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Research Article

Increased ^{18}F-THK5351 Uptake at Bilateral Primary Motor Cortex in Patients with Progressive Pseudobulbar Palsy

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Background. Although patients can present with progressive pseudobulbar palsy due to neurodegenerative diseases, detection of the precise location of radiological abnormalities can be difficult. ^{18}F-THK5351 was initially developed as a tau positron emission tomography (PET) tracer. Later, it was found to sensitively detect astrogliosis associated with neurodegeneration. Therefore, it has been used in diagnosis of various diseases. However, its utility in progressive pseudobulbar palsy was unknown. *Methods*. ^{18}F-THK5351 PET results of two patients presenting with progressive pseudobulbar palsy are reported. *Results*. Patient 1 was a 77-year-old man with a two-year history, and Patient 2 was a 61-year-old woman with a 1-year history. Both patients presented with gradually progressive spastic dysarthria, suggesting pseudobulbar palsy without clinical lower motor neuron signs. Facial asymmetry was detected in both patients, while left-dominant pyramidal signs in the extremities were detected only in Patient 2. Brain magnetic resonance imaging did not show signal abnormality explaining pseudobulbar palsy. However, ^{18}F-THK5351 PET clearly visualized bilateral increased uptake in limited areas of the posterior portion of the precentral gyrus, corresponding to the midportion of the primary motor cortex. Laterality of increased ^{18}F-THK5351 uptake corresponded to the symptom laterality and was higher on the left and right side in patients 1 and 2, respectively. After one year, Patient 1 was unable to vocalize and could only produce grunts; concomitant apraxia of speech was suspected. *Conclusions*. ^{18}F-THK5351 PET is a useful method to detect bilateral primary motor cortex involvement in patients presenting with progressive pseudobulbar palsy, likely by imaging astrogliosis.

1. Introduction

Pseudobulbar palsy is caused by bilateral disturbance of the motor cortex or corticobulbar tracts and characterized by spastic dysarthria, dysphagia, and facial and tongue weakness [1]. Various etiologies have been reported, including vascular, traumatic, metabolic, inflammatory, and neurodegenerative diseases [1]. Although rare, patients can present with gradually progressive pseudobulbar palsy as a chief complaint likely because of neurodegeneration of the motor cortex later progressing to upper motor neuron- (UMN-) predominant ALS or primary lateral sclerosis (PLS) [2–4]. Previous studies have shown that analysis of white matter volume [2] or iron-related hypointensities [5] can identify abnormality in the motor

cortex. However, detection of abnormalities in the motor cortex can be difficult by conventional imaging techniques at least in some patients.

Although ^{18}F-THK5351 was initially developed as a tau positron emission tomography (PET) tracer, its ability of strong off-target binding to monoamine oxidase B (MAO-B) was found later [6]. Since MAO-B is predominantly expressed in reactive astrocytes [7–9], it is currently used to detect astrogliosis observed in a wide range of neurological diseases [8–11]. Several previous reports suggested that ^{18}F-THK5351 PET may identify motor cortex involvement in patients with amyotrophic lateral sclerosis (ALS) [9, 12, 13]. However, it was unknown if ^{18}F-THK5351 PET could also identify motor cortex involvement in patients presenting with progressive pseudobulbar palsy.

Herein, we report the results of ^{18}F-THK5351 PET of two patients presenting with progressive pseudobulbar palsy.

2. Methods

Patients presenting with progressive pseudobulbar palsy were recruited for the study. The study was approved by the Institutional Review Board of Tokyo Metropolitan Institute for Geriatrics and Gerontology. Written informed consent was obtained from the patients.

^{18}F-THK5351 PET was conducted according to tracer preparation and PET image acquisition methods described previously [14]. The distribution pattern of ^{18}F-THK5351 in the healthy brain has been described in detail in a previous report [15]. PET images were normalized using the cerebellar cortex as a reference region, with the uptake set to one (uptake ratio index (URI)). Three-dimensional (3D) renderings of high uptake regions on individual brain structures based on 3D T1-weighted MRI images were created using PMOD medical image analysis software ver 3.7 (PMOD Technologies LLC).

3. Results

3.1. Patient 1. A right-handed 77-year-old man presented with a one-year history of gradually worsening dysarthria and dysphagia. Detailed neurological assessment and brain MRI results did not show specific findings for diagnosis (Figure 1(a)). After one year, the patient was referred to our hospital for further evaluation. Neurological examination revealed dysarthria and slow and effortful speech with regular rhythm, thereby suggesting spastic dysarthria [1]. Although slight slowing of right facial movement and mildly increased jaw jerk reflex was observed, the patient was otherwise neurologically intact. Needle electromyography (nEMG) showed no signs of lower motor neuron (LMN) involvement. ^{18}F-THK5351 PET showed bilateral increased uptake in limited areas of the posterior portion of the precentral gyrus, corresponding to the midportion of the primary motor cortex with slight dominance on the left (Figures 1(b)–1(d)). After one year, the patient's symptoms had worsened; he was unable to produce simple phonemes and could only produce grunt sounds with similar pitch. However, the patient did not have a comprehension problem and communicated well through writing; he was able to eat soft meals and was functionally independent. Neurological examination showed right-dominant facial weakness, impaired soft palatal elevation, and slow tongue movement. These findings were insufficient to explain the patient's motor speech impairment, and concomitant apraxia of speech was suspected. Automatic-voluntary dissociation was suspected for smiling and coughing. Tongue pressure, bolus transportation, and nasopharyngeal closure were affected, and the swallowing reflex was delayed. No clinical or electrophysiological signs of LMN involvement or UMN signs in the extremities were observed at the follow-up, 3 years after from disease onset.

3.2. Patient 2. A right-handed 61-year-old woman presented with a 6-month history of slowly progressing dysarthria and dysphagia. Detailed neurological assessment, nEMG, and brain MRI (Figure 1(e)) did not reveal any specific abnormality that could explain the patient's symptoms. After 6 months, the patient was referred to our hospital for further examination. Her speech was slow, effortful, punctuated by short phrases and in a regular rhythm, and concordant with spastic dysarthria [1]. Neurological examination showed hyperactive gag reflex, facial weakness, and dominant pyramidal tract signs in both upper and lower extremities on the left side, mild bradykinesia, and postural instability. Oral diadochokinesis and tongue pressure were impaired; however, the swallowing function was relatively preserved. nEMG showed fibrillation potentials and positive sharp waves in trapezius and first dorsal interosseous (FDI) muscles, and fasciculation potentials in the FDI muscle. Recruitment patterns in voluntary activity were normal. ^{18}F-THK5351 PET showed right-dominant bilateral increased uptake in limited areas of the posterior portion of the precentral gyrus, corresponding to the midportion of the primary motor cortex (Figures 1(f)–1(h)). ^{18}F-THK5351 uptake in the striatum and midbrain was asymmetric and was higher on the right side (Figures 2(a)–2(c)). Dopamine transporter (DAT) SPECT showed decreased right-dominant striatal uptake (Figure 2(d)). During the first year follow-up, disease progression was slow, and the patient was able to talk slowly without signs of apraxia of speech, could eat soft meals, and was functionally independent. Clinical signs of LMN involvement at follow-up, 2 years after disease onset, were absent.

4. Discussion

Here, we report the ^{18}F-THK5351 PET results of two patients who presented with progressive pseudobulbar palsy. In both patients, bilateral lesions in limited areas of the primary motor cortex were clearly depicted corresponding to clinical symptoms and signs.

Dysarthria can be classified into four categories: spastic dysarthria due to pseudobulbar palsy, flaccid dysarthria due to bulbar palsy, ataxic dysarthria due to cerebellar ataxia, and hypokinetic dysarthria due to basal ganglia impairment [1]. The two cases presented here were characterized by slow, regular, effortful, and short speech and met the characteristics of spastic dysarthria [1]. Although there have been occasional case reports of isolated progressive

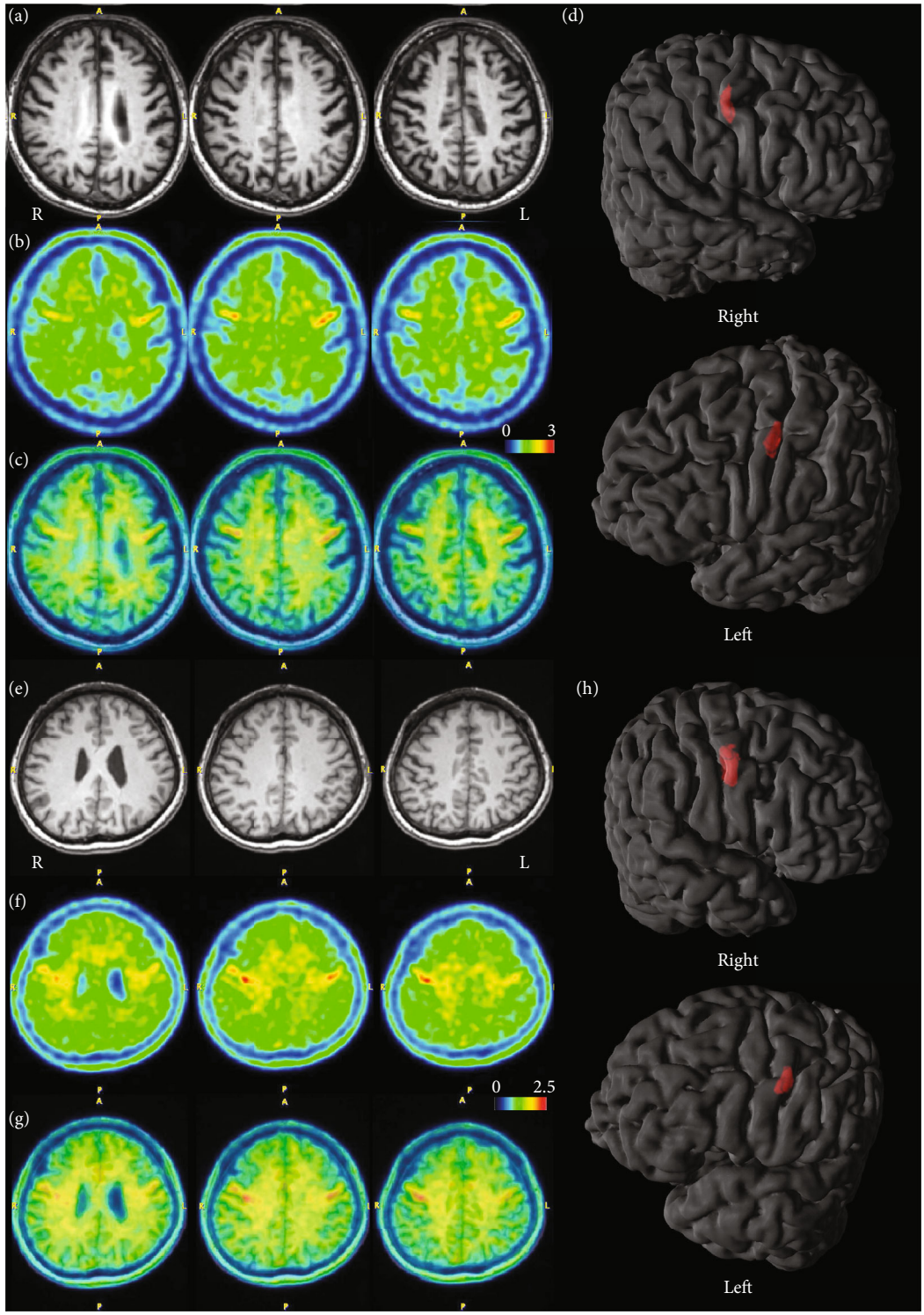

FIGURE 1: Brain MRI and ^{18}F-THK5351 PET images of patients with progressive pseudobulbar palsy. (a) T1-weighted brain MRI images of Patient 1. Mild bilateral frontal lobe dominant brain atrophy is observed without accent in the precentral gyrus. (b) ^{18}F-THK5351 PET images of Patient 1, (c) overlayed images on brain MRI, (d) and 3D renderings on individual brain structures. Bilateral increased uptake is observed in limited areas of the posterior portion of the precentral gyrus, corresponding to the midportion of the primary motor cortex. (b, c) Although the distribution was symmetric, uptake was slightly higher on the left side. (e) T1-weighted brain MRI images of Patient 2. Apparent focal atrophy is not observed. (f) ^{18}F-THK5351 PET images of patient 2, (g) overlayed images on brain MRI, (h) and 3D renderings. Right-dominant bilateral increased uptake is observed in limited areas of the posterior portion of the precentral gyrus, corresponding to the midportion of the primary motor cortex. Color scales represent the uptake ratio index (URI), with the cerebellum as the reference region (=1). Red areas in (d) and (h) are cerebral regions with URI > 2. R: right; L: left.

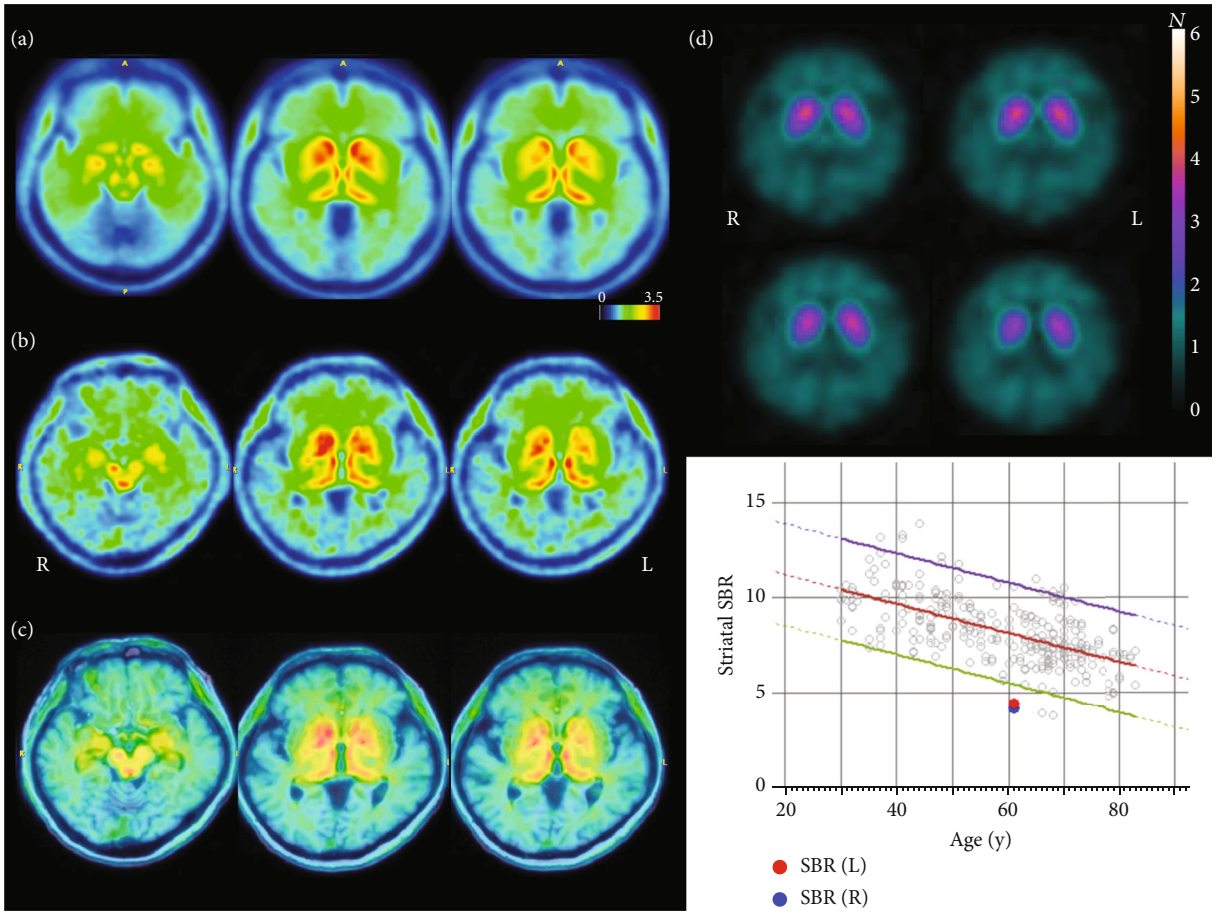

Figure 2: Striatal and midbrain imaging findings of Patient 2. (a) Average ^{18}F-THK5351 PET images of healthy volunteers. Symmetric physiological tracer uptake is observed in striatum, thalamus, periaqueductal gray, and substantia nigra as previously reported [15]. (b) ^{18}F-THK5351 PET images and (c) overlayed images of Patient 2. Although tracer uptake is observed in these regions, uptake in the substantia nigra and striatum was higher on the right side. (d) Dopamine transporter SPECT results using ^{123}I-ioflupane as a tracer analyzed by DAT VIEW software. Tracer uptake was visually decreased in the right dorsal putamen. The specific binding ratio (SBR) after phantom calibration was right 4.21 and left 4.44, which were both below 2 standard deviations from age- and sex-matched controls. R: right; L: left.

pseudobulbar palsy in the literature [3, 4], Clark et al. were the first to describe the clinical and imaging characteristics of these patients [2]. The two cases presented here matched the concept of progressive spastic dysarthria/pseudobulbar palsy including the following: (i) speech difficulties as the presenting/primary neurological complaint; (ii) duration of symptoms—at least 6 months; (iii) speech diagnosis of spastic dysarthria; and (iv) absence of clinical signs of LMN involvement [2]. The symptoms of Patient 1 progressed to later stages; the case was likely complicated by apraxia of speech, which has been reported in 12% of cases in a previous report [2].

Studies conducted in the past have suggested that visual assessment of brain MRI yields nonspecific findings, at least in the early stages of progressive pseudobulbar palsy [2–4]. In a subgroup of patients, MRI volumetric analysis suggested white matter volume loss, and fluorodeoxyglucose- (FDG-) PET showed subtle bilateral cortical hypometabolism in half of the patients, mainly in the premotor and motor cortices [2]. A study in patients with ALS showed that iron-related hypointensities can identify abnormality in the motor cortex more frequently in bulbar-onset than in spinal-onset patients [5]. Although these results suggested bilateral motor cortex involvement in patients with progressive pseudobulbar palsy, a better imaging modality was needed to visualize the precise location of radiological abnormalities for pathophysiological understanding and diagnosis. In this study, ^{18}F-THK5351 PET clearly depicted bilateral precentral gyrus lesions in both patients. The lesions were confined to the posterior portion of the precentral gyrus corresponding to the primary motor cortex (Brodmann area 4). The lesions were located lateral to the precentral knob (hand motor area) but did not involve the most ventral part of the precentral gyrus and seemed to be relatively confined to the mid-portion of the precentral gyrus. Interestingly, this part of the primary motor cortex likely includes regions related to vocalization (referred to as dorsal laryngeal motor cortex) and some portion of those related to articulation [16–18]. Left-dominance or subsequent expansion of the legion may have attributed to the appearance of additional features later

in Patient 1. Our findings suggest that ^{18}F-THK5351 PET is a promising imaging modality for assessing the precise location of abnormality in patients with progressive pseudobulbar palsy for a better understanding of this condition, although validation in a larger patient sample is needed. ^{18}F-THK5351 PET may also have the potential as a biomarker to monitor the severity and extent of UMN impairment and astrogliosis in future clinical trials.

The underlying pathology of these two patients remains undetermined. However, previous reports suggested that progressive pseudobulbar palsy is a presenting form of motor neuron disease (MND) [2–4]. Patient 1 showed only pseudobulbar palsy and apraxia of speech, and increased uptake of ^{18}F-THK5351 was confined to bilateral motor cortices. The patient did not show clinical or electrophysiological signs in LMN at the follow-up, 3 years after disease onset. The patient would most likely progress to bulbar-onset ALS or PLS [19] as suggested by previous reports [2–4]. In Patient 2, although LMN signs were absent clinically and even electrophysiologically at initial evaluation, mild acute denervation findings were detected on follow-up nEMG at one and a half years from disease onset. The most likely diagnosis is UMN-dominant ALS. TDP-43 proteinopathy is assumed in both ALS and PLS. Decreased striatal DAT binding may suggest the possibility of parkinsonian disorders such as atypical progressive supranuclear palsy or globular glial tauopathy that could present with clinical phenotype of MND [20, 21], although this is a pure speculation since cases presenting with progressive pseudobulbar palsy have not been reported. Autopsy and histopathological study would be required to determine the underlying pathology in both patients.

In conclusion, ^{18}F-THK5351 PET can be a useful method to detect the precise location of bilateral primary motor cortex involvement in patients presenting with progressive pseudobulbar palsy, likely by imaging astrogliosis.

Data Availability

The data set and full protocol of the present study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no conflicts of interest to declare related to this manuscript.

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