A Pilot Study of F-18 FP-CIT PET Imaging in Early-onset Patients with Parkinson’s Disease: Parkin versus Non-parkin Mutation

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ABSTRACT

Striatal dopaminergic dysfunction in early-onset Parkinson's disease (PD) remains to be further elucidated. Thus, as a preliminary study, we aimed to investigate detailed patterns of dopaminergic depletion in five early-onset PD patients with dynamic N-(3-[(18)F]fluoropropyl)-2-carbomethoxy-3-(4-iodophenyl) nortropane (FP-CIT) positron emission tomography (PET) scans. Two patients with parkin mutation showed more symmetric decrease of dopamine transporter (DAT) density in the putamen, whereas others displayed asymmetric reduction of DAT density in the putamen. Notably, only those with parkin mutation revealed more severe dopaminergic deficits in the anteroventral putamen rather than the posterodorsal putamen. Our observation suggests, among PD patients, patients with parkin mutation may exhibit the different pattern of striatal dopaminergic depletion.

Key Words: Parkinson's Disease, Early-Onset, Dopamine Depletion, Parkin Mutation

Introduction

The pathologic hallmark of Parkinson's disease (PD) is nigrostriatal dopaminergic degeneration, thereby resulting in cardinal motor symptoms such as tremor, rigidity, and bradykinesia. In vivo study of the striatonigral dopaminergic system provides helpful information, including the differential diagnosis of parkinsonism, in clinical as well as scientific fields (Cummings et al., 2011; Brooks and Piccini 2006; Thobois, Guillouet and Broussolle 2001). Among several means of studying the dopaminergic deficits, the dopamine transporter (DAT) imaging has shown very high sensitivity (up to 98%) and specificity (up to 100%) for the diagnosis of PD (Wang et al., 2013; Madras et al., 1998; Jennings et al., 2004). However, a majority of research using the DAT scans for striatal dopaminergic integrity was focused on elderly or late-onset PD patients (Cummings et al., 2011; Hauser and Grosset 2012). Moreover, most DAT studies were conducted using single-photon emission computed tomography (SPECT) with relatively lower resolution (Varrone et al., 2004; Hauser and Grosset 2012). Accordingly positron emission tomography (PET) imaging with high resolution in early-onset PD remains little known. Therefore, this study was aimed to perform the detailed analysis of the striatal DAT density in patients with early-onset PD using N-(3-[(18)F]fluoropropyl)-2-carbomethoxy-3-(4-iodophenyl) nortropane (FP-CIT) PET scans.

Methods

Subjects

We reviewed clinical data of all early-onset PD
patients with $[^{18}\text{F}]$ FP-CIT PET in our hospital. Clinical diagnosis of PD was made by one movement disorder specialist (S-B.K.) at Parkinson’s disease center in the hospital according to the UK Brain Bank criteria (Hughes et al., 1992). Early-onset PD was defined as the onset age of parkinsonian motor symptom was below 45 years old. We excluded if the patient with PD revealed stroke, head trauma, or other structural brain lesions. Patients were assessed through the review of medical records of the Unified Parkinson’s Disease Rating Scale (UPDRS) part 3 (motor function) and Hoehn and Yahr (HY) stage in off state for anti-parkinsonian medication. Asymmetry of motor symptoms was also determined according to the original medical record from each patient.

$[^{18}\text{F}]$ FP-CIT PET and imaging analysis
To evaluate the pattern of nigrostriatal DAT density in early-onset PD, PET scan was performed and acquired 90 min after intravenous injection of $[^{18}\text{F}]$ FP-CIT with 185 MBq. After brain CT scanning was undergone in spiral mode (50mAs; 120 kVp; 2 mm slice thickness), PET data were acquired in 3-dimensional mode. CT data were used for attenuation correction. The PET images were reconstructed according to an ordered subsets expectation maximization algorithm incorporating TOF information (TOF- OSEM) with $128 \times 128$ matrix with a pixel size of 2mm.

Blinded to the clinical diagnosis of each patient, one movement disorder specialist (K-Y.K.) performed a visual analysis for PET/CT scans. After that, the other movement disorder specialist (S-B.K.) also reviewed the PET images, and discussed with the first investigator (K-Y.K.) for the conclusion of detailed remarkable findings on the PET scans of all subjects. Final conclusions for the specific pattern of striatal dopaminergic depletion in each patient were derived from the consensus of two investigators. For control analysis of DAT density in the striatum, we selected $[^{18}\text{F}]$ FP-CIT PET scans of a patient diagnosed with classic essential tremor (ET), because the nigrostriatal dopaminergic system in patients with ET has been known to be unaffected (Cummings et al. 2011). The current study was approved by the Institutional Review Board of the Korea University Guro Hospital.

Results

Clinical details in patients with early-onset Parkinson’s disease
Among all 98 patients performing $[^{18}\text{F}]$ FP-CIT PET scans in Korea University Guro Hospital, only 5 patients were diagnosed and compatible with early-onset PD. The detailed clinical characteristics were described in Table 1. Age at onset of motor symptom was distributed from 21 to 45 years. All patients presented hand tremor as the chief complaint. Three patients showed symmetric parkinsonian feature, whereas two patients exhibited asymmetric parkinsonism. Results of genetic analysis for parkin mutation were also examined in the current study. Parkin gene mutation was documented in two patients: patient B displayed c.719C>G (p.Thr240Arg) and exon 3 deletion, and patient C exhibited compound heterozygous deletion of exons 2-3 and 3-4. Patient D and E revealed a negative study for parkin mutation. Patient F did not undergo the genetic test.

$[^{18}\text{F}]$ FP-CIT PET in patients with early-onset Parkinson’s disease
Compared to a control subject (Fig. 1A), all patients with early-onset PD revealed significant losses of DAT density in the putamen. Both patient B (Fig. 1B) and patient C (Fig. 1C) showed more symmetric decrease of DAT density in the putamen compared to caudate nucleus. Intriguingly, the DAT density of both patient B and C was more severely reduced in the anteroventral putamen in the comparison with the posterodorsal putamen. Patient D (Fig. 1D) exhibited asymmetric reduction of DAT density in the putamen: the posterodorsal loss of DAT density in left side of putamen is more dominant compared to that of right side. Patient E (Fig. 1E) displayed relatively symmetric decrease of DAT density especially in posterodorsal part of the putamen. Patient F (Fig. 1F) revealed asymmetric reduction of DAT density in the posterodorsal putamen with more severe loss in right than left side.

Discussion
This is the first report for $[^{18}\text{F}]$ FP-CIT PET study in early-onset PD. The DAT scans with FP-CIT uptake reflecting presynaptic dopaminergic neurodegeneration could reveal a significant reduction of striatal dopamine in early as well as advanced PD (Booij et al., 1997).
Figure 1. [18F] FP-CIT PET findings in early-onset patients with Parkinson’s disease; (A) a control subject, (B) patient with parkin mutation of c.719C>G (p.Thr240Arg) and exon 3 deletion, (C) patient with parkin mutation of compound heterozygous deletion of exons 2-3 and 3-4, (D) patient without parkin mutation, (E) patient without parkin mutation, and (F) patient who did not performed genetic analysis for parkin mutation. Arrow indicates dopaminergic depletion in anteroverentral putamen, whereas arrow head represents dopaminergic reduction in posterodorsal putamen.

Table 1. Clinical details in patients with early-onset Parkinson’s disease

<table>
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<tr>
<th>Case</th>
<th>H</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
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<td>12</td>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
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</tr>
</tbody>
</table>

Since dopaminergic deficits lead to compensatory processing of down-regulation of DAT in the early stage of the disease, the DAT imaging could overestimate the striatal dopaminergic depletion, implying that the DAT scans might be useful even in the prodromal stage of PD (Wang et al., 2013). We found [18F] FP-CIT PET scans of early-onset PD exhibited significant dopaminergic deficits in the putamen. Our observation is in line with the previous studies for dopaminergic depletion in early-onset PD (Varrone et al., 2004; Scherfler et al., 2004; Ribeiro et al., 2009; Thobois et al., 2003; Hu et al., 2006). Most previous studies showed the mean disease duration of PD patients was about 10 years or more, whereas disease duration of our patients was less than 2 years. Moreover, we used PET scan, which is known to have higher resolution, rather than SPECT conducted by others. Taken together, our data suggest [18F] FP-CIT PET could be useful in the early stage of early-onset PD.

Until now, imaging of dopaminergic depletion in patients with parkin mutation has shown more symmetric and severe deficits when compared with non-parkin patients (Varrone et al., 2004; Thobois et al., 2003; Broussolle et al.,...
2000; Portman et al., 2001). Furthermore, the existing concept for the pattern of dopaminergic deficits among various variable PD patients, including those with parkin mutation, has shown a similar pattern with more prominent decrease in the posterior putamen (Varrone et al., 2004, Hauser and Grosset 2012; Scherfler et al., 2004). However, we noticed a remarkable finding of dopaminergic depletion in two patients with parkin mutation, revealing the more prominent dopaminergic deficits in anteroven tral part rather than posterodorsal part of the putamen. This discrepancy cannot be clearly explained. One important difference is relatively short disease duration in the current study, as described previously. Therefore, we suppose that our findings may reflect alteration of striatal dopaminergic dysfunction in the early stage of parkin mutation. Besides, the clinical significance of more severe loss of DAT density in the anteroven tral putamen remains unknown. One possibility is that such pattern could be associated with more occurrence of levodopa-induced dyskinesia (Khan et al., 2003; Lucking et al., 2000). Collectively, the detailed and careful examination of dopaminergic depletion not only in parkin mutation, but also in other genetic parkinsonism including PINK1 mutation, which is highly related to parkin gene in the PINK1-Parkin pathway (Kane and Youle 2011), is required for the pathophysiologic analysis.

In the view of symmetry in FP-CIT uptake, two specific patterns of dopaminergic depletion were observed in early-onset PD. Three patients (Patient B, C, and E) displayed symmetric decrease of striatal dopamine, whereas other two patients (Patient D and F) exhibited asymmetric reduction of striatal dopamine. The clinical or pathologic implications for such patterns of early-onset PD remains uncertain. Intriguingly, two patients with parkin mutation (patient B and C) revealed symmetric decrease of dopaminergic deficits. Although Ribeiro et al. described PET findings of dopaminergic dysfunction were similar between parkin patients and non-parkin patients (Ribeiro et al., 2009), our observation indicates early-onset patients with parkin mutation could show some different pattern compared to those without parkin mutation. In addition, we found that asymmetry of in vivo dopaminergic reduction was in accordance with clinical asymmetry. Patient D, showing dominant parkinsonism in right side, exhibited more loss of DAT density in the left putamen (Fig. 1D). Patient F, presenting pronounced parkinsonism in left limb, revealed more decrease of DAT density in the right putamen (Fig. 1F). All other patients displayed symmetric parkinsonism as well as symmetric reduction of DAT density. Thus, our results support the established view of ipsilateral striatal dopaminergic dysfunction is responsible for contralateral parkinsonian motor symptom (Seibyl et al., 1995).

This study has several short comings. Firstly, our results were derived from a retrospective and preliminary study with small sample size. Thus, our observations could not be generalized. Secondly, the investigation of [18F] FP-CIT PET was performed only through a visual inspection. Thereby, no quantitative data was obtained, resulting in the weak point in terms of the objectivity of evaluation. Thirdly, careful and detailed investigation of caudate nucleus was not assessed because of the limitation of visual analysis.

In summary, we evaluated striatal dopaminergic deficits in early-onset PD patients. Notably, we observed a distinct pattern of dopaminergic depletion in parkin positive patients exhibiting more loss in anteroven tral putamen. In addition, we found that the pattern of striatal dopaminergic depletion in early-onset PD could be symmetric or asymmetric. These findings of [18F] FP-CIT PET will deepen a clinicopathologic understanding of early-onset PD patients including parkin positive patients. The large-scaled and well-designed studies are required to confirm our findings.

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Conflicts of interest/financial disclosures
Nothing to report.

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