*Neurology Asia 2015; 20(1) : 23 – 27*

# Parkinsonism in corticobasal syndrome may not be primarily due to presynaptic dopaminergic deficiency

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### *Abstract*

The clinical features of corticobasal degeneration (CBD) are quite asymmetric. The severity of clinical symptoms and dopamine transporter (DAT) bindings were less correlated compared to other parkinsonisms, suggesting that presynaptic nigrostriatal dopaminergic dysfunction may not explain extrapyramidal manifestations in CBD. Therefore we wanted to reexamine asymmetry and severity between DAT imaging and clinical findings. We studied patients meeting the diagnostic criteria for CBD based on clinical features. We collected their clinical information and imaging retrospectively. Seven patients were enrolled and all had asymmetric rigidity, bradykinesia and unilateral limb dystonia. These symptoms did not improve with levodopa. All patients showed symptoms bilaterally in the last visit, but asymmetry of clinical symptoms was remarkable at the time of DAT imaging. The DAT bindings were decreased in six subjects. However, one patient showed normal DAT binding. Four patients had a more evident DAT reduction on the side contralateral to the more clinically affected side, however, two patients had a more prominent reduction on the ipsilateral side. The symptoms that we regard as parkinsonian features in CBD are not only explained by presynaptic dopaminergic dysfunction. Our findings suggest that postsynaptic dopaminergic or nondopaminergic systems may play a major role in parkinsonian symptoms in corticobasal syndrome.

## INTRODUCTION

Corticobasal degeneration (CBD) is a progressive neurodegenerative disease that presents with asymmetrical cortical and extrapyramidal manifestations.[1,2] Previous studies have reported diagnostic difficulties in CBD.[3-5] Therefore, 'corticobasal syndrome (CBS)' was suggested as a clinical diagnosis without pathologic evidence.[6,7]

Extrapyramidal symptoms (EPS) may be the dominant findings in CBS. In the EPS of CBS, rigidity and bradykinesia are prominent and they are usually refractory to levodopa. Neuronal cell loss of the substantia nigra pars compacta (SNc) is a pathological finding necessary for a definitive diagnosis of CBD.[6,8]

Reduction of dopamine transporter (DAT) binding is sensitive to the neuronal loss in the SNc.[9] Presynaptic dopaminergic dysfunction was suggested to play a role in akinetic rigidity in CBD. In most previous studies, the DAT bindings were decreased distinctively in CBD.[10-12] A previous report showed that presynaptic DAT bindings were reduced in CBD patients while postsynaptic $D_2$ receptor binding was reduced in only one of eight

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patients.[13] Although the DAT binding uptake is not as marked as the clinical asymmetry, laterality of bradykinesia and rigidity were correlated with DAT bindings in parkinsonism.[14,15]

In CBD cases, however, the severity of clinical symptoms and DAT bindings were less correlated compared to other parkinsonisms.[13,16,17] Therefore, given the differences mentioned above and that there is no benefit from levodopa, presynaptic nigrostriatal dopaminergic dysfunction may not primarily explain the EPS in CBS. To investigate the congruity between the DAT binding and symptoms in CBS, we reexamined the DAT images and clinical features of our CBS patients.

## METHODS

### *Patients*

Patients included in this study met the diagnostic criteria for CBD based on clinical features.[1] We collected their clinical information and imaging data retrospectively. All subjects were registered at the Movement Disorder Clinic, Seoul National University Hospital (SNUH). From our database, all the CBD patients with DAT image were included in this study. Written informed consent to participate in the study was obtained from each patient. The institutional review board of SNUH approved the use of the protocol for this study.

### *Dopamine transporter (DAT) imaging*

DAT imaging was performed for all patients with either $^{99m}$Tc-2β[N, N'-bis(2-mercaptoethyl) ethylenediamino] methyl, 3β-(4-chlorophenyl) tropane single-photon emission computed tomography[18] ($^{99m}$Tc-TRODAT-1 SPECT) or N-(3-$^{18}$F-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane positron emission tomography ($^{18}$F-FP-CIT PET). The patients did not take any medication that could have influenced the test, such as antidepressants[19] and central nervous system stimulants.[20]

## RESULTS

We enrolled 7 patients (5 men and 2 women) and reviewed their clinical findings. Their age at onset ranged from 59 to 74 years (mean, 68.7 ± 6.2 years). No patient had a family history of CBS or other parkinsonian disorders. Disease duration ranged from 1.5 to 10 years (mean, 4.1 ± 2.9 years). $^{99m}$Tc-TRODAT-1 SPECT was done in five patients (n = 5, Patient 1, 2, 3, 4 and 5), and $^{18}$F-FP-CIT PET was done in two patients (n = 2, Patient 6 and 7).

All patients had asymmetric rigidity, bradykinesia and unilateral limb dystonia, and they had a dominant side for these symptoms. These asymmetric extrapyramidal features were refractory to levodopa therapy. Four of the patients had cortical sensory impairment, and two patients showed cortical reflex myoclonus. Four patients had alien limb syndrome, and three had limb apraxia. Five patients showed nonfluent aphasia. We reviewed their brain magnetic resonance imaging (MRI). Cortical atrophy was evident in three patients contralateral to the more affected side (Patient 3, 5 and 6). The clinical findings of the subjects are summarized in Table 1. All patients showed symptoms bilaterally at their last visit, but the asymmetry of the clinical symptoms was prominent at the time of the DAT image.

The striatal DAT bindings were decreased in all the patients except for Patient 7 (Figure 1). Patients 3–6 (4 of the 7 patients, 57.1%) had a more evident DAT reduction on the side contralateral to the more clinically affected side. In contrast, Patient 1 and 2 had a more prominent reduction on the ipsilateral side of the more affected limbs. Patient 7 showed no reduction in DAT bindings. Thus, in 3 of the 7 patients (42.9%), dopaminergic presynaptic binding was not congruous in laterality with their extrapyramidal symptoms. Moreover, these three patients did not have definite cortical atrophy.

## DISCUSSION

CBD has characteristic neuropathological findings and affects the nigrostriatal system and the subcortical and cortical structures heterogeneously. In CBD, pathologic findings are always found in the substantia nigra.[21] DAT binding has a good correlation with clinical parkinsonian symptoms caused by SNc pathology.[22]

Substantia nigra neuronal loss is a core pathologic feature of CBD, and DAT images may reflect the pathologic finding in SNc. Six patients showed bilateral reduction in DAT bindings and these findings suggest that they had bilateral SNc pathology. In two of the seven patients, however, dopaminergic presynaptic binding was decreased more on the side that was more prominently affected clinically. In patient 7, the DAT image was normal even when the patient had definite extrapyramidal symptoms. These mismatches in laterality with clinical symptoms might reflect that their akinetic rigidity may not only be caused by the neuronal loss of the SNc but also by extra-nigral pathology.

**Table 1: Clinical data of the patients with corticobasal syndrome**

| Case no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Age(yr)/Sex | 71/M | 77/M | 65/F | 60/F | 71/M | 63/M | 74/M |
| Disease duration (yrs) | 5 | 10 | 3 | 2 | 1.5 | 3 | 4 |
| Initial symptom | Weakness on right leg | Dysarthria | Dystonia on left hand | Pain on left side | Paresthesia and weakness on left arm | Weakness on left hand | Weakness on left hand |
| Clinical asymmetry* | Yes (R) | Yes (R) | Yes (L) | Yes (L) | Yes (L) | Yes (L) | Yes (L) |
| Response to L-dopa | No | Poor | No | Poor | No | No | Poor |
| Asymmetric bradykinetic | + | + | + | + | + | + | + |
| Limb dystonia | + | + | + | + | + | + | + |
| Reflex myoclonus | - | - | + | Nd | - | + | + |
| Alien limb | - | - | + | + | + | + | - |
| Paresthesia or pain/sensory extinction | -/- | -/- | +/+ | +/Nd | +/- | +/- | - |
| Cognitive impairment/apraxia | +/- | +/+ | +/- | -/ | +/+ | +/+ | - |
| Falls | + | + | - | + | + | - | + |
| DAT image | ↓, Ipsilateral | ↓, Ipsilateral | ↓, Contralateral | ↓, Contralateral | ↓, Contralateral | ↓, Contralateral | Normal |

* Clinically more affected side.

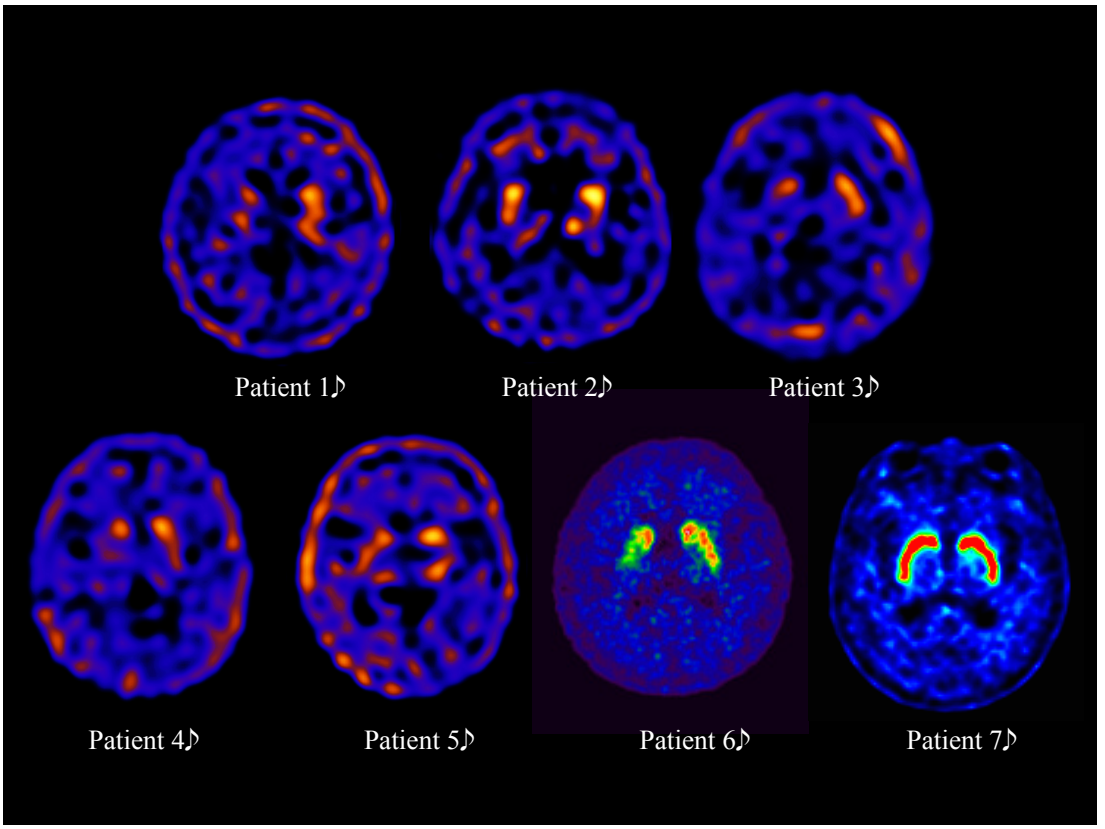


Figure 1. DAT images of the patients.
$^{99m}$Tc-TRODAT-1 SPECT was done in five patients (Patient 1, 2, 3, 4 and 5), and $^{18}$F-FP-CIT PET was done in two patients (Patient 6 and 7). Dopaminergic presynaptic binding was reduced bilaterally in Patients 1–6, but not in Patient 7. In Patient 1 and 2, the DAT bindings were decreased more on the right side, ipsilateral to the clinically more affected side. Patients 3–6 showed a greater DAT reduction contralateral to the clinically more affected side.

A previous study by Ceravolo *et al*. investigated 6 patients with CBS, and their DAT bindings were preserved at baseline, although they had asymmetric akinetic rigidity.[17] Their DAT bindings were decreased at the follow-up scan performed 10-15 months later after the baseline scan, and these findings support that the parkinsonism-like symptoms in some CBS patients might be caused by extra-nigral pathology including postsynaptic or cortical pathology. The heterogeneous correlation between CBD nigral pathology and clinical features was also reported in other large cohort studies on CBS.[23]

The limitation of this study was that the cases were pathologically unproven. And we enrolled the patients lacking clinical improvements with levodopa. Although this finding is observed in most patients with CBS, it might act as a factor causing selection bias.

However, these findings may reflect that the parkinsonian features in CBS may not be primarily explained by presynaptic dopaminergic dysfunction. Postsynaptic dopaminergic or nondopaminergic systems could have a role in parkinsonism-like symptoms in CBS.

## ACKNOWLEDGEMENTS

This study was supported by a grant of the Korea Health technology R&D Project, Ministry of Health & Welfare, Republic of Korea. (A101273, B.S.J. and HI09C14440100, S.E.K.). The study sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.
We thank Jin-Kyoung Kim for technical assistance.

## DISCLOSURE

### *Financial Disclosures of all Authors for the Past Year*

BSJ has received funding for travel from Korea Research-Based Pharmaceutical Industry Association, Korean Pharmaceutical Manufacturers Association and has received research support as PI from Ipsen, Norvartis, Boehringer Ingelheim, the Korea Health 21 R&D project, Ministry of Health & Welfare, Republic of Korea, the National Research Foundation of Korea(NRF), Ministry of Education, Science and Technology, ABRC (Advanced Biometric Research Center), KOSEF (Korean Science and Engineering Foundation), Seoul National University Hospital, the Mr. Chung Suk-Gyoo and Sinyang Cultural Foundation, and the Song Foundation. Other authors have no financial disclosures.

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