Clinical Case Report

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Degeneration of corticofugal fibers in a patient with primary progressive freezing gait

A case report

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Abstract

Rationale: To report a patient with primary progressive freezing gait (PPFG) whose degeneration of corticofugal tract (CFT) from the supplementary motor area (SMA) was demonstrated using diffusion tensor tractography (DTT).

Patient concerns: A 66-year-old woman presented with a solitary symptom of a sudden transient break on walking (i.e., freezing gait), which slowly progressed for 4 years.

Diagnoses: Imaging evidence using magnetic resonance imaging and ^{18}F-florinated-N-3-fluoropropyl-2-β-carboxymethoxy-3-β-(4-Iodophenyl) nortropane positron emission tomography scanning was unremarkable, and our patient's symptom was not affected by dopamine agonist medication. Based on the clinical symptoms and imaging findings, we diagnosed our patient as having PPFG.

Interventions: From the patient and 20 age- and sex- matched normal controls, diffusion tensor imaging data were acquired using a 1.5 T magnetic resonance scanner.

Outcomes: In DTT findings, the CFT from the left SMA was partially torn and thinned. Moreover, the fractional anisotropy value and tract volume of CFT from the left SMA were more than two standard deviations lower than those of normal controls.

Lessons: In our opinion, the lesion in the CFT from the left SMA in our patient was attributed to the occurrence of PPFG. We believe that the results of this study suggest one of the pathological mechanisms for the occurrence of gait difficulty in PPFG.

Abbreviations: ^{18}F-FP-CIT = ^{18}F-florinated-N-3-fluoropropyl-2-β-carboxymethoxy-3-β-(4-Iodophenyl) nortropane, CFT = corticofugal tract, CST = corticospinal tract, CT = computed tomographic, dPMC = dorsal premotor cortex, DTI = diffusion tensor imaging, DTT = diffusion tensor tractography, FA = fractional anisotropy, MRI = magnetic resonance imaging, PD = Parkinson disease, PET = positron emission tomography, PPFG = primary progressive freezing gait, ROI = region of interest, SMA = supplementary motor area, SPECT = single-photon emission computed tomography.

Keywords: corticofugal tract, diffusion tensor tractography, primary progressive freezing gait, supplementary motor area

1. Introduction

The freezing gait is a unique gait disorder characterized by start hesitation and sudden break in the walking motion as if the feet were "glued" or "magnetized" to the floor.[1] Characteristically, once patients break the freeze, they can walk normally or nearly normally. This abnormal gait has been observed in various disorders, such as Parkinson disease (PD), normal-pressure hydrocephalus, cortical atrophy, multiple cerebral infarctions, and progressive supranuclear palsy.[2,3] However, some patients present with a freezing gait without any clinical or laboratory evidence of possible disorders. Some clinicians have considered freezing gait of unknown cause a distinct clinical syndrome, and referred to this freezing gait as primary progressive freezing gait (PPFG).[1,2] Due to under-recognition of this syndrome, it has not been well-defined clinically or pathologically.

Thanks to the recent neuroimaging technological development, freezing gait without a cause is recognized as being associated with central neurologic changes. Magnetic resonance imaging (MRI), computed tomography (CT), and single-photon emission computed tomography (SPECT) were used to determine the cause of PPFG.[1,2,4–6] These tools are useful for evaluating the gross anatomic lesions and metabolic changes in the brain. By these modalities, pathologies such as lacunar infarct, cortical atrophy, and reduced metabolism in the medial frontal lobe were found to be associated with the occurrence of PPFG.[1,2,4–6] However, clinicians are still not able to identify the lesions in many cases of PPFG with these neuroimaging modalities. Recently developed diffusion tensor tractography (DTT), derived from diffusion tensor imaging (DTI), provides a unique advantage for 3-dimensional visualization and estimation of the neural tract of the brain. DTT was used to find the neural tract lesions in various disorders, including stroke, traumatic brain injury, motor neuron disease, and encephalitis.[7,8] We think that the pathology in neural tracts related to motor planning can result in the

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occurrence of PPFG, and evaluation of these neural tracts using DTT can be helpful for clarifying the cause of PPFG. Because the secondary motor area (dorsal premotor cortex [dPMC] and supplementary motor area [SMA]) participates in the planning of movement, we supposed that lesions in the corticofugal tracts (CFTs) originating from the dPMC or the SMA can result in the occurrence of PPFG.[8]

In the current study, we report a patient with PPFG who showed degeneration of the CFT from the SMA, using DTT.

2. Methods

2.1. Subject

A 66-year-old right-handed woman presented with a 4-year history of gait difficulty, which had slowly progressed. She complained of a solitary symptom of a sudden transient break on walking (ie, freezing gait). Particularly, it most commonly occurred when initiating gait and turning, and aggravated when there were obstacles in her way. Once the freezing was overcome, the gait became normal. The severity of freezing gait fluctuated with her physical condition or emotional state. Other than freezing gait, we could not observe other parkinsonian symptoms, such as tremor and rigidity. The motor weakness, sensory deficit, and signs of cerebellar pathology, such as ataxia, nystagmus, and balance problem, were not manifested. In addition, the patient showed no signs of cognitive deficit (Mini-Mental State Examination score: 30). Vertical and horizontal saccadic and pursuit eye movements were normal. Also, she did not show any symptoms of dysautonomia. The conventional brain and whole spine MRI, and a nerve conduction study/electromyography did not show any abnormal finding. Pramipexole and carbidopa/levodopa were administered at a dose of 0.75 and 75/750 mg, respectively, but her freezing gait was not relieved. The patient provided informed consent for participation in the study. The study was approved by the Institutional Review Board of Yeungnam University Hospital.

To rule out PD and related disorders, ^{18}F-florinated-N-3-fluoropropyl-2-β-carboxymethoxy-3-β-(4-Iodophenyl) nortropane (^{18}F-FP-CIT) positron emission tomography (PET) scanning was performed using a Biograph 40 True-Point PET/CT camera (Siemens/CTI, Knoxville, TN). ^{18}F-FP-CIT PET detects striatal dopamine transporter loss, and it has been usefully applied for the diagnosis and monitoring of PD.[9,10] No loss of dopamine transporter was detected by ^{18}F-FP-CIT PET finding in our patient (Fig. 1). Freezing gait in our patient occurred as a solitary and progressive symptom without any clinical, imaging, or electrodiagnostic evidence for other known neurological entities such as PD, PD-related disease, cerebrovascular disease, or hydrocephalus. Moreover, our patient's symptom was not affected by dopamine agonist medication. Therefore, we diagnosed our patient as having a PPFG.

2.2. Diffusion tensor tractography

From the patient and 20 age and sex-matched normal controls (20 controls: mean age 59.7 years, range 53–64 years), DTI data were acquired using a 6-channel head coil on a 1.5-T Philips Gyroscan Intera (Philips, Ltd, Best, the Netherlands) with single-shot echoplanar imaging. Imaging parameters were as follows: acquisition matrix = 96 × 96; reconstructed to matrix = 192 × 192 matrix; field of view = 240 mm × 240 mm; TR = 10,398 ms; TE = 72 ms; parallel imaging reduction factor (SENSE factor) = 2; EPI factor = 59; b = 1000 s/mm^2; NEX = 1; and a slice thickness of 2.5 mm. For analysis of the corticospinal tract (CST), fiber tracking was performed using the fiber assignment continuous tracking algorithm implemented within the DTI task card software (Philips Extended MR Work Space 2.6.). The seed region of interest (ROI) was placed on the lower pons, and the target ROI was placed on the upper pons on the color map. Termination criteria used for fiber tracking were fractional anisotropy (FA) <0.15 and angle <27°.[11] FA value and tract volume were measured within depicted CSTs. The tract volume was calculated from the number of voxels contained within the neural tract. For analysis of the CFTs from the dPMC and SMA, the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; www.fmrib.ox.ac.uk/fsl) was used. Fiber tracking was performed using a probabilistic tractography method based on a multifiber model and applied in the current study using tractography routines implemented in FMRIB Diffusion (5000 streamline samples; 0.5 mm step lengths; curvature thresholds = 0.2) The seed ROI was placed on the cerebral peduncle of the midbrain, and the target ROIs were defined as the dPMC and SMA.[6] Out of 5000 samples generated from each seed voxel, results for each contact were visualized threshold at a minimum of 2 streamlines through each voxel for analysis. Values of FA and tract volume of the CFTs were measured.

The FA value and tract volume showing a deviation of more than 2 standard deviations from normal control values were defined as significant differences.

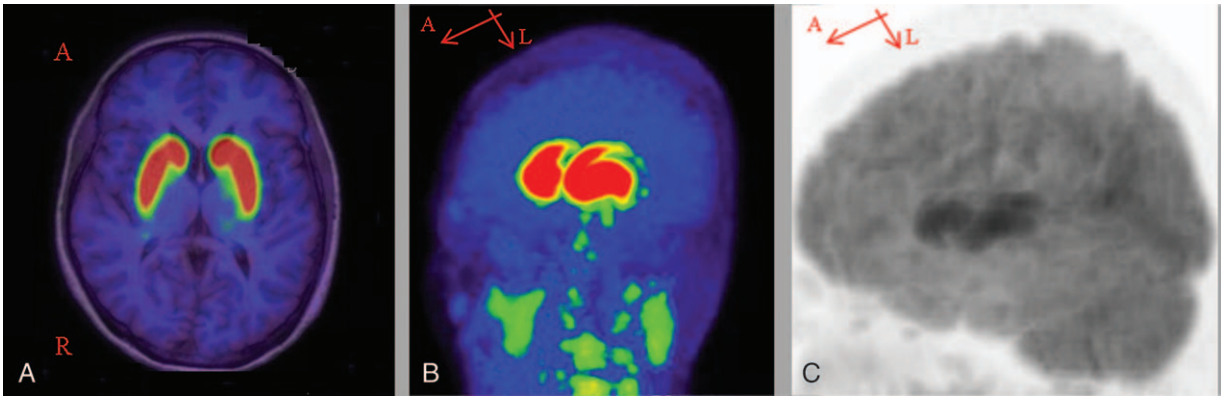

Figure 1. (A) Positron emission tomography/computed tomography; and (B) brain positron emission tomography. (C) Maximum intensity projection images of ^{18}F-florinated-N-3-fluoropropyl-2-β-carboxymethoxy-3-β-(4-Iodophenyl) nortropane demonstrating no striatal dopamine transporter loss.

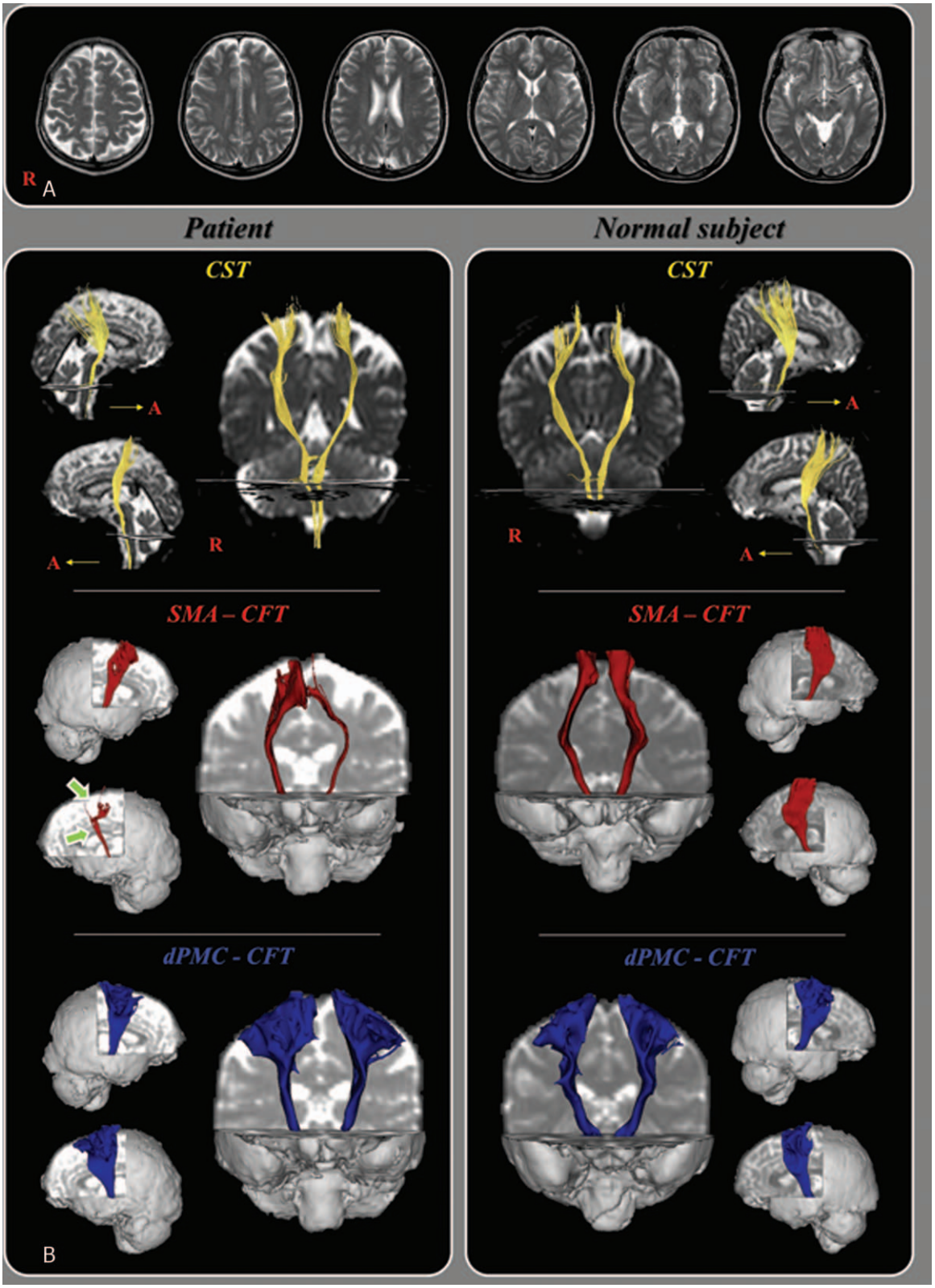

Figure 2. (A) Brain magnetic resonance (MR) images showing no abnormality. (B) Results of diffusion tensor tractography of the patient and normal subjects. The corticofugal tract from the left supplementary motor area is partially torn and thinner than those of normal controls.

3. Results

The CSTs and CFTs from the dPMC in both hemispheres and the CFT from the SMA in the right hemisphere were well preserved without any abnormality (Fig. 2). However, CFT from the left SMA was partially torn and thinned (Fig. 2). The FA value and tract volume of the CFT from the left SMA were significantly lower compared with those of normal controls (Table 1), and no

Table 1

Diffusion tensor image parameter values of the patient and controls.

		CST		CFT from the SMA		CFT from the dPMC	
		FA	Tract volume	FA	Tract volume	FA	Tract volume
Patient	Rt	0.499	1504	0.380	2317	0.289	6432
	Lt	0.517	1075	0.336*	554*	0.311	5386
Controls	Mean (SD)	0.536 (0.024)	1529.8 (278.2)	0.403 (0.030)	2784.3 (0.020)	0.352 (0.020)	4999.6 (0.020)

Control data are presented as means (±standard deviations).

CFT = corticofugal tract, CST = corticospinal tract, dPMC = dorsal premotor cortex, FA = fractional anisotropy, SD = standard deviations, SMA = supplementary motor area.

* More than 2 standard deviations of that of normal control values.

significant differences were observed in the FA value and tract volume of the CFTs from the dPMC of both hemispheres and the right SMA, and the CSTs compared with those of normal controls (Table 1).

4. Discussion

In the current study, using DTT, we tried to investigate the neural tract lesions as a cause of freezing gait in PPFG. Based on the findings of DTT in our patient, damage of the CFT from the left SMA was found. FA value and tract volume of the CFT from the left SMA were significantly decreased compared with those of normal controls. FA value represents the degree of directionality and integrity of microstructures of the white matter, such as axon, myelin, and microtubule.[12] By contrast, the tract volume is determined by counting the number of voxels contained within a neural tract; therefore, a decrease in the tract volume with or without a decrease in the FA value reflects injury of the neural tracts.[12] In our patient, decreases in the FA value and tract volume of the CFTs in both hemispheres indicated damage of those neural tracts. The pathogenic mechanism of the occurrence of PPFG has been reported to be the result of atrophy or degeneration in the brain cortex or subcortex.[1,2,4–6] Likewise, damage of the CFT from the left SMA in our patient seems to be associated with degenerative processes.

In PPFG, initiation or execution of gait movement (ie, motor planning) is inhibited. The SMA participates in the internal guidance or planning of movement, and patients with lesions in the SMA or CFT from the SMA were reported to show limb apraxia.[6] Considering the fact that apraxia is the symptom related to difficulty in the motor planning, and other names of PPFG are apraxia of gait and magnetic apraxia, we can consider that the symptom of PPFG might be related to the pathology of the SMA or CFT from the SMA. We demonstrated the degeneration of the CFT from the left SMA in our patient with PPFG. Because we could not find any abnormal clinical findings other than freezing gait and any abnormal findings on the conventional brain and spine MRIs and ^{18}F-FP-CIT PET, we attribute the lesion in the CFT from the left SMA in our patient to the occurrence of PPFG. Furthermore, given the facts that CST is the most important neural tract in motor function and our patient's CST was intact as shown by DTT, we believed that gait difficulty of our patient was induced by PPFG, and not by motor weakness. In addition, several previous studies reported that limb-kinetic apraxia was caused by injury of the CFT from SMA after stroke or traumatic brain injury.[8,13–15] Considering the fact that both limb-kinetic apraxia and PPFG are execution disorders of movements of the limbs, the findings of these previous studies support our interpretation that our patient's PPFG was induced by a lesion in the CFT originating from the SMA.

To the best of our knowledge, 5 studies have evaluated the pathology causing PPFG.[1,2,4–6] In 1993, Achiron et al[1] performed CT and MRI in 18 patients with PPFG. Eleven patients had mild cortical atrophy, and 6 patients had a lacunar infarct in the periventricular white matter. Three patients had no abnormal finding. In 2002, Factor et al[2] performed MRI in 23 patients, and found mild cortical atrophy or isolated lacunar infarction in 9 patients. One patient had an ^{18}F-labeled deoxyglucose PET scan demonstrating a marginal reduction in the medial frontal glucose metabolism. The other patients showed no specific abnormality. In 2006, Factor et al[4] followed up 9 patients with PPFG for 6 to 16 years. Out of these patients, 2 patients were diagnosed with progressive supranuclear palsy and corticobasal degeneration. Four other patients evolved into progressive supranuclear palsy and corticobasal degeneration. In 2010, Lee et al[6] reported a patient who presented with PPFG after CO intoxication. T2-weighted brain MRI showed diffuse atrophy predominantly affecting frontal lobes and high signal intensity lesions in the bilateral globus pallidus and the right putamen. In 2012, Fasano et al[5] followed up 13 patients who had freezing gait and finally diagnosed PPFG in 6 patients. Out of these patients, 5 patients had cortical and subcortical atrophy or mild lacunar infarction. Taken together, the cortical or subcortical atrophy, lacunar infarction, and reduced metabolism in the medial frontal area were found to be the cause of PPFG. This is the first study to demonstrate degeneration of neural tracts in a patient with PPFG; in our patient, the CFT from the left SMA was degenerated.

In conclusion, we describe a patient with PPFG. Using DTT, we demonstrated degeneration of the CFT from the left SMA as the cause for PPFG. We believe that the results of this study suggest a pathological mechanism for the occurrence of gait difficulty in PPFG. Furthermore, our study showed that DTT could be helpful in diagnosing PPFG. However, 2 limitations of the current study should be considered. First, this study reports a single case. Second, we did not perform a long-term follow-up, and thus cannot rule out the possibility of the development of other disorders over time. Further studies addressing these limitations are therefore necessary.

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