Clinical Case Report

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Degeneration of the corticofugal tract from the secondary motor area in a Parkinson's disease patient with limb-kinetic apraxia

A case report

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Abstract

Rationale: In this case report, we describe a Parkinson's disease (PD) patient with limb-kinetic apraxia (LKA) in whom degeneration of the corticofugal tract (CFT) from the supplementary motor area (SMA) was observed in diffusion tensor tractography (DTT).

Patient concerns: A 63-year-old woman presented with a loss of dexterity in both upper extremities, which indicated LKA, and typical PD-related symptoms, including a gait disturbance with a short step, resting tremor in both upper extremities, and rigidity, and these symptoms had been present for 2 years. The ^{18}F-florinated-*N*-3-fluoropropyl-2-β-carboxymethoxy-3-β-(4-Iodophenyl) nortropane positron emission tomography scanning findings were consistent with PD. Based on the clinical symptoms and imaging findings, we diagnosed the patient with PD. In a coin-rotation test that was used to evaluate the severity of the LKA, the patient's results significantly decreased compared to the results of the normal controls.

Diagnoses: The DTT showed that the CFTs from the SMAs in both hemispheres were partially torn and thinned. The fractional anisotropy values and CFT volumes in both SMAs were >2 standard deviations lower than those of the normal controls.

Interventions: The patient was treated with an initial dose of 150/37.5 mg/day of levodopa/benserazide, and the dose was gradually increased to 400/100 mg/day.

Outcomes: After treatment, although the bradykinesia, rigidity, and resting tremor of the patient significantly decreased, the dexterity of the patient's hands did not improve.

Lessons: These observations indicated degeneration of the CFTs from the SMAs in both hemispheres in the patient. This degeneration might have, at least in part, contributed to the patient's LKA. The results of this study suggest that CFT degeneration could be one of the pathological mechanisms underlying LKA in patients with PD.

Abbreviations: ^{18}F-FP-CIT = ^{18}F-florinated-*N*-3-fluoropropyl-2-β-carboxymethoxy-3-β-(4-Iodophenyl) nortropane, CFT = corticofugal tract, CR = coin rotation, CRP = corticoreticular pathway, CST = corticospinal tract, dPMC = dorsal premotor cortex, DTI = diffusion tensor imaging, DTT = diffusion tensor tractography, FT = finger-tapping, LKA = limb-kinetic apraxia, MRI = magnetic resonance imaging, PD = Parkinson's disease, ROI = region of interest, SMA = supplementary motor area, UPDRS = Unified Parkinson Disease Rating Scale.

Keywords: corticofugal tract, diffusion tensor tractography, limb-kinetic apraxia, Parkinson's disease, supplementary motor area

1. Introduction

Limb-kinetic apraxia (LKA), which is defined as impairments in fine motor control, frequently manifests in patients with Parkinson's disease (PD) and results in difficulties performing daily tasks.[1–3] LKA is independent of bradykinesia and rigidity in patients with PD.[1–3] Most PD-related symptoms, such as bradykinesia and rigidity, show good responses to dopaminergic treatments, but LKA is usually less responsive to dopaminergic drugs.[1–3] Although the mechanisms underlying LKA have not been precisely elucidated, LKA has been attributed to damage of the secondary motor area (dorsal premotor cortex [dPMC] and supplementary motor area [SMA]), which participates in the planning of movement, or the neural tracts that originate from this area.[4,5] In addition, cortical–basal ganglia network dysfunction has been proposed to cause LKA because the nuclei of the basal ganglia are strongly connected with the secondary motor area.[3,6]

While conventional magnetic resonance imaging (MRI) has limited utility as an investigative and diagnostic tool in patients with PD, recent advances in neuroimaging techniques have allowed for detailed assessments of PD-related pathology. In particular, diffusion tensor tractography (DTT), which is derived from diffusion tensor imaging (DTI), provides the unique advantage of the 3-dimensional visualization and estimation of neural tracts.[7–9] In the current report, we used DTT to examine the corticofugal tracts (CFTs) from the SMAs in a patient with PD who showed LKA.

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2. Case report

2.1. Patient characteristics

A 63-year-old right-handed woman visited the rehabilitation department of a university hospital for evaluation of her gait disturbance and loss of dexterity. Two years ago, the patient had begun to notice a gait disturbance and loss of fine motor function of both upper extremities. Over the last 2 years, her symptoms had gradually worsened. A physical examination showed that she was alert and oriented. The patient presented with a gait disturbance with a short step and a loss of dexterity and resting tremor in both upper extremities. We diagnosed the loss of dexterity in both upper extremities as LKA. In addition, bradykinesia and mild rigidity were observed in both upper and lower extremities. She had no motor weaknesses or sensory deficits, and she scored full 30 points on a mini-mental state examination. The ^{18}F-florinated-*N*-3-fluoropropyl-2-β-carboxymethoxy-3-β-(4-Iodophenyl) nortropane (^{18}F-FP-CIT) positron emission tomography showed decrease in dopamine transporter binding in the posterior putamen in both hemispheres (Fig. 1). Conventional brain MRI and electromyography/nerve conduction studies revealed no abnormal findings. Thus, based on the patient's physical examination and ^{18}F-FP-CIT positron emission tomography findings,[10] she was diagnosed with PD. The modified Hoehn and Yahr score[11] of the patient was 2.5, and Unified Parkinson Disease Rating Scale (UPDRS) part III score[12] was 20. The patient provided informed consent for participation in the study. The study was approved by the Institutional Review Board of a university hospital.

2.2. Clinical testing

In order to evaluate the severity of the bradykinesia and LKA, the patient and 10 right-handed age- and sex-matched normal control patients performed the finger-tapping (FT) and coin-rotation (CR) tests.[1–3] Because the FT assesses the speed of repeated movements, it is used to measure bradykinesia. The CR assesses coordinated precise finger movements, and it is therefore used to measure LKA. These 2 tests were separately performed by each hand while the subject was in a sitting position. For the FT, the patient was instructed to place her forefinger on the key of the FT device and then press it as rapidly as possible for 10 seconds while keeping her other fingers and the heel of her hand on the board. In the CR test, she was asked to rotate a nickel 360° between her forefinger, middle finger, and thumb as rapidly as possible for 10 seconds. Every 180° flip was counted as 1 rotation. The FT and CR tests consisted of 3 trials of each hand. In the FT, the patient's right and left hands performed 21.0 and 20.3 taps, respectively. In the CR test, the patient's right and left hands performed 6.3 and 6.0 rotations, respectively. In contrast, the right and left hands of the normal controls performed 30.5 ± 0.9 and 29.9 ± 0.8 taps, respectively, in the FT test and 15.1 ± 0.7 and 14.3 ± 0.5 rotations, respectively, in the CR test. All of the patient's FT and CR results were >2 standard deviations (SD) lower than the results of the normal controls.

2.3. Diffusion tensor tractography

DTI was performed on the patient and 10 age- and sex-matched normal controls (mean age: 63.3 years, range: 60–66 years) with a 1.5 T Philips Gyroscan Intera (Philips Healthcare, Amsterdam, the Netherlands) with a 6-channel head coil and single-shot echo planar imaging. The imaging parameters were as follows: acquisition matrix, 96×96; reconstructed to matrix, 192×192 matrix; field of view, 240 mm × 240 mm; repetition time, 10,398 ms; echo time, 72 ms; parallel imaging reduction factor (Sensitivity encoding factor), 2; echo planar imaging factor, 59; b, 1,000 s/mm^2; number of excitations, 1; and slice thickness, 2.5 mm. For analysis of the corticospinal tract (CST) and corticoreticular pathway (CRP), fiber tracking was performed via fiber assignment with the continuous tracking algorithm that is implemented within the DTI task card software (Extended MR WorkSpace 2.6, Philips Healthcare). For the CST analysis, 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. For the CRP analysis, the seed ROI was placed on the reticular formation of the medulla, and the target ROI was placed on the midbrain tegmentum. The termination criteria that were used for the fiber tracking were fractional anisotropy (FA) <0.15 and angle <70°. For analysis of the DTI data for the CFTs from the dPMC and SMA, the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library (www.fmrib.ox.ac.uk/fsl) was used. For the CFT, the seed ROI was placed on the cerebral peduncle of the midbrain. The target ROIs were defined as the dPMC and SMA. Of the 5000 samples that were generated from each seed voxel, the results for each contact were visualized with thresholds and weightings of the tract probabilities with a minimum of 2 streamlines through each voxel in the analysis. The FA values and tract volumes of the CSTs, CRPs, and CFTs were measured.

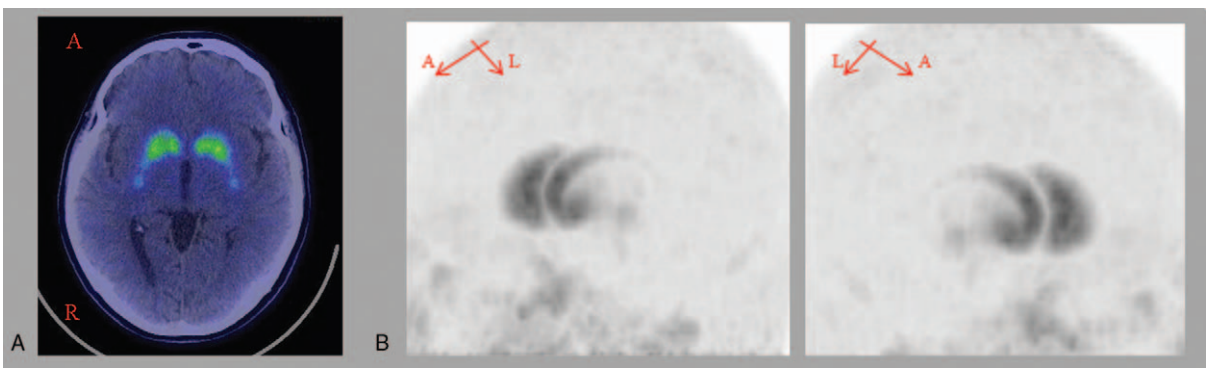

Figure 1. (A) Brain position emission tomography/computed tomography and (B) maximum intensity projection images of ^{18}F-FP-CIT demonstrating dopamine transporter loss in the posterior putamen in both hemispheres. ^{18}F-FP-CIT = ^{18}F-florinated-*N*-3-fluoropropyl-2-β-carboxymethoxy-3-β-(4-Iodophenyl) nortropane.

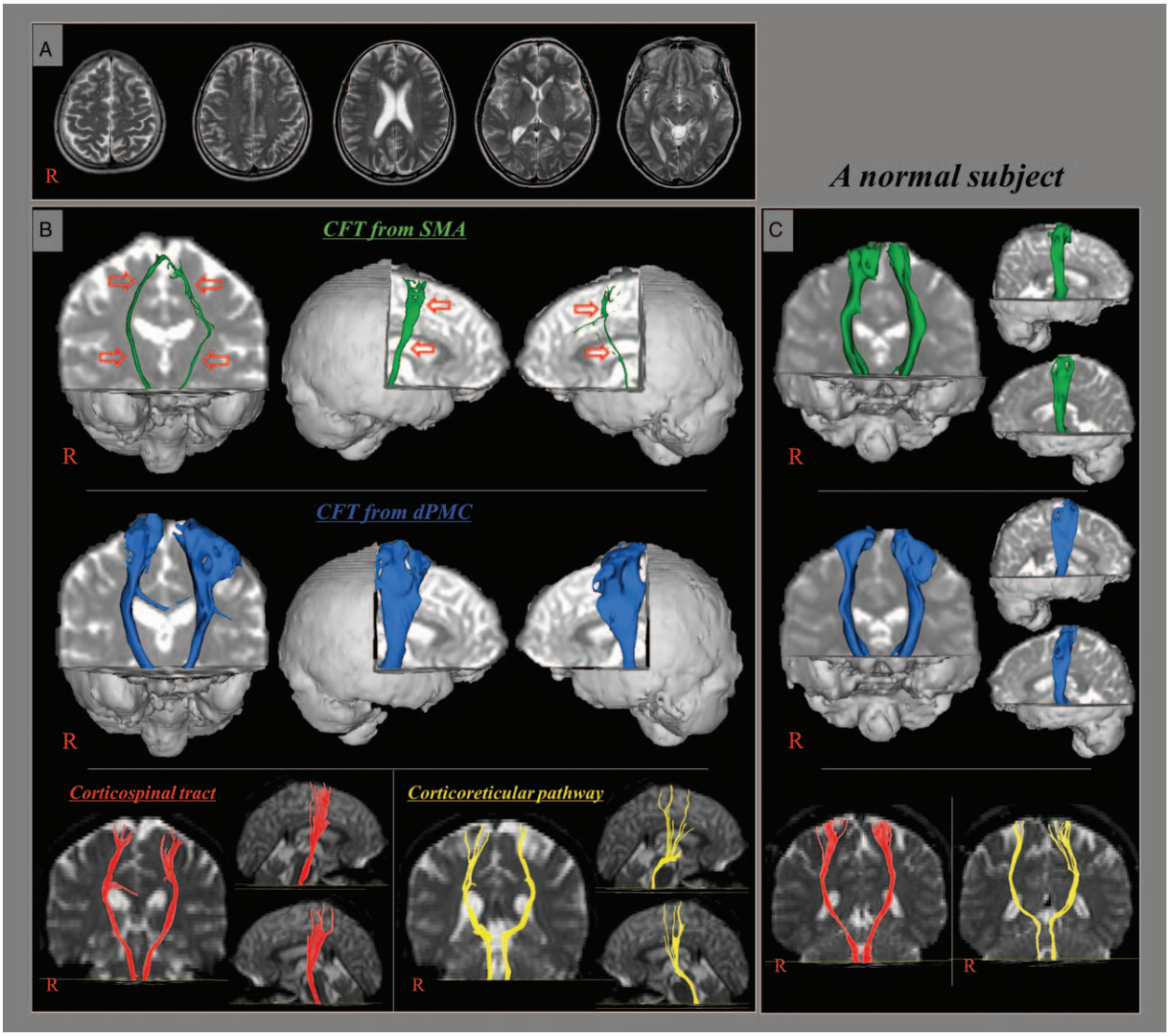

Figure 2. (A) Brain MRI of the patient showing no abnormalities. DTT images of the (B) patient and (C) a normal subject. In the patient, the CFTs from both SMAs were partially torn and thinner than the tracts in the normal control. The CFTs from thedPMC, CST, and CRP in the patient were well preserved and did not show any abnormalities. CFT = corticofugal tract, CRP = CRP = corticoreticular pathway, CST = corticospinal tract, dPMC = dorsal premotor cortex, DTT = diffusion tensor tractography, MRI = magnetic resonance imaging, SMA = supplementary motor area.

2.4. Imaging results

The CSTs, CRPs, and CFTs from the dPMCs in both hemispheres were well preserved and did not exhibit any abnormalities (Fig. 2). However, the CFTs from the SMAs in both hemispheres were partially torn and thinned (Fig. 2). The FA values and tract volumes of the CFTs from both SMAs decreased >2 SD compared to the normal control values (Table 1), while the FA values and tract volumes of the CFTs of the dPMCs, CSTs, and CRPs of both hemispheres were within the 2 SD margins of the mean FA values and tract volumes of the control subjects (Table 1).

2.5. Treatment

The patient was treated with an initial dose of 150/37.5 mg/day of levodopa/benserazide, and the dose was gradually increased to 400/100 mg/day during 1 month. After treatment, the bradykinesia and rigidity of the patient significantly decreased, and the patient's resting tremor almost disappeared. The patient's Hoehn and Yahr scores changed from 2.5 to 1, and UPDRS part III score was improved from 20 to 5.

However, the dexterity of the patient's hands did not improve. Although the FT results for the right and left hands improved from 21.0 and 20.3 to 26.0 and 25.3, respectively, the CR results did not change after treatment with the medication (Fig. 3).

3. Discussion

In the current case report, we used DTT to investigate the CFTs from the SMAs in both hemispheres of a patient with PD who presented with LKA of both upper extremities. The DTT results showed that the CFTs from both SMAs were partially torn and thinned. The FA values and tract volumes of the CFTs from both SMAs significantly decreased compared with those of normal controls. The FA values decreased due to deterioration of directional microstructures, such as axons, myelin, and microtubules.[13] The tract volumes were measured by counting the

Table 1

Diffusion tensor parameter values for the patient and controls.

		CFT from the SMA		CFT from the dPMC		CST		CRP	
		FA	Tract volume	FA	Tract volume	FA	Tract volume	FA	Tract volume
Patient	Rt	0.32*	1332*	0.41	4778	0.45	935	0.47	626
	Lt	0.31*	190*	0.42	5446	0.46	944	0.45	598
Controls mean (SD)	Rt	0.42 (0.02)	5583.1 (500.63)	0.39 (0.03)	5515.6 (589.81)	0.42 (0.03)	1001.2 (217.5)	0.45 (0.03)	752 (104.88)
	Lt	0.42 (0.03)	5275.5 (332.22)	0.43 (0.01)	5630.8 (245.64)	0.44 (0.02)	1045.0 (311,27)	0.44 (0.02)	711 (198.35)

The control data are presented as mean (± SD).

CFT = corticofugal tract, CRP = corticoreticular pathway, CST = corticospinal tract, dPMC = dorsal premotor cortex, FA = fractional anisotropy, Lt = left, Rt = right, SD = standard deviation, SMA = supplementary motor area.

* >2 SD away from the normal control values.

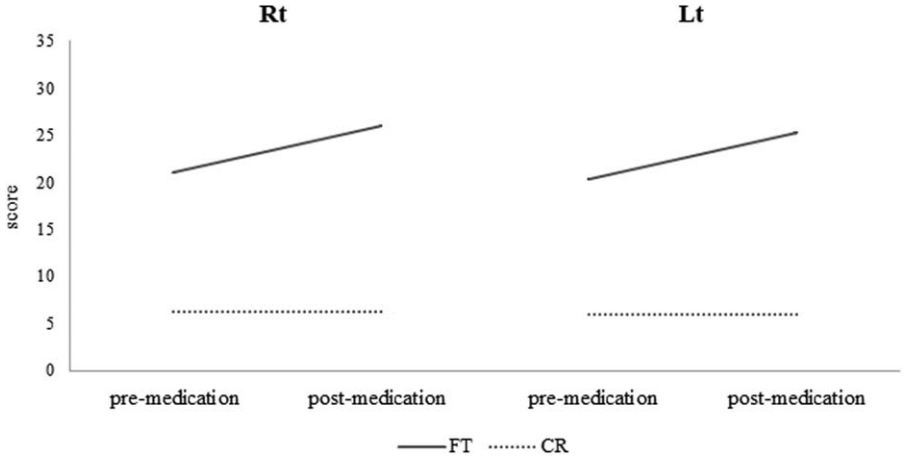

Figure 3. The results of the FT and CR tests before and after dopaminergic treatment in the patient. After treatment, the FT results improved from 21.0 and 20.3 to 26.0 and 25.3 for the right and left hands, respectively, but the CR results did not change. CR = coin rotation, FT = finger tapping.

number of voxels that were contained within a neural tract.[13] Therefore, the decreased FA values and tract numbers in both CFTs of the patient indicated damage of those neural tracts.

In PD, the primary pathological changes involve the loss of nigrostriatal dopaminergic neurons, which results in the typical symptoms of PD, including bradykinesia, rigidity, resting tremor, and gait disturbance.[14,15] In addition to the dopamine-related symptoms, nondopaminergic deficits in other brain areas have been increasingly recognized.[16,17] Several studies have demonstrated alterations in several brain areas, including the SMA, cingulum, corpus callosum, superior longitudinal fasciculus, central olfactory area, and visual pathways.[16–20] In our patient, the gait disturbance with a short step, bradykinesia, rigidity, and resting tremor were induced by dopaminergic deficits. However, the LKA-related loss of dexterity in both hands seemed to be related to nondopaminergic alterations in the brain. In addition, after being treated with a dopaminergic drug, the patient's bradykinesia significantly reduced. However, the patient's impaired dexterity was not improved. These treatment responses were in agreement with the results of previous studies that showed differential responsiveness of bradykinesia and dexterity to dopaminergic treatments in patients with PD.[1–3] These responses suggest that LKA does not result from dopamine depletion but rather from deterioration of nondopaminergic systems.

The SMA participates in internal guidance or the planning of movement, and patients with lesions in the SMA or CFT from the SMA show limb apraxia. Considering that apraxia is a symptom of motor planning difficulties, the LKA in the patient might be related to pathology of the CFT from the SMA.[5] In addition, the DTT demonstrations of the integrity of the motor-related neural tracts (CST and CRP) confirmed that the fine motor deficits in the upper extremities were not induced by motor weakness.

Several previous DTI studies that used DTI parameters, such as FA, mean diffusivity, and apparent diffusion coefficients, have demonstrated neurodegenerative changes in several areas beyond dopamine-related brain structures.[16–22] In order to examine the alterations in the SMA in patients with PD, Karagulle Kendi et al[16] performed DTI in 2008 in 12 patients with PD and found decreased FA in both SMAs. In 2014, Wei et al[23] performed resting-state functional MRI in 37 patients with PD and found that the patients had significantly decreased efficiency in their cortical–basal ganglia motor pathways, with the most pronounced changes in the right rostral SMA and left caudal SMA. However, no studies to date have reported degeneration of neural tracts in patients with PD. In the present study, we used DTT to examine motor-related neural tracts and observed degeneration of the CFTs from both SMAs.

In conclusion, we showed the degeneration of the CFTs from both SMAs in a PD patient who showed LKA of the upper extremities. These findings suggest that the patient's LKA resulted, at least in part, from degeneration of the CFTs from the SMAs, which presumably resulted in cortical–basal ganglia network dysfunction. Therefore, the results of this study suggest that one of the pathological mechanisms underlying LKA in patients with PD might be degeneration of the CFTs from the

SMA. To the best of our knowledge, this is the first study to show a relationship between injury of the neural tracts and the symptoms of PD. However, because this study only involved a single case, further studies involving a large number of patients are necessary.

References

[1] Foki T, Vanbellingen T, Lungu C, et al. Limb-kinetic apraxia affects activities of daily living in Parkinson's disease: a multi-center study. Eur J Neurol 2016;23:1301–7.

[2] Gebhardt A, Vanbellingen T, Baronti F, et al. Poor dopaminergic response of impaired dexterity in Parkinson's disease: bradykinesia or limb kinetic apraxia? Mov Disord 2008;23:1701–6.

[3] Quencer K, Okun MS, Crucian G, et al. Limb-kinetic apraxia in Parkinson disease. Neurology 2007;68:150–1.

[4] Jang SH, Chang CH, Lee HD. Limb-kinetic apraxia due to injury of the corticofugal tract from the secondary motor area in a stroke patient. Am J Phys Med Rehabil 2016;95:e115–6.

[5] Jang SH, Seo JP. Limb-kinetic apraxia due to injury of corticofugal tracts from secondary motor area in patients with corona radiata infarct. Acta Neurol Belg 2016;116:467–72.

[6] Lawrence DG, Kuypers HG. The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. Brain 1968;91:1–4.

[7] Jang SH, Chang CH, Jung YJ, et al. Hypersomnia due to injury of the ventral ascending reticular activating system following cerebellar herniation: a case report. Medicine (Baltimore) 2017;96:e5678.

[8] Jang SH, Kwon HG. Aggravation of excessive daytime sleepiness concurrent with aggravation of an injured ascending reticular activating system in a patient with mild traumatic brain injury: a case report. Medicine (Baltimore) 2017;96:e5958.

[9] Jang SH, Seo JP. Restoration of the ascending reticular activating system compressed by hematoma in a stroke patient. Medicine (Baltimore) 2017;96:e6103.

[10] Lee SJ, Oh SJ, Chi DY, et al. One-step high-radiochemical-yield synthesis of [18F]FP-CIT using a protic solvent system. Necl Med Biol 2007; 34:345–51.

[11] Goetz CG, Poewe W, Rascol O, et al. Movement disorder society task force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord 2004;19:1020–8.

[12] Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease. The unified Parkinson's disease rating scale (UPDRS): status and recommendations. Mov Disord 2003;18:738–50.

[13] Assaf Y, Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. J Mol Neurosci 2008;34: 51–61.

[14] Braak H, Del Tredici K, Rüb U, et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197–211.

[15] Hodaie M, Neimat JS, Lozano AM. The dopaminergic nigrostriatal system and Parkinson's disease: molecular events in development, disease, and cell death, and new therapeutic strategies. Neurosurgery 2007;60:17–28.

[16] Karagulle Kendi AT, Lehericy S, Luciana M, et al. Altered diffusion in the frontal lobe in Parkinson disease. AJNR Am J Neuroradiol 2008;29: 501–5.

[17] Tessitore A, Giordano A, Russo A, et al. Structural connectivity in Parkinson's disease. Parkinsonism Relat Disord 2016;22(suppl 1):S56–9.

[18] Ibarretxe-Bilbao N, Junque C, Marti MJ, et al. Olfactory impairment in Parkinson's disease and white matter abnormalities in central olfactory areas: A voxel-based diffusion tensor imaging study. Mov Disord 2010;25:1888–94.

[19] Lee JY, Yoon EJ, Lee WW, et al. Lateral geniculate atrophy in Parkinson's with visual hallucination: a trans-synaptic degeneration? Mov Disord 2006;31:547–54.

[20] Vercruysse S, Leunissen I, Vervoort G, et al. Microstructural changes in white matter associated with freezing of gait in Parkinson's disease. Mov Disord 2015;30:567–76.

[21] Blain CR, Barker GJ, Jarosz JM, et al. Measuring brain stem and cerebellar damage in parkinsonian syndromes using diffusion tensor MRI. Neurology 2006;67:2199–205.

[22] Schwarz ST, Abaei M, Gontu V, et al. Diffusion tensor imaging of nigral degeneration in Parkinson's disease: a region-of-interest and voxel-based study at 3 T and systematic review with meta-analysis. Neuroimage Clin 2013;3:481–8.

[23] Wei L, Zhang J, Long Z, et al. Reduced topological efficiency in cortical-basal Ganglia motor network of Parkinson's disease: a resting state fMRI study. PLoS One 2014;9:e108124.