7.76 ± 4.14 mmol/L, serum homocysteine 13.28 ± 1.67 mmol/L, serum sodium 142.30 ± 2.73 mmol/L, serum potassium 4.14 ± 0.34 mmol/L, total T3 87.45 ± 8.49 ng/dL, total T4 81.52 ± 17.48 ng/mL, thyroid uptake (TU) rate (42.64 ± 1.73)%. The EEG, SEP of lower-extremity, and NCV in four limbs were normal.

All 5 cases had uncomfortable sensation in the limbs associated with an urge to move at the day or the next day of onset. The sensation was described as pain, numbness, itch, fatigue, twitching, and so on, urging patients to move the limbs. The body part involved: 1 in bilateral legs, 3 only in contralateral leg, 1 in contralateral arm and leg. Their uncomfortable sensation presented only in the night or worsened in the night, urged them to move, and walking around could completely or partially release the uncomfortable sensation. Their clinical features met the criteria of RLS. The MRI-DWI examination of these 5 patients showed there were infarction lesions in the pons, including 4 acute and 1 sub-acute (Fig. 1). Three lesions located in rostral interior part of pons only, 1 located in the rostral lateral part of pons, and 1 located in lateral and inner side of the rostral part of pons. All the infarcts of these 5 cases located in the rostral part of the pons. They were given anti-platelet drugs, statins, and Chinese herbs for the ischemic disturbance. Their neurological deficit improved significantly after two-week treatment of cerebral infarction, but the symptom of RLS continued. Subsequently, 2 patients were given piribedil 25−100 mg/day, 1 was given Madopa 125 mg/day, and their symptom of RLS improved. The other 2 patients did not receive dopaminergic drugs due to their mild features. The RLS symptoms in 3 patients disappeared 2−3 months later, but persisted in 2 patients (Table 1).

The mean IRLS-RS score at the last follow-up was 5.60 ± 8.76, significantly lower than that at the onset (20.60 ± 10.04, $P = 0.035$, paired *t*-test). There were significant differences in the NIHSS and mRS scores at the onset and the last follow-up ($P = 0.024$ and 0.049, respectively, paired *t*-test), but no significant difference in the ERS, HDS and HAS scores ($P = 0.477$, 0.226 and 0.778, respectively, paired *t*-test) (Table 2).

Discussion

Pontine infarction, a common ischemic disease in the central nervous system, is often manifested by contralateral paralysis, contralateral sensory deficit, ataxia, vertigo, or crossed syndromes such as Millard-Gubler syndrome, Raymond-Cestan syndrome, and Foville syndrome.[5,7] RLS is a distinct clinical syndrome, and some clinical studies have observed that RLS can also be associated with stroke.[7] However, RLS as a major manifestation of pontine infarction is extremely rare. Lee et al[3] investigated the prevalence and the lesion topography of infarction-related RLS; they found 4 out of 18 patients with a pontine ischemic lesion presented with RLS. Gupta et al[5] analyzed the clinical characteristics of RLS following acute cerebral infarction, and they found 24 out of 35 infarction-related RLS patients had symptoms in the leg contralateral to the infarction lesion. Han et al[2] also reported two cases with akathisia and RLS as the main clinical manifestation of acute pontine infarction, and both complained an uncomfortable feeling in the contralateral legs with paresis at night. In the current study, 4 out of 5 patients

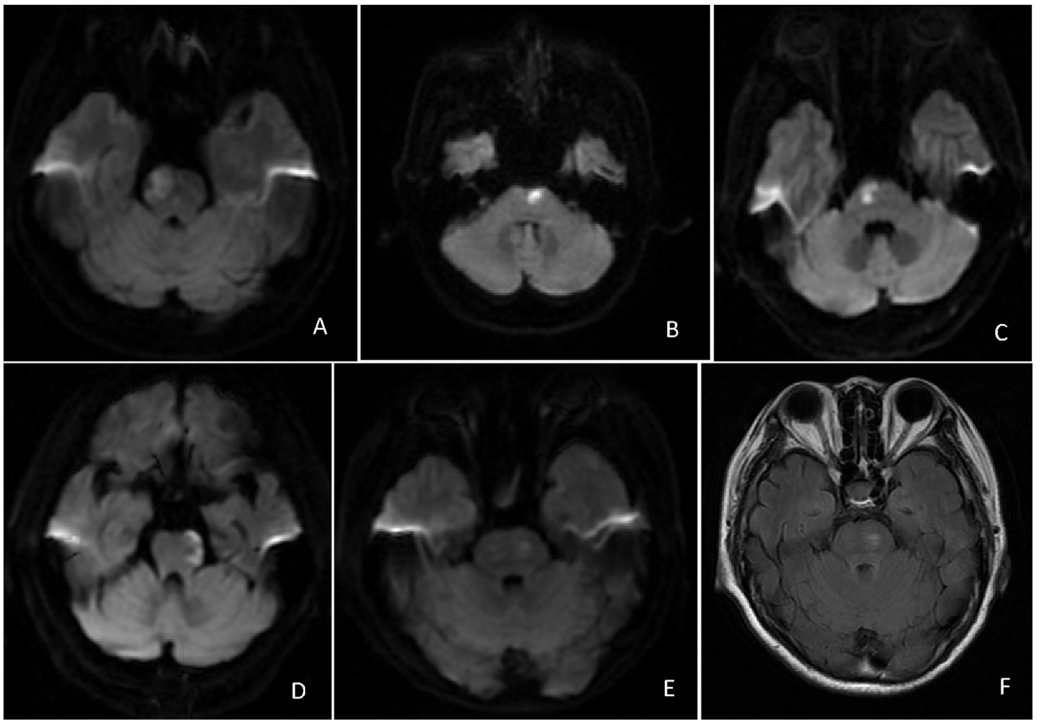

Fig. 1. Magnetic resonance imaging of the patients with pontine infarction and RLS. Axial diffusion-weighted brain MRI showing focal hyperintensity in the right pons of Case 1 (A) and Case 3 (C), in the left pons of Case 2 (B) and 4 (D) and 5 (E), and axial FLAIR MRI of Case 5 (F). RLS: restless leg syndrome; FLAIR: fluid-attenuated inversion-recovery.

experienced uncomfortable sensations in the paralyzed limbs contralateral to the ischemic lesion, while 1 out of 5 patients had bilateral leg involvement, which was consistent with the previous findings in literature.[2,5] Additionally, Sechi et al[4] also reported cases with ischemic stroke in one side of lenticulostriate region who had RLS in both legs. The definitive prevalence and the lesion topography of infarction-related RLS

Table 1
The detailed clinicoradiological data of the 5 patients.

Item	Age (years)/gender	Location of pontine infarction	Neurological deficit	Involved limbs of RLS	Dopaminergic therapy	RLS period
Case 1	51/M	Rostral lateral & inner	CP	CL	None	Until the last follow-up
Case 2	59/M	Rostral inner	CP	CL	Madopa 125 mg/d	3 months
Case 3	57/M	Rostral inner	CP, ataxia	CAL	Piribedil 100 mg/d	Until the last follow-up
Case 4	78/F	Rostral lateral	CP, CSD, ataxia	BL	None	3 months
Case 5	60/F	Rostral inner	None	CL	Peribedil 25−50 mg/d	2 months

RLS: restless legs syndrome; M: male; F: female; CP: contralateral paralysis; CL: contralateral leg; CAL: contralateral arm and leg; CSD: contralateral sensory deficit; BL: bilateral legs.

Table 2
Scores of rating scales at the onset and follow-up.

Items	NIHSS	mRS	ERS	HDS	HAS	IRLS-RS
Onset	2.60 ± 1.67	1.20 ± 1.10	0.80 ± 1.30	3.60 ± 5.13	2.20 ± 3.35	20.60 ± 10.04
Follow-up	0.20 ± 0.45	0.20 ± 0.45	0.40 ± 0.55	0.80 ± 1.30	2.00 ± 3.08	5.60 ± 8.76
P-value	0.024	0.049	0.477	0.226	0.778	0.035

NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale; ERS: Epworth Rating Scale; HDS: Hamilton Depression Scale; HAS: Hamilton Anxiety Scale; IRLS-RS: International Restless Legs Syndrome Rating Scale.

still need further research involving a much larger cohort.

In this study, the 5 patients showed highly consistent clinical courses. Four out of 5 patients presented with mild paresis, and the uncomfortable sensation was in the same limbs of paresis. Interestingly, in case 5, the symptom of RLS was the only clinical manifestation of pontine ischemic lesion without paralysis or sensory deficit. Their uncomfortable sensation worsened during the night and improved in the daytime or after walking.

As to the location of the lesion, the lesion located in rostral pons in all of patients, which is the area that pyramidal tracts go through, and the clinical features of them manifested as mild paralysis companioned with RLS in contralateral limbs in most of the patients.

The exact etiopathogenesis of RLS has not yet been well elucidated. In the present study, 4 out of 5 patients had RLS in the unilateral limbs with paresis; however, RLS persisted after the paresis recovered, suggesting that the pathway of RLS may be associated with but not limited to the pyramidal tracts. Piribedil and levo-dopa effectively improved RLS in most cases, indicating the dopaminergic pathway may be involved in the occurrence and development of RLS. The classical dopaminergic pathways include the nigrostriatal pathway, the mesocortical/mesolimbic system, and the tuberoinfundibular/tuberohypophysial system.[7,8] These pathways are mainly related with movement disorders or extrapyramidal diseases, such as Parkinson's disease; however, RLS is characterized by sensory disturbances, indicating that there may be another potential dopaminergic pathway. Some researchers hypothesized a pathway projecting from the A11 cell groups in thalamic parafascicular nucleus to interomediolateral column of spinal cord, which may be implicated in the pathogenesis of RLS.[9–12] The location of A11 cell groups is close to the hypothalamic suprachiasmatic nucleus that regulates the circadian clock, and this could explain the phenomenon that the RLS symptoms are usually nocturnal.

Conclusion

Pontine lacunar infarction can be manifested by RLS, and clinicians should be aware of this potential symptom. RLS usually occurs in the contralateral limbs with paresis. MRI and detailed history taking can facilitate the diagnosis, and dopaminergic drugs may be effective treatment. The pathogenesis and the exact pathway involving in RLS still need further large-cohort research.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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