Altered Cerebral Perfusion of Motor Cortex in Patients with Periodic Limb Movement Disorder

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Objectives: The pathophysiology of sleep-related motor diseases and sleep dysfunction in movement disorders is widely unknown as yet. Functional brain imaging, in particular radioisotope techniques, is considered to be a powerful tool to investigate pathomechanisms of periodic limb movement disorder (PLMD).

Methods: We performed 99mTc-ethyl cisteminate dimer brain single-photon emission computed tomography in 25 drug-naïve patients with PLMD and 23 age- and gender matched normal controls during wakefulness. For statistical parametric mapping analysis, single-photon emission computed tomography images were spatially normalized to the standard template and then smoothed using a 14-mm full width at half maximum Gaussian kernel. Results: Mean age of patients and normal controls was 48.6 years and over half of them were male. Most patients reported the sleep onset and maintenance insomnia due to repetitive leg jerks. Average duration of insomnia was 7.5 years. They denied the history of restless leg syndrome and there was no sleep disorders such as obstructive sleep apnea syndrome which was confirmed by polysomnography. Mean PLM during sleep index and movement arousal index were markedly increased to 45.3/hr and 7.5/hr, respectively. Their sleep quality was poorer than that of normal patients. In PLMD patients, cerebral blood flow was significantly increased in the bilateral precentral gyri as compared to normal controls. There was no brain region showing decreased perfusion in patients. Regional cerebral perfusion was not correlated to any polysomnography parameter including PLMS index or movement arousal index. Conclusions: Different perfusion pattern in bilateral primary motor cortices may provide the evidences of motor cortical impairment in patients with PLMD.

Key Words: PLMD, Cerebral perfusion, SPECT, Statistical parametric mapping.

Introduction

Periodic leg movements disorder (PLMD) is characterized by periodic episodes of repetitive, highly stereotyped, limb movements that occur during sleep (PLMS) and by clinical sleep disturbances that cannot be accounted by another primary sleep disorder. PLMS occur most frequently in the lower extremities.

They typically involve extension of the big toe, often in combination with partial flexion of the ankle, the knee, and sometimes the hip. Similar movement can occur in the upper limbs. Individual movements may be associated with an autonomic arousal, a cortical arousal, or an awakening. Typically, the patient is unaware of the limb movements or the frequent sleep disruption.

An arousal may precede, coincide with, or follow the limb movement, suggesting that a central generator may give rise to both periodic movements and the related sleep disturbance. PLMS are commonly found in association with the restless legs syndrome (RLS), narcolepsy, and rapid eye movement sleep behavior disorder. The effectiveness of dopaminergic agents in the treatment of PLMS and RLS and results of neuroimaging studies reveal increasing evidence of a reduced dopaminergic activity in the central nervous system as an underlying pathomechanism. But, to our knowledge, there was no report to investigate the functional derangement of cerebral perfusion in patients with idiopathic PLMD without other sleep disorders such as RLS, RBD or obstructive sleep apnea syndrome.

Here we examined 25 drug-naïve patients with PLMD confirmed by overnight polysomnography (PSG), and by means of 99mTc-ethyl cisteminate dimer (99mTc-ECD) brain single-photon emission computed tomography (SPECT) to evaluate a possible association of cerebral perfusion abnormalities and PLMD.
Patients and Methods

Patients
Twenty five patients with PLMD and 23 age-and sex matched normal controls were recruited. Patients were recruited from the Sleep clinic, Samsung Medical Center located in Korea. Inclusion criteria were as follows: 1) older than 18 but younger than 55 years old; and 3) a history of sleep onset and/or maintenance insomnia due to repetitive leg jerks for more than 1 month. Normal controls were recruited using an advertisement in a local community. Each candidate had a detailed clinical interview, sleep questionnaire, and overnight PSG. Exclusion criteria for patients and normal controls were those with 1) mean daily sleep time <6 hours, 2) shift worker, 3) apnea-hypopnea index greater than 5 if airflow measured by thermistor, 4) hypertension, diabetes, heart, and respiratory diseases, 5) history of cerebrovascular disease, 6) other neurological (neurodegenerative diseases, epilepsy, head injury) or psychiatric diseases (psychosis, current depression), 7) alcohol or illicit drug abuse or current intake of psychoactive medications, and 8) a structural lesion on brain MRI.

Overnight polysomnography
Subjects wereecctographom drinkectsograpyomnogra- phy MRI disease, 6) other neurolo. Polysomnographies were recorded using a Somnologica (Embla, USA). Overnight polysomnography was performed using a four-channel electroencephalogram (C3/A2; C4/A1; O1/A2; O2/A1), a four-channel electrooculogram, an electromyogram (of submental, intercostal, and anterior tibialis muscles), and an electrocardiogram with surface electrodes. A thermistor (for monitoring nasal airflow), a nasal air pressure monitor, an oximeter (for measuring oxygen saturation), piezoelectric bands (for determining thoracic and abdominal wall motion), and a body position sensor were also attached to patients. Detailed methods of performing and scoring PSG data were described in a previous article.8

99mTc-ECD brain SPECT
99mTc-ECD was injected intravenously for the SPECT studies. A brain SPECT scan was performed within 30 to 60 min of radotracer injection (25 mCi) using a 3-headed Triad XLT system equipped with low-energy and high-resolution collimators (Trionix Research Laboratory, Twinsburg, OH, USA). The transaxial system resolution of this camera was 6.9 mm full width at half maximum. Images were reconstructed by filtered back-projection using a Butterworth filter. Attenuation correction was performed using Chang's method (attenuation coefficient=0.12 cm-1).9 The SPECT voxel dimension was 3.56×3.56×3.56 mm (x, y, z). All participants were asked to refrain from drinking caffeinated beverages but were allowed to drink water from 07:00 until the end of the SPECT study. Patients were instructed not to fall asleep after ECD injection. Wakefulness after an ECD injection was monitored using a 4-channel electroencephalogram, a 2-channel electrooculogram, and 1-channel electromyogram. Informed consent was obtained from all study subjects after the study protocol, the SPECT procedure, and the potential hazards of radiisotope injection had been explained. The Institutional Review Board at Samsung Medical Center authorized the informed consent form used and the study protocol, which included the administration of a radioactive substance and SPECT scanning.

Statistical parametric mapping (SPM) analysis of SPECT studies
SPECT images of the PLMD patients and normal controls were manipulated using MATLAB 7.1 (The MathWorks, Natick, MA, USA) incorporated into statistical parametric mapping (SPM) 2 software (Wellcome Trust Centre for Neuroimaging, University College London, UK). Raw SPECT images (interfile 3.0 format) were converted to 16 bits SPM format (*.img and *.hdr). All of the SPECT images of the patients and normal controls were spatially normalized to the standard SPECT template with the default options. The accuracy of the spatial normalization was checked using a cross-registration function. Spatially normalized images were then smoothed by convolution using an isotropic Gaussian kernel with a 14-mm full width at half maximum to increase the signal to noise ratio.10,11 The count of each voxel normalized to the mean intensity of the white matter to remove differences in the global CBF between individuals.12 The results were superimposed on the 2-D planes of the averaged MRI template of normal subjects which was normalized to Montreal Neurological Institute space.

Statistics
A one-way ANCOVA with covariates of age and gender was used for the regional CBF (rCBF) difference between the two groups. The voxel clusters were corrected with an extent threshold of k>100 voxels.

Results
Clinical and polysomnographic characteristics
In PLMD patients, most were middle-aged (mean age 48.6 years, 16 male) and normal body weighted (mean body mass index=24.8 kg/m²). The mean onset age of insomnia related to leg jerks during sleep was 40.5 years (range 35-55), and
the mean duration of presumed PLMD was 9.0 years (range 1-35). Compared to normal controls, PLMD patients showed poorer sleep quality. Detailed PSG data of subjects were summarized and compared in Table 1.

Wakefulness monitoring during SPECT studies

Electroencephalograms, electrooculograms, and electromyograms were monitored during SPECT studies to measure the duration of wakefulness after an ECD injection in all patients. Mean sleep latency after an ECD injection was 11.3±2.9 minutes (range 8.5-20). Thus, we confirmed that all subjects underwent brain SPECT during the waking state because brain uptake of the radiotracer is completed within 1 to 2 minutes after the injection.

SPM analysis of 99mTc-ECD SPECT

In patients with PLMD, SPM results demonstrated brain regions with rCBF increase compared to normal controls. According to SPM overlaid on T1 MR images increased rCBF was found in bilateral precentral gyri (left x, y, z=-28.13, -13.28, 71.6, t=3.2; right x, y, z=50.10, -14.18, 55.94, t=2.96) at an uncorrected p<0.001 as shown in Fig. 1. There were no brain areas showing reduced rCBF in PLMD patients than normal controls. There were no significant corre-

Table 1. The results of overnight polysomnography in patients with periodic limb movement disorder (PLMD) and normal controls

<table>
<thead>
<tr>
<th></th>
<th>PLMD patients</th>
<th>Normal controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time (min)</td>
<td>345.1 (35.1)</td>
<td>387.5 (42.1)</td>
<td>0.552</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>80.3 (9.0)</td>
<td>90.0 (3.2)</td>
<td>0.034*</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>35.1 (9.7)</td>
<td>8.8 (5.6)</td>
<td>0.012*</td>
</tr>
<tr>
<td>REM sleep latency (min)</td>
<td>134.9 (49.3)</td>
<td>87.0 (60.2)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Apnea-hypopnea Index (per hr)</td>
<td>3.5 (3.2)</td>
<td>1.3 (1.1)</td>
<td>0.655</td>
</tr>
<tr>
<td>Arousal Index (per hr)</td>
<td>15.7 (4.9)</td>
<td>5.2 (3.1)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Total PLMS Index (per hr)</td>
<td>55.3 (15.3)</td>
<td>1.8 (0.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Movement arousal index (per hr)</td>
<td>7.5 (3.1)</td>
<td>0.5 (0.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>NREM (1%)</td>
<td>19.7 (5.1)</td>
<td>10.7 (5.1)</td>
<td>0.020*</td>
</tr>
<tr>
<td>NREM (2%)</td>
<td>63.2 (10.0)</td>
<td>54.2 (15.2)</td>
<td>0.060</td>
</tr>
<tr>
<td>NREM (3%)</td>
<td>5.3 (6.5)</td>
<td>9.5 (3.7)</td>
<td>0.043*</td>
</tr>
<tr>
<td>REM (%)</td>
<td>15.8 (5.1)</td>
<td>24.1 (5.1)</td>
<td>0.030*</td>
</tr>
</tbody>
</table>

Mean values (standard deviation). *independent t-test, p<0.05. PLMS: periodic limb movement during sleep, REM: rapid eye movement, NREM: non-rapid eye movement

Fig. 1. A statistical brain map showing brain regions with increased rCBF in patients with periodic limb movement disorder compared to normal controls. A: rCBF was increased in patients with periodic limb movement disorder at the level of uncorrected p<0.001 in bilateral precentral gyri. The results were superimposed on the 2-D planes of the averaged MRI template of normal controls which was normalized to Montreal Neurological Institute space. Scales in the colored bars are t scores. B: The overall areas with increased rCBF are shown in a three-dimensional brain rendering view. The left-hand sides of the images represent the left hemisphere of the brain (radiological views).

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lations between rCBF and any clinical profile or PSG parameters in PLMD patients and normal controls (independent t-test).

Discussion

We hypothesized that PLMD patients with sleep onset and/or maintenance insomnia would have rCBF abnormality during wakefulness. The present study showed significantly increased rCBF in the bilateral precentral gyri in PLMD patients relative to normal controls.

PLMS appear to be generated directly within the spinal cord, with disinhibition of the locomotor central pattern generator. However, there had been a lot of neurophysiological evidences of cortical involvement in the pathomechanism of PLMS. When analyzing the cortical function of patients with PLMS via movement-related beta and mu rhythm reactivity, the absence of cortical involvement was found in PLMS generation but observed a variation in cortical reactivity preceding PLM during wakefulness. They showed that the sensorimotor cortex plays a role in the generation of these movements even though the latter occur involuntarily. Previous transcranial magnetic stimulation study in PLMS patients with RLS had demonstrated the impairment of cortico-subcortical motor structures in the pathogenesis of RLS and PLMS. They insisted that these functional motor changes could cause consequently a disinhibition of supraspinal network, which most likely influences the spinal cord generator, only secondary responsible of the appearance of PLMS.

The human primary motor cortex is located in the dorsal part of the precentral gyrus and the anterior bank of the central sulcus and contains large neurons known as Betz cells, which send long axons down the spinal cord to synapse onto alpha motor neurons, which connect to the muscles. There is a broadly somatotopic representation of the different body parts in the primary motor cortex in an arrangement called a motor homunculus. In humans, the lateral area of the primary motor cortex is arranged from top to bottom in areas that correspond to the buttocks, torso, shoulder, elbow, wrist, fingers thumb, eyelids, lips, and jaw. Interior sections of the motor area folding into the medial longitudinal fisure correspond with the legs. In PLMS, leg muscles were more frequently involved, often with alternation of side. Axial muscles were rarely and upper limb muscles sometimes involved. The tibialis anterior was the most frequent starting muscle. Our finding, increased cerebral perfusion in bilateral precentral gyri suggested that cortical dysfunction of primary motor cortex may contribute to the generation of PLMS.

Night sleep quality of our PLMD patients was poorer than that of normal controls. PLMS are quite common, but PLMD, i.e., PLMS with symptomatic sleep disruption, is thought to be rare. Most of our patients came to the sleep clinic due to sleep onset and/or maintenance insomnia related to repetitive leg jerks. Ten of them reported the sleep onset insomnia, 9 complained frequent arousals resulted in sleep maintenance insomnia, and 6 patients had both problems. Nine patients who had frequent arousals were unaware of the limb movements: their total PLMS indices and arousal indices were higher than mean values (PLMS index, 60.3/hr in 9 vs. 55.3/hr in 25 patients; Arousal index, 19.3/hr in 9 vs. 15.7/hr in 25 patients), but it did not reach statistical significance. The proportion of movement arousal index to total arousal index was similar; mean movement arousal index was 9.6/hr (47.3% in 9 vs. 45.3% in 25 patients). There was no significant association between PSG parameters with rCBF of patients. Usually PLMS index and movement arousal index are considered as markers for PLMD severity. It is not clear why PLMD severity is not related to rCBF pattern of patients in this study.

We intentionally excluded the PLMD patients who were accompanied with RLS from the subjects to investigate the sole rCBF pattern accountable for PLMS. To the best our knowledge, it is first study to demonstrate the cerebral dysfunction in PLMD patients. This finding may contribute to revealing the pathomechanism of PLMD.

Acknowledgments

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REFERENCES