

[ CASE REPORT ]

## Marked Reduction in the Striatal Dopamine Transporter Uptake During the Early Stage of Motor Symptoms in Patients with the *MAPT* N279K Mutation

Haruka Takeshige, Sachiko Nakayama, Kenya Nishioka, Yuanzhe Li,  
Yumiko Motoi and Nobutaka Hattori

### Abstract:

We herein report two patients harboring the mutation N279K in microtubule-associated protein tau (*MAPT*), who showed parkinsonism with a disease duration within three years from the onset, evaluated by dopamine transporter (DAT) [<sup>123</sup>I]N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) tropane single-photon emission computed tomography. We performed a quantification analysis, comparing five age- and severity-matched PD patients and six normal controls. The patients with the N279K mutation showed a more marked reduction in their DAT densities, especially in the caudate nucleus and anterior putamen, than the others. An early marked reduction in the DAT densities in the caudate nucleus and anterior putamen may be an early biomarker of patients with *MAPT* mutations.

**Key words:** frontotemporal dementia, frontotemporal lobar degeneration, *MAPT*, dopamine transporter scan, parkinsonism

(Intern Med 57: 3015-3019, 2018)

(DOI: 10.2169/internalmedicine.0454-17)

### Introduction

Dominantly-inherited mutations in microtubule-associated protein tau (*MAPT*) associated with frontotemporal dementia (FTD) are linked to chromosome 17 (1). The *MAPT* N279K mutation induces middle-age-onset parkinsonism with progressive cognitive decline. The onset symptoms resemble the common form of Parkinson's disease (PD). Therefore, the early diagnosis of FTD-linked *MAPT* mutations is sometimes difficult for clinicians.

In the present study, we examined [<sup>123</sup>I]N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) tropane (<sup>123</sup>I-FP-CIT) in two patients harboring the *MAPT* N279K mutation and evaluated the levels of dopamine transporter, comparing them with sporadic PD and control patients.

### Case Reports

We enrolled two patients clinically diagnosed with the be-

havioral variant FTD based on international criteria (2). Our genetic analysis confirmed the *MAPT* N279K mutation in both patients, using direct sequencing by the Sanger method, after obtaining informed and written consent from their caregiver. The procedures and sequencing analysis were previously described (3). The scores of the Unified Parkinson's Disease Rating Scale (UPDRS), the Mini-Mental State examination (MMSE), and the Frontal Assessment Battery (FAB) are shown in Table.

#### Patient 1

The patient was a 40-year-old woman. At 37 years of age, she developed postural instability and personality changes. She was initially diagnosed with PD. However, her parkinsonism was not ameliorated by levodopa/carbidopa. At 40 years of age, she developed palilalia, euphoric expression, executive dysfunction, apraxia of the eyelids, and mouth-opening, symptoms known to be related to frontal lobe dysfunction. She had rigidity of bilateral upper extremities, masked facies, small voice, bradykinesia, and limb akinesia,

**Table. Clinical Overviews of the Enrolled Patients and Normal Controls.**

	Gender	Age at examination	Disease duration	UPDRS part III	MMSE	FAB
Patient 1 (N279K)	Female	41	4	23	26/30	15/18
Patient 2 (N279K)	Male	41	1	8	30/30	16/18
Average of patients		41 (0)	2.5 (1.5)	15.5 (7.5)		
PD 1	Male	40	6	29		
PD 2	Male	41	2	4		
PD 3	Female	42	6	27		
PD 4	Female	42	2	6		
PD 5	Male	37	1	11		
Average of PD		40.4 (1.9)	3.4(2.2)	15.4 (10.6)		
NC 1	Male	42				
NC 2	Male	40				
NC 3	Male	40				
NC 4	Female	46				
NC 5	Male	43				
NC 6	Male	36				
Average of NC		41.2 (3.4)				
p value	Patients (N279K) versus PD	0.71	0.67	0.99		
	Patients (N279K) versus NC	0.95				
	PD versus NC	0.67				

NC: normal control, PD: Parkinson's disease, UPDRS: Unified Parkinson's Disease Rating Scale, MMSE: Mini-Mental State examination, FAB: Frontal Assessment Battery at bedside

predominantly on the right side. Her father also manifested parkinsonism and cognitive decline at 37 years of age and died at 44 years of age.

### Patient 2

The patient was a 43-year-old man. At 41 years of age, he developed topographic disorientation, loss of attention, and irritability. He showed akinesia and rigidity in the left limbs and masked facies with a decreased rate of blinking. His deep tendon reflexes were brisk in all limbs. His walking was unsteady. His father had developed depression, cognitive decline, and postural instability at 45 years of age before ultimately becoming bed-ridden and dying in his 50s.

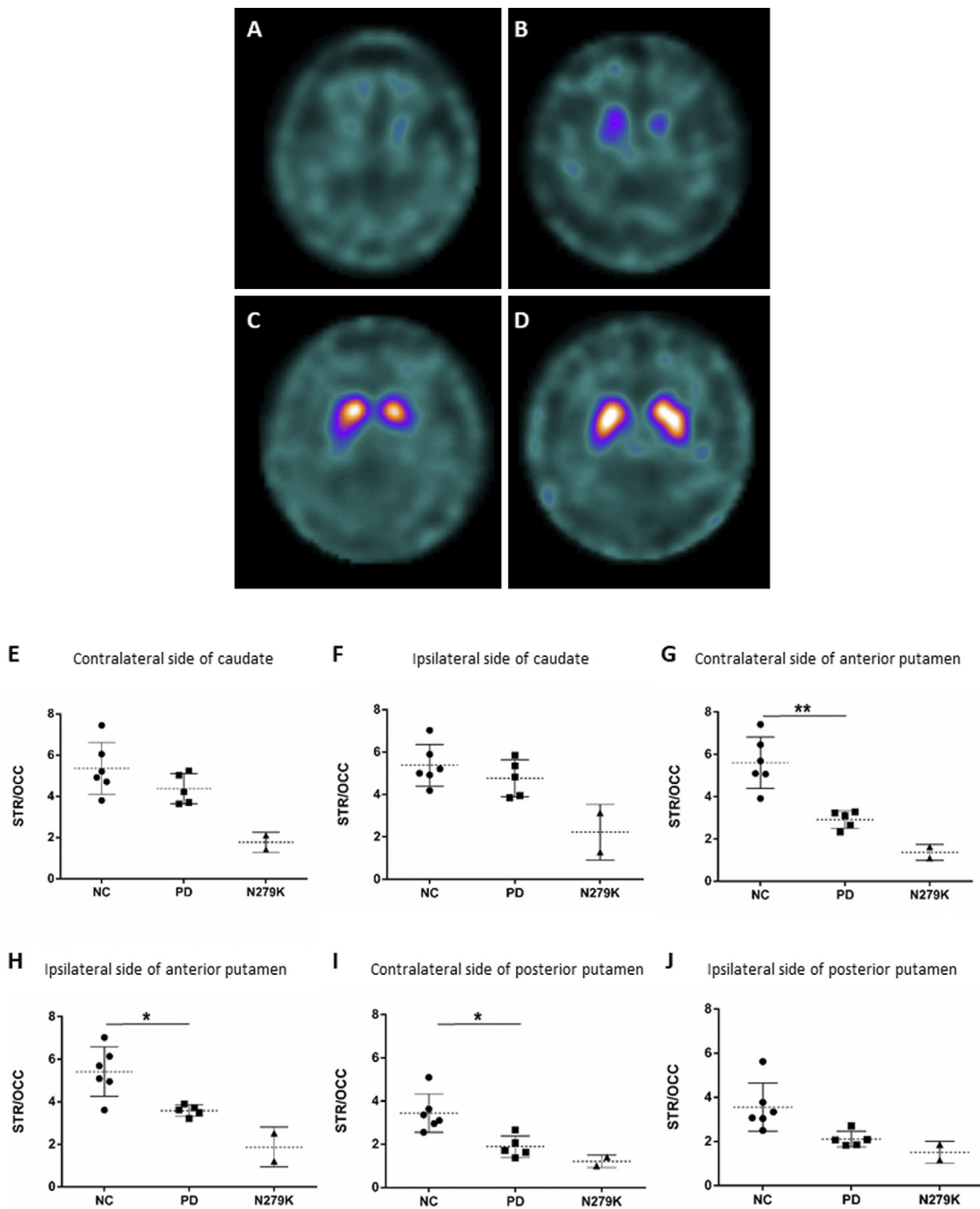
Dopamine transporter (DAT) scans of both patients revealed a marked reduction in the density of the bilateral striatum compared with patients with PD and controls (Figure A-D). With respect to the motor symptoms of PD, we noted the time when a good response to levodopa was observed, called the "ON" time. To evaluate the DAT densities, we carried out a region of interest analysis based on a method described previously (Supplementary material) (4). We first chose a regular circular region of interest on the bilateral caudate, anterior putamen, and posterior putamen of three adjacent slices with the densest DAT and calculated the average of the three slices. We also chose six regular circular areas in the occipital lobes of each of these three slices

as non-specific areas. We then calculated their ratios using the following formula:

$$^{123}\text{I-FP-CIT binding value} = \text{STR/OCC}$$

STR represents the mean radioactivity level in the caudate, anterior putamen, and posterior putamen. OCC represents the mean radioactivity level in the occipital lobes. The contralateral side was defined as the side opposite from the clinically worst affected side (arbitrarily set as the left side in the control subjects). We verified the results of PD patients and controls using a one way analysis of variance and parametric tests. We did not statistically analyze the differences between patients with N279K due to the small number of cases.

We compared the STR/OCC of patients with N279K to those of 6 age-matched controls (41.2±3.4) and 5 age-matched PD patients (40.4±2.4). In the PD group, the average score of UPDRS part III was 15.4±10.6, and the disease duration was 3.4±2.2 years (Table). Except for in the ipsilateral posterior putamen, the DAT densities of the N279K-mutated patients were markedly lower in both the putamen and caudate than in the controls (Figure E-J). Regarding the DAT densities of the N279K-mutated patients and PD patients, there marked differences were noted in the caudate and average of the striatum, but no marked differences were detected in the bilateral posterior putamen or ipsilateral caudate nucleus. In the early stages, patients with N279K



**Figure.** Dopamine transporter imaging of patients 1 and 2, and the results of the region of interest analysis of  $^{123}\text{I}$ -FP-CIT binding in the striatum. DAT-SPECT imaging findings of patient 1 (A) and patient 2 (B) are presented. Representative images are noted for age-matched Parkinson's disease (PD) patients (C) and normal controls (NCs) (D). A region of interest analysis of  $^{123}\text{I}$ -FP-CIT binding in the striatum of patients with N279K, PD patients, and NCs in the regions of the contralateral caudate (E), ipsilateral caudate (F), contralateral anterior putamen (G), ipsilateral anterior putamen (H), contralateral posterior putamen (I), and ipsilateral posterior putamen (J). The "contralateral side" was defined as the side opposite from the limbs presenting with more severe parkinsonism. The "ipsilateral side" was defined as the same side as the limbs presenting with more severe parkinsonism. The top and bottom bars indicate 95% confidence intervals. The middle bar represents the average STR/OCC value. The DAT densities of N279K group were markedly reduced compared with PD patients and NCs. \* $p < 0.05$ , \*\* $p < 0.01$ . NC: normal control, PD: Parkinson's disease, STR/OCC: radioactivity ratio striatum/occipital cerebral cortex

showed severely decreased levels of DAT densities in the caudate and posterior putamen compared to PD patients and controls. The DAT densities of the PD group were significantly decreased in the bilateral anterior putamen and contralateral posterior putamen compared with the control group, although there were no significant differences in values in the bilateral caudate nucleus.

## Discussion

In the present study, we identified differences in DAT densities between patients with N279K and PD, and the controls. Compared with patients with PD and controls, a marked decrease was noted in the DAT densities of the N279K-mutated patients in the striatum, particularly in the caudate nucleus and anterior putamen of patients with N279K. DAT scan may therefore represent an early biomarker in patients with N279K mutations. In a previous study, both FTD and PD patients commonly showed a marked reduction in DAT densities related to the severity of motor symptoms (1, 5). [<sup>18</sup>F]fluorodeoxyglucose-positron emission tomography (FDG-PET) demonstrated significant hypometabolism in the basal ganglia (putamen and globus pallidus), extensive prefrontal area, and anterior temporal region in patients with FTD (6). Another [<sup>18</sup>F]FDG-PET study indicated significant reduction of glucose metabolism in the region of the caudate nuclei and thalamus of patients with FTD in the early stages (7). After a year of follow-up, glucose hypometabolism of the basal ganglia preceded frontal cortex hypometabolism. The hypometabolism of the basal ganglia was significantly related to the cognitive function and behavioral disturbances in patients with FTD (8). The reduction in the dopamine transporter ligand [<sup>11</sup>C]-labeled 2  $\beta$ -carbomethoxy-3 $\beta$ -(4-fluorophenyl) tropane (CFT) in the caudate nucleus and putamen is also related to the clinical severity of extrapyramidal symptoms of FTD (9). This evidence suggests that severe hypometabolism in the basal ganglia precedes neurodegeneration in the frontal cortex in the early stage of FTD. We therefore emphasize the importance of performing DAT scans in patients with FTD and parkinsonism in the early stage of motor symptom manifestation.

<sup>123</sup>I-FP-CIT SPECT showed a more rapid decline in the DAT densities in the striatum of atypical parkinsonism patients than in PD patients. However, in the early stage (within 2.4 years), <sup>123</sup>I-FP-CIT SPECT showed the same rates of decrease between PD and atypical parkinsonism patients (10). The DAT densities were more severely reduced in the caudate nucleus of patients with progressive supranuclear palsy (PSP) than in patients with PD (11). Pal et al. reported a severe reduction in the fluorodopa uptake in both the putamen and caudate of patients with N279K mutations occurring within 1-2 years from the disease onset (12). The alteration of DAT densities, especially in the caudate, may be a distinctive feature for distinguishing between patients with N279K mutations and PD or PSP at the early stage. Furthermore, a DAT scan is more accessible to clinicians

than [<sup>18</sup>F]fluorodopa (FD) or L- $[\beta$ -<sup>11</sup>C]dopa PET. Further studies involving a larger sample size are required to confirm our results, as our sample size was relatively small.

PET with [<sup>18</sup>F]fluorodopa revealed a significant reduction in the striatum of symptomatic patients harboring the N279K mutation (13). Severe reductions were also observed in the striatum of asymptomatic carriers in the same family, although the level of reduction was relatively mild. Another study using L- $[\beta$ -<sup>11</sup>C]dopa PET also demonstrated dopaminergic dysfunction in the putamen of asymptomatic carriers with the N279K mutation (14). These carriers also showed mild dopamine neuronal loss in the basal ganglia. These findings suggest that the modifying effects of the N279K mutation may help estimate the degree of neuronal loss in the basal ganglia among individuals with this mutation.

In conclusion, <sup>123</sup>I-FP-CIT revealed marked neuronal loss in the basal ganglia among patients with *MAPT* N279K, even in the early stages. Further studies are needed to confirm our findings using more samples.

**The authors state that they have no Conflict of Interest (COI).**

## Financial Support

Dr. Yumiko Motoi was recognized as an Endowed Associate Professor of the Department of Diagnosis, Prevention and Treatment of Dementia, sponsored by Nippon Medi-Physics Co., Ltd. Dr. Nobutaka Hattori has received a speaker honorarium from Nippon Medi-Physics Co., Ltd. Dr. Nobutaka Hattori and Dr. Yumiko Motoi have received research grants from the same company.

## References

- Baizabal-Carvallo JF, Jankovic J. Parkinsonism, movement disorders and genetics in frontotemporal dementia. *Nat Rev Neurol* **12**: 175-185, 2016.
- Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* **134** (Pt 9): 2456-2477, 2011.
- Ogaki K, Li Y, Takanashi M, et al. Analyses of the *MAPT*, *PGRN*, and *C9orf72* mutations in Japanese patients with FTL, PSP, and CBS. *Parkinsonism Relat Disord* **19**: 15-20, 2013.
- Walker Z, Costa DC, Walker RW, et al. Differentiation of dementia with Lewy bodies from Alzheimer's disease using a dopaminergic presynaptic ligand. *J Neurol Neurosurg Psychiatry* **73**: 134-140, 2002.
- Ottaviani S, Tinazzi M, Pasquin I, et al. Comparative analysis of visual and semi-quantitative assessment of striatal [<sup>123</sup>I]FP-CIT-SPET binding in Parkinson's disease. *Neurol Sci* **27**: 397-401, 2006.
- Jeong Y, Cho SS, Park JM, et al. <sup>18</sup>F-FDG PET findings in frontotemporal dementia: an SPM analysis of 29 patients. *J Nucl Med* **46**: 233-239, 2005.
- Diehl-Schmid J, Grimmer T, Drzezga A, et al. Decline of cerebral glucose metabolism in frontotemporal dementia: a longitudinal <sup>18</sup>F-FDG-PET-study. *Neurobiol Aging* **28**: 42-50, 2007.
- Garibotto V, Borroni B, Agosti C, et al. Subcortical and deep cortical atrophy in Frontotemporal Lobar Degeneration. *Neurobiol Aging* **32**: 875-884, 2011.
- Rinne JO, Laine M, Kaasinen V, Norvasuo-Heila MK, Nagren K, Helenius H. Striatal dopamine transporter and extrapyramidal

- symptoms in frontotemporal dementia. *Neurology* **58**: 1489-1493, 2002.
- 10.** Pirker W, Djamshidian S, Asenbaum S, et al. Progression of dopaminergic degeneration in Parkinson's disease and atypical parkinsonism: a longitudinal beta-CIT SPECT study. *Mov Disord* **17**: 45-53, 2002.
- 11.** Whitwell JL, Hoglinger GU, Antonini A, et al. Radiological biomarkers for diagnosis in PSP: where are we and where do we need to be? *Mov Disord* **32**: 955-971, 2017.
- 12.** Pal PK, Wszolek ZK, Uitti R, et al. Positron emission tomography of dopamine pathways in familial Parkinsonian syndromes. *Parkinsonism Relat Disord* **8**: 51-56, 2001.
- 13.** Kishore A, Wszolek ZK, Snow BJ, et al. Presynaptic nigrostriatal function in genetically tested asymptomatic relatives from the pallido-ponto-nigral degeneration family. *Neurology* **47**: 1588-1590, 1996.
- 14.** Miyoshi M, Shinotoh H, Wszolek ZK, et al. In vivo detection of neuropathologic changes in presymptomatic MAPT mutation carriers: a PET and MRI study. *Parkinsonism Relat Disord* **16**: 404-408, 2010.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).