Journal of Neurology (2019) 266:717–725
https://doi.org/10.1007/s00415-019-09194-3

ORIGINAL COMMUNICATION

Painful legs and moving toes syndrome evaluated through brain single photon emission computed tomography: a case series

Kenya Nishioka[1] · Michimasa Suzuki[2] · Madoka Nakajima[3] · Takeshi Hara[3] · Masako Iseki[4] · Nobutaka Hattori[1]

Received: 2 October 2018 / Revised: 5 January 2019 / Accepted: 8 January 2019 / Published online: 14 January 2019

Abstract

Painful legs and moving toes (PLMT) syndrome is a clinical entity characterized by persistent pain in the feet or legs and involuntary movements of one or more toes. The precise patho-mechanisms of PLMT still remain unknown. Herein, we examined ten patients clinically identified with PLMT syndrome. All patients first presented persistent pain prior to the onset of motor symptoms. Each patient was examined by neurological investigation, neuro-imaging methods including brain magnetic resonance imaging (MRI) and electrophysiological methods. The brain single photon emission computed tomography (SPECT) images of eight patients indicated hypoperfusion of frontal lobes and cerebellum. The conjunction analysis of brain SPECT imaging data of all eight patients, using the 3D-SSP program, compared to 34 controls indicated significant hypoperfusion in the prefrontal cortical, occipital cortical, and cerebellar surfaces, and thalamus, and hyperperfusion in the surface of the anterior cingulate gyrus and parietal cortices including primary and secondary somatosensory cortices, bilaterally. These areas reflected on a part of the pain matrix. Other electrophysiological examinations did not indicate specific abnormalities to explain the patients' symptoms. On treatment with clonazepam, four out of nine patients could resolve their foot-related motor symptoms, but not the sensory symptoms. Overall, their pain was an intractable and persistent symptom throughout their clinical course. Our study infers that PLMT syndrome is fundamentally a chronic pain disorder, possibly relating to the central sensitization, involving the region of a part of pain matrix. Further studies need to confirm our results by adding more patients.

Keywords Painful legs and moving toes syndrome · SPECT · Chronic pain · Pain matrix

Introduction

Painful legs and moving toes (PLMT) syndrome is characterized by symptoms of persistent pain in one or more limbs and is accompanied by persistent, non-rhythmic toe movements [1, 2]. Hassan et al., summarized 76 cases of PLMT syndrome as the largest cohort, which indicated a middle-age onset, most commonly appearing in the hemi-lower limbs, and presenting various types of chronic pain, such as tingling, numbness, aching, dullness, cramp, shooting, sharp, burning, and prickling. Several case reports have described PLMT syndrome, wherein patients shared clinical presentations comprising common symptoms. PLMT syndrome is believed to be induced by various types of disorders and conditions: peripheral nerve neuropathies, herpes zoster myelitis, lumbar canal stenosis, tethered cord syndrome, and sacral Tarlov cyst and following surgical removal of a spinal tumor [3–8]. The speculated affected region seems to be widespread over the peripheral nerves to the central

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-019-09194-3) contains supplementary material, which is available to authorized users.

✉ Kenya Nishioka
nishioka@juntendo.ac.jp

[1] Department of Neurology, Juntendo University School of Medicine, 3-1-3 Hongo, Bunkyo-ku, Tokyo 113-8431, Japan

[2] Department of Radiology, Juntendo University School of Medicine, 3-1-1 Hongo, Bunkyo, Tokyo 113-8421, Japan

[3] Department of Neurosurgery, Juntendo University School of Medicine, 3-1-1 Hongo, Bunkyo, Tokyo 113-8421, Japan

[4] Department of Anesthesiology, Juntendo University School of Medicine, 3-1-1 Hongo, Bunkyo, Tokyo 113-8421, Japan

nervous system. It is debatable whether PLMT syndrome is an organic or psychogenic disorder [9] and the precise patho-mechanisms underlying the development of the syndrome still remain unclear. To explore these patho-mechanisms, we examined ten patients exhibiting PLMT syndrome by methods such as, electroencephalography, brain magnetic resonance imaging (MRI), and brain single photon emission computed tomography (SPECT) N-isopropyl-p-[^{123}I]-iodoamphetamine imaging. To our knowledge, this is the first report summarizing brain SPECT analysis in a single cohort of PLMT syndrome. Our discoveries may support the hypothesis of PLMT syndrome being a centralized pain disorder.

Materials and methods

Participants

This is a retrospective single-center study. The local ethics committee of Juntendo University approved the study according to the Helsinki Declaration. We collected clinical information from medical records of nine consecutive patients with clinically defined PLMT syndrome, who came to our hospital between 2015 and 2018. The clinical diagnosis was determined according to the standard definition of PLMT syndrome [1]. We gathered ten patients' data according to the initial symptoms and several indices related to the pain scale such as, numerical rating scale (NRS), widespread pain index (WPI), symptom severity (SS) [10], brain MRI, lumbar MRI, electroencephalogram, needle electromyogram, surface electromyogram, and somatosensory-evoked potential. Regarding brain single photon emission computed tomography (SPECT), we collected the data from eight patients (Case 1, 2, 3, 4, 5, 8, 9, and 10). We could not obtain the data of brain SPECT of Case 6 and 7, because they left our hospital. All clinical presentations of each patient (cases 1–10) are described in the supplementary data.

Brain SPECT

All SPECT studies were performed in a triple-headed gamma camera (GCA-9300A/UI, Toshiba Medical Systems, Nasu, Japan) with a fan beam collimator, by injecting IMP. Projection data were obtained in continuous rotation collimation with 150 s/rotation in the 10 × view. A Butterworth filter was used for SPECT image reconstruction, and attenuation correction was performed using Chang's method. All SPECT image data were transferred to an offline personal computer and converted to a binary format. Data analysis was performed using 3D-SSP. The relative cerebral blood flow in each voxel was calculated by normalizing the activity in each voxel to the institutional normal database. In this study, we used the freeware program "iSSP" (Nihon Medi-Physics, Nishinomiya, Hyogo, Japan), in which a 3D-SSP program with a graphic user interface was developed for clinical use. The *Z*-score (normal mean individual value / normal standard deviation) image of each subject was calculated. Visual inspection was performed to detect regional cerebral blood flow (CBF)-reduced areas in each patient on the individual *Z*-score maps. Next, group comparisons of the CBF images between normal controls and patients with PLMT syndrome were performed using a two-sample Student's *t* test on a pixel-by-pixel basis. The obtained *t* values were converted to *Z* values using significance integral transformation for comparison, and *Z*-score maps were obtained. In this comparative study, *Z*-scores over 2.0 were considered significant between patients with and without systemic pain. We analyzed one group of eight patients with PLMT syndrome in comparison to normal controls ($n = 34$, male:female = 17:17, average age at examination 69.8 ± 12.2 years (± SD), range 46–86 years). We set the left side as the afflicted side for analysis. To accommodate cases 2, 8, and 9 with the right side afflicted, SPECT data was changed to a right and left reversed image.

Results

Clinical findings

The clinical overview of all ten patients is presented in Table 1. The majority of the patients were female (male:female = 2:8). The dominant afflicted side was mostly the same (right:left = 4:6). The average age at onset was 51.7 ± 11.6 years (± SD, range 26–69 years). Past medical history was varied, such as, following an operation for lumbar canal stenosis, lumbar laminectomy or hemorrhoid, post-infection of poliomyelitis, depression, restless legs syndrome and Parkinson's disease (PD). Initial symptoms were involuntary movements of toe and persistent pain in one lower limb. All patients first experienced pain in the lower limbs or toe, prior to involuntary movements. Three patients (cases 6, 7, and 9) apparently presented psychiatric problems such as, depression, anxiety, and irritability. The other seven patients did not claim any symptoms related to psychiatric disorders. Pain score indices of numerical rating scale, widespread pain index, and severity scores indicated 6.8 ± 2.6, 3.9 ± 1.7, and 5.6 ± 2.8, respectively, denoting a moderate degree of pain severity and lower limb localization of this pain in patients with PLMT syndrome. Three of our patients (cases 5, 8, and 9) fulfilled the criteria for fibromyalgia syndrome, presenting not only the localized pain but also widespread pain through the body [10].

Table 1 Clinical overview of patient cohort (ten cases) with painful legs and moving toes syndrome

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Average or ratio
Gender	Female	Female	Female	Female	Female	Female	Female	Male	Male	Female	Male:female = 2:8
Age at onset	53	48	26	44	53	52	69	61	50	61	51.7 ± 11.6
Age at exam	71	51	54	45	55	55	73	61	51	81	59.7 ± 11.6
Past medical history	Post operation of laminectomy at L4/5 for lumbar canal stenosis	Post operation of hemorrhoid	Hypoplasia at left foot due to poliomyelitis at childhood	None	None	Depression	Post operation of breast cancer, lumbar canal stenosis	Parkinson's disease	Depression	None	
Initial symptom	Involuntary movements and persistent pain in lower limb	Painful legs and involuntary movements	Severe pain in the lower limb	Involuntary movements and persistent pain in lower limb	Involuntary movements and persistent pain in lower limb	Involuntary movements and persistent pain in lower limb	Involuntary movements in lower limb	Involuntary movements in right lower limb and pain	Involuntary movements in the toes and pain	Involuntary movements in the toes and pain	
Pain at onset	+	+	+	+	+	+	+	+	+	+	10/10
Involuntary movements at onset	−	−	−	−	−	−	−	−	−	−	0/10
Affected side	Left	Right	Left	Left	Left	Right	Left	Right	Right	Left	Right:Left = 4:6
Psychiatric problem	−	−	−	−	−	Depression	Depresion	−	Depresion and anxiety	−	
Parkinsonism	−	−	−	−	−	−	−	+	−	−	1/10
Pain score indices											
NRS at first examination	4	2	8	8	4	8	7	9	10	8	6.8 ± 2.6
Widespread pain index	2	5	3	5	7	2	3	5	5	2	3.9 ± 1.7
Symptom severity	4	3	5	8	6	1	8	9	9	3	5.6 ± 2.8

NRS numerical rating scale

Results of neurological examinations

The results of all examinations are summarized in Table 2. Brain MRI showed no morphological abnormalities in any of the ten patients. Average years from disease onset to assessment of brain SPECT was 7.88 ± 10.5 years (range 0–28) (Table 2). Our raw data from the brain SPECT analysis of seven patients (cases 1, 2, 3, 4, 5, 8, and 10) indicated hypoperfusion in the surface of the frontal lobe and hyperperfusion in the surface of the parietal lobe (Fig. 1a–f, h). Case 9 only showed local hypoperfusion in the surface of the occipital lobe (Fig. 1g, o). This program showed significant hypoperfusion in the surface of bilateral frontal tips (dark blue triangles), occipital lobes (light blue triangles), cerebellar (light red triangles), and thalamus (dark red triangles) (Fig. 1q). On the contrary, the temporal and parietal lobe remained unchanged. Regarding the views of hyperperfusion, it was observed on the surface of the anterior cingulate gyrus (yellow triangles), and on the primary and secondary somatosensory cortices (green triangles) (Fig. 1r). Visually, there was no disproportionate perfusion between the right and left sides. Lumbar MRI showed normal findings in eight patients, and lumbar canal stenosis in two patients (Table 2). Electroencephalograms indicated normal findings in all ten patients. Surface electromyograms revealed various results such as, tremors, dystonia, rhythmic muscle contractions, and non-rhythmic grouping discharge. One case (case 8) showed only mild sensory axonal neuropathy which may be due to spinal canal stenosis, but the other nine patients presented normal findings of nerve conduction study. Needle electromyograms indicated normal findings in seven patients, and myokymic discharge in the muscle of tibialis anterior in one patient (case 2), with no symptoms related to neuromyotonia.

Treatments

The efficacy of our treatments is summarized in Table 3. Retrospectively, clonazepam ameliorated the motor symptoms, but not the sensory symptoms, in four patients. Intrathecal baclofen and quetiapine showed good response for one patient (case 6). Gabapentin did not show any improvements in either motor or sensory symptoms in six patients. Generally, all ten patients claimed persistent pain even after disappearance of involuntary movements.

Discussion

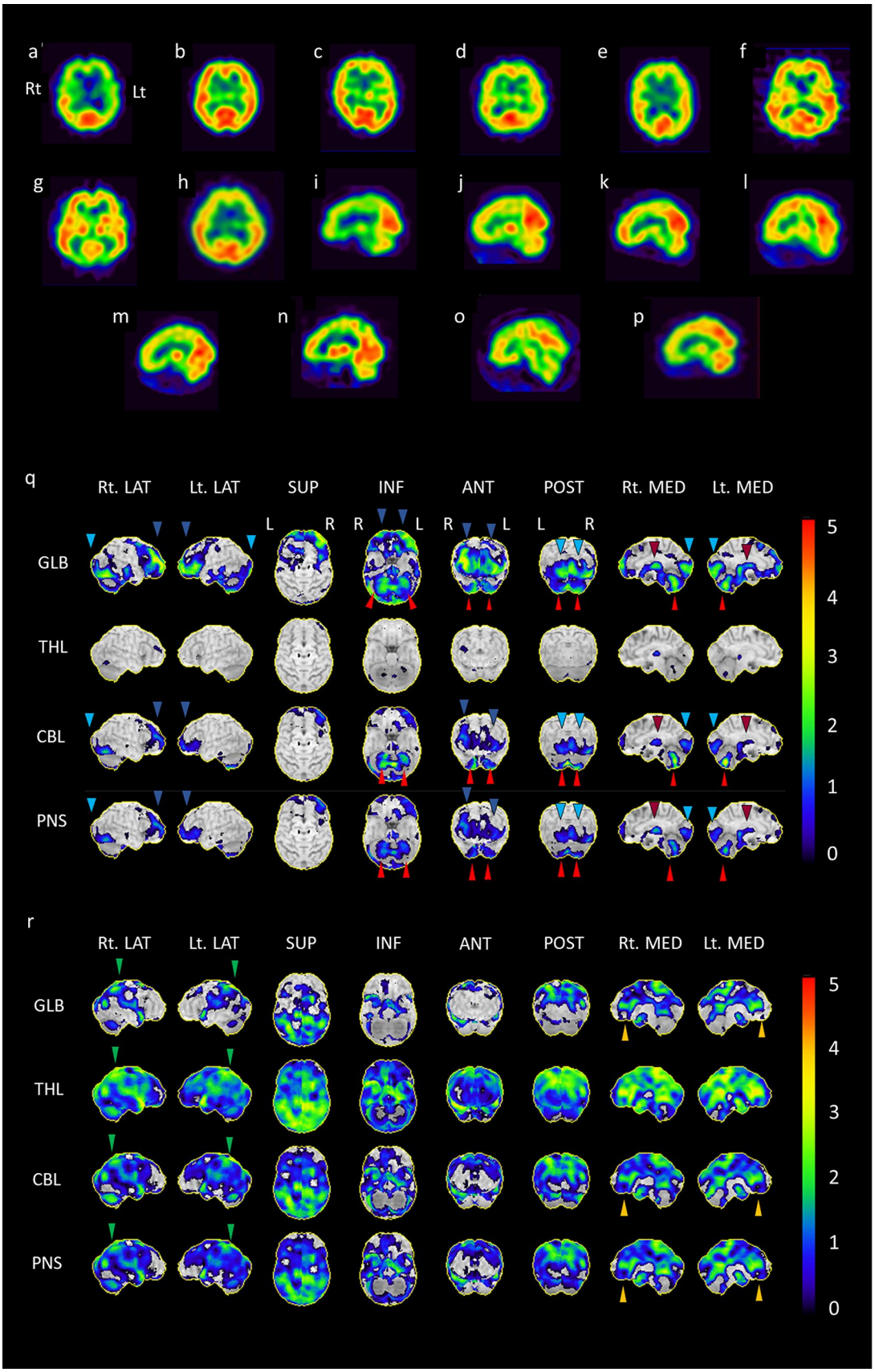
The precise patho-mechanisms of PLMT syndrome still remain obscure. It is not entirely clear whether the cause of the disease is an organic or a psychogenic disorder, even though the patients shared common clinical entities: painfulness and involuntary movements in one lower limb. Previous studies have suggested that there could be heterogenous factors responsible for the development of PLMT syndrome [3, 6, 8, 11, 12]. The possible cause is thought to be the injuries of peripheral tissues, nerves or nerve roots, inducing alterations in afferent sensory information with subsequent reorganization of segmental efferent motor activity [12]. However, our clinical examinations revealed most of the results to be within normal limits with respect to brain MRI, lumbar MRI, and electrophysiological studies, none of which could explain the reason for the development of the symptoms seen in the patients. Through our studies of patients with PLMT syndrome, pain emerges as a more fundamental symptom compared to the motor symptoms. In fact, most of the patients (over 90%) predominantly experienced persistent pain in the legs for a long duration, prior to onset of motor symptoms [1]. After multiple treatments, the pain remained constant, whereas the involuntary movements in the toe responded well to treatments and diminished soon.

In our examinations, brain SPECT showed common tendencies in eight patients, indicating significant hypoperfusion in the bilateral surface of the prefrontal, occipital, cerebellar lobe, and thalamus, and hyperperfusion in the bilateral primary and secondary somatosensory cortices, and anterior cingulate gyrus. These areas relate to the pain matrix, which have been known as brain network areas involved in the multiple dimensions of pain perception [13]. These findings matched the previous trials of brain SPECT in patients with chronic pain or fibromyalgia syndrome [14–16]. In the patients with fibromyalgia syndrome, which is thought to be a chronic pain disorder with patients presenting widespread pain, brain SPECT studies indicated hypoperfusion in the bilateral frontal, cingulate, temporal and cerebellar cortices, and hyperperfusion in the somatosensory cortex [15]. A 99mTc-ECD SPECT indicated hypoperfusion in the medial temporal, inferior, medial frontal lobes and cingulate, and hyperperfusion in the somatosensory cortices [14]. Brain SPECT studies in the patients with chronic pain, including various type of disorders such as lower back pain, lumbar canal stenosis, Morton disease, somatoform pain disorder, and complex regional pain syndrome (CRPS), depicted decreased blood flow in the dorsolateral prefrontal area, anterior cingulate gyrus, and orbitofrontal cortex [16]. The SPECT study in patients with CRPS type I demonstrated lower cerebral blood flow in the thalamus, and higher than that in the parietal lobe and frontal lobe [17]. These brain SPECT studies shared common results of the hypoperfusion in the prefrontal lobe, cingulate gyrus, and thalamus, and hyperperfusion in the somatosensory cortices, with the distinctive findings of brain SPECT among the patients with chronic pain syndrome. Our study also matches these findings, except for the hypoperfusion of cingulate gyrus. An increased activity in the pain matrix was related to central

Table 2 Summary of clinical examinations of the ten patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Average
Electrophysiological examinations											
Electroencephalogram	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	
Somatosensory-evoked potential (SEP)	Normal	NA	Normal	Normal	Left disturbance in the funiculus posterior	Left disturbance in the funiculus posterior	Giant SEP	NA	NA	NA	
Needle electromyogram	Normal	Myokymic discharge in tibialis anterior	Cannot be assessed due to severe pain	Normal	Normal	Normal	Normal	NA	Normal	Normal	
Surface electromyogram	NA	NA	Cannot be assessed due to severe pain	Tremor	Normal	Rhythmical muscle contraction in the right lower limbs	Dystonia	NA	Tremor	Non-rhythmic grouping discharge	
Nerve conduction study	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Sensory axonal neuropathy, mild	Normal	Normal	
Neuroimagings											
Brain MRI	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	
Lumbar MRI	Normal	Normal	Normal	Lumbar canal stenosis at L2/3	Normal	Normal	Normal	Lumbar canal stenosis (mild)	Normal	Normal	
Years from disease onset to brain SPECT	8	3	28	1	2			0	1	20	7.88 ± 10.5

MRI magnetic resonance imaging, *SPECT* single photon emission computed tomography, *NA* not assessed


a
Rt
Lt
b
c
d
e
f
g
h
i
j
k
l
m
n
o
p
q
Rt. LAT
Lt. LAT
SUP
INF
ANT
POST
Rt. MED
Lt. MED
L R
R L
R L
L R
GLB
THL
CBL
PNS
5
4
3
2
1
0
r
Rt. LAT
Lt. LAT
SUP
INF
ANT
POST
Rt. MED
Lt. MED
GLB
THL
CBL
PNS
5
4
3
2
1
0

◂**Fig. 1** Brain single photon emission computed tomography imaging of seven patients with painful legs and moving toes syndrome. Brain single photon emission computed tomography (SPECT)-N-isopropyl-p-[^{123}I]-iodoamphetamine (IMP) images **a**–**h** show axial views at the level of lateral ventricles, and **i**–**p** show sagittal views at the level of the central position. The images (**a, i**) are for case 1 (**b, j**), depict case 2 (**c, k**), for case 3 (**d, l**), for case 4 (**e, m**), are for case 5 (**f, n**), for case 6, and (**g, o**) for case 7, and (**h, p**) for case 8. Images (**a**–**h**) indicate hypoperfusion in the bilateral frontal lobes. Images (**i**–**o**) indicate hypoperfusion in the frontal lobe and hyperperfusion in the parietal lobe. Images (**g**) and (**o**) indicate hypoperfusion localized in the bilateral occipital lobes. Image (**o**) depicts the three-dimensional stereotactic surface projection of SPECT-IMP, and a comparative study of the conjunctive analysis of our eight patients and 34 normal controls significantly revealed severe hypoperfusion on the surface of bilateral frontal lobes (dark blue triangle), occipital lobe (light blue triangle), and bilateral cerebellum (light red triangle), and thalamus (dark red triangle). Image (**p**) indicates remarkable hyperperfusion in the surface of bilateral primary and secondary somatosensory cortices (green triangle) and anterior cingulate gyrus (yellow triangle). *Rt* right, *Lt* left, *LAT* lateral, *SUP* superior, *INF* inferior, *ANT* anterior, *POST* posterior, *MED* medial, *GLB* global, *THL* thalamus, *CBL* cerebellum, and *PNS* pons

sensitization among the patients with fibromyalgia syndrome [18]. The alterations in the cerebral blood flow may reflect on the chronic pain of the patients with PLMT syndrome.

There were no visual differences between sides in the alterations of brain SPECT, although all patients clearly presented laterality in the lower limb. The alterations without laterality of our SPECT analysis may reflect on intractable pain, similar to fibromyalgia syndrome or chronic pain disorder. Another reason may explain in the basal ganglia, especially in the thalamus, where our analysis could not demonstrate. Previous reports mentioned the alterations of cerebral blood flow in the thalamus among patients with chronic pain [19, 20]. Further study is needed to evaluate the functions or cerebral flow in the region of basal ganglia for PLMT syndrome.

In the patients harboring chronic pain, allodynia, or hyperalgesia, the area of pain perception networks has been known as the 'pain matrix', which is evoked by nociceptive pain or neuropathic pain, which is thought to be located in the anterior cingulate gyrus, the insular cortex, and the primary and secondary somatosensory cortices [21–23]. Our SPECT imaging also showed hyperperfusion in the parietal lobe and cingulate gyrus, which constitute a part of the region of the pain matrix, possibly evoked by the chronic pain perception from PLMT syndrome. Although, the brain SPECT technique is limited in depicting the region of the basal ganglia or the insular cortex, our study clearly demonstrated the similarity of those of the patients with chronic pain, fibromyalgia syndrome or CRPS type I.

With respect to motor symptoms, it has been known that persistent pain and motor symptoms coexist with chronic pain disorders. For instance, there was a relatively high prevalence of complications in CRPS and involuntary movements: 30.3% of tremors, and 21.0% of dystonia among 195 Japanese cases [24]. A review demonstrated 50% prevalence of tremors and 30% prevalence of myoclonus or focal dystonia in the patients with CRPS [25]. The putative pathomechanisms of CRPS type I was believed to be via injured nerve tissue-induced spinal plasticity or central sensitization, causing an alteration in sensorimotor processing in the spinal cord [26]. These changes can finally develop into motor symptoms in CRPS. A relatively high prevalence of tremors (16%) and abnormal clumsiness (38%) was also observed in fibromyalgia syndrome [27]. Although tremors and dystonia are completely different symptoms with piano-playing movements, these findings point towards an intimate connection between persistent sensory symptoms and involuntary movements.

Intriguingly, nine patients did not present any parkinsonism. However, one male (case 8) only had 2 years of history of parkinsonism prior to onset of PLMT syndrome. His symptoms fulfilled the criteria of PD, but his involuntary movements in the toe were different from the symptoms associated with parkinsonism. Recently, a case report mentioned a female patient with PD and PLMT syndrome, showing a positive response to levodopa administered to improve her motor symptoms [28]. Our patient also presented partial improvements of motor symptoms by clonazepam and pain symptoms by pregabalin, but not by levodopa, which means that the symptoms related to PLMT syndrome can be differentiated from those of PD. There were no records of complication of neurodegenerative disorders in the case series of 76 PLMT patients [1]. Another male patient (case 9) manifested irritability, severe depression, and anxiety. His brain SPECT showed localized hypoperfusion in the bilateral occipital lobe, which is commonly seen in patients with dementia with Lewy bodies. His symptoms may be caused by tactile hallucinations, as this is one of the symptoms of dementia with Lewy bodies.

On treatment with clonazepam, our nine patients presented a partial amelioration of motor symptoms (4/9). Other treatments such as, anti-epileptic drugs, analgesics including pregabalin or nonsteroidal anti-inflammatory drugs, or muscle-relaxant drugs did not show an apparent improvement. Other case reports have mentioned the efficacy of gabapentin or pregabalin [8, 29–31]. However, retrospectively, all of our six cases did not show any improvement with gabapentin with respect to both motor and sensory symptoms. Further studies are needed to evaluate the efficacies under the same conditions, periods, and dosage of candidate drugs. Overall, in our cases, pain persistently remained even after several kinds of treatments.

The specific alteration of brain SPECT may help us understand the patho-mechanisms of PLMT syndrome. The pain matrix is possibly associated with the chronic pain syndrome, which presumably means that PLMT syndrome

Table 3 Retrospective evaluation of efficacies of treatments for the ten patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Ratio
Effective treatments	Clonazepam and imipramine	Clonazepam	No response	Clonazepam	Pain persistent	Intrathecal baclofen therapy	No response	Clonazepam and pregabalin	Quetiapine	No response	
Efficacy of gabapentin	NA	NA	NA	–	–	–	–	NA	–	–	0/6
Improvement of involuntary movements	+	–	–	–	+	+	–	–	+	–	4/10
Persistent pain after treatments	+	+	+	+	+	+	+	+	+	+	10/10
Prognosis	Better	Better	No change	Better	Better	Better	No change	No change	Worse	No change	

NA not assessed

shares clinical features of fibromyalgia syndrome or chronic pain syndrome, which are related to the central sensitization. The coexistence of persistent pain and involuntary movements in the toe of one limb establishes the clinical characteristics of PLMT syndrome. Further studies are needed to confirm our results with the addition of more number of patients.

Compliance with ethical standards

Conflicts of interest The authors report no conflicts of interest relevant to the manuscript.

Ethical standards This study was approved by the ethical committee of the Juntendo University School of Medicine in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

References

1. Hassan A, Mateen FJ, Coon EA et al (2012) Painful legs and moving toes syndrome: a 76-patient case series. Arch Neurol 69:1032–1038
2. Spillane JD, Nathan PW, Kelly RE et al (1971) Painful legs and moving toes. Brain J Neurol 94:541–556
3. Ikeda K, Deguchi K, Touge T et al (2004) Painful legs and moving toes syndrome associated with herpes zoster myelitis. J Neurol Sci 219:147–150
4. Alvarez MV, Driver-Dunckley EE, Caviness JN et al (2008) Case series of painful legs and moving toes: clinical and electrophysiologic observations. Mov Disord Off J Mov Disord Soc 23:2062–2066
5. Azzi J, Atweh S, Saade N et al (2014) Neuroleptics as a cause of painful legs and moving toes syndrome. BMJ Case Rep 2014
6. Pandey S, Soni G (2016) Painful leg and moving toes syndrome in secondary tethered cord syndrome. J Spinal Cord Med 39:363–365
7. Alrawashdeh O (2016) Painless legs and moving toes syndrome associated with a sacral Tarlov cyst: a case report. J Med Case Rep 10:52
8. Kim SS, Hwang YS, Kim YC (2016) Painful legs and moving toes syndrome in a 16-year-old girl. Korean J Pediatr 59:381–383
9. Stone J, Erro R (2014) Functional (psychogenic) painful legs moving toes syndrome. Mov Disord Off J Mov Disord Soc 29:1701–1702
10. Wolfe F, Clauw DJ, Fitzcharles MA et al (2010) The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res 62:600–610
11. Brigo F, Vogrig A, Bratti A et al (2018) Probable dysimmune epilepsia partialis continua manifesting as epileptic moving toes syndrome: electroclinical features of a challenging case. Epileptic Disord Int Epilepsy J Videotape 20:301–312
12. Dressler D, Thompson PD, Gledhill RF et al (1994) The syndrome of painful legs and moving toes. Mov Disord Off J Mov Disord Soc 9:13–21
13. Moisset X, Bouhassira D (2007) Brain imaging of neuropathic pain. NeuroImage 37(Suppl 1):S80–S88
14. Guedj E, Taieb D, Cammilleri S et al (2007) 99mTc-ECD brain perfusion SPECT in hyperalgesic fibromyalgia. Eur J Nucl Med Mol Imaging 34:130–134

15. Guedj E, Cammilleri S, Colavolpe C et al (2007) Predictive value of brain perfusion SPECT for ketamine response in hyperalgesic fibromyalgia. Eur J Nucl Med Mol Imaging 34:1274–1279
16. Honda T, Maruta T, Takahashi K (2007) Brain perfusion abnormality in patients with chronic pain. Keio J Med 56:48–52
17. Wu CT, Fan YM, Sun CM et al (2006) Correlation between changes in regional cerebral blood flow and pain relief in complex regional pain syndrome type 1. Clin Nucl Med 31:317–320
18. Cagnie B, Coppieters I, Denecker S et al (2014) Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI. Semin Arthritis Rheumat 44:68–75
19. Kwiatek R, Barnden L, Tedman R et al (2000) Regional cerebral blood flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami. Arthritis Rheumat 43:2823–2833
20. Cesaro P, Mann MW, Moretti JL et al (1991) Central pain and thalamic hyperactivity: a single photon emission computerized tomographic study. Pain 47:329–336
21. Tracey I (2005) Nociceptive processing in the human brain. Curr Opin Neurobiol 15:478–487
22. Treede RD, Kenshalo DR, Gracely RH et al (1999) The cortical representation of pain. Pain 79:105–111
23. Mouraux A, Diukova A, Lee MC et al (2011) A multisensory investigation of the functional significance of the "pain matrix". NeuroImage 54:2237–2249
24. Sumitani M, Shibata M, Sakaue G et al (2010) Development of comprehensive diagnostic criteria for complex regional pain syndrome in the Japanese population. Pain 150:243–249
25. Birklein F (2005) Complex regional pain syndrome. J Neurol 252:131–138
26. van Hilten JJ (2010) Movement disorders in complex regional pain syndrome. Pain Med (Malden Mass) 11:1274–1277
27. Watson NF, Buchwald D, Goldberg J et al (2009) Neurologic signs and symptoms in fibromyalgia. Arthritis Rheumat 60:2839–2844
28. Kawajiri S, Hoshino Y, Nakamura R et al (2016) A case of painless legs and moving toes syndrome in Parkinson's disease responsive to dopaminergic therapy. Case Rep Neurol Med 2016:6829410
29. Guler S, Yavuz S, Nakus E et al (2016) A case of painful legs and moving toes syndrome treated with gabapentin. Agri 28:109–112
30. Rossi FH, Liu W, Geigel E et al (2015) Painful legs and moving toes syndrome responsive to pregabalin. J Postgrad Med 61:116–119
31. Bhargava P, Pandav V, Peche S (2013) A pediatric case of painful legs and moving toes syndrome. Pediatr Neurol 49:298–299