Differential Diagnosis of Parkinsonism Using Dual-Phase F-18 FP-CIT PET Imaging

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Abstract

Purpose Dopamine transporter (DAT) imaging can demonstrate presynaptic dopaminergic neuronal loss in Parkinson's disease (PD). However, differentiating atypical parkinsonism (APD) from PD is often difficult. We investigated the usefulness of dual-phase F-18 FP-CIT positron emission tomography (PET) imaging in the differential diagnosis of parkinsonism.

Methods Ninety-eight subjects [five normal, seven drug-induced parkinsonism (DIP), five essential tremor (ET), 24 PD, 20 multiple system atrophy-parkinson type (MSA-P), 13 multiple system atrophy-cerebellar type (MSA-C), 13 progressive supranuclear palsy (PSP), and 11 dementia with Lewy bodies (DLB)] underwent F-18 FP-CIT PET. PET images were acquired at 5 min (early phase) and 3 h (late phase) after F-18 FP-CIT administration (185 MBq). Regional uptake pattern of cerebral and cerebellar hemispheres was assessed on early phase images and striatal DAT binding pattern was assessed on late phase images, using visual, quantitative, and statistical parametric mapping (SPM) analyses.

Results Striatal DAT binding was normal in normal, ET, DIP, and MSA-C groups, but abnormal in PD, MSA-P, PSP, and DLB groups. No difference was found in regional uptake on early phase images among normal DAT binding groups, except in the MSA-C group. Abnormal DAT binding groups showed different regional uptake pattern on early

phase images compared with PD in SPM analysis ($FDR < 0.05$). When discriminating APD from PD, visual interpretation of the early phase image showed high diagnostic sensitivity and specificity (75.4 % and 100 %, respectively). Regarding the ability to distinguish specific APD, sensitivities were 81 % for MSA-P, 77 % for MSA-C, 23 % for PSP, and 54.5 % for DLB.

Conclusions Dual-phase F-18 FP-CIT PET imaging is useful in demonstrating striatal DAT loss in neurodegenerative parkinsonism, and also in differentiating APD, particularly MSA, from PD.

Keywords Atypical parkinsonism · Dual-phase · F-18 FP-CIT · Positron emission tomography · PET

Introduction

Parkinsonism is a neurological syndrome characterized by tremor, bradykinesia, rigidity, and postural instability [1]. The underlying causes of parkinsonism are numerous. Idiopathic Parkinson's disease (IPD) is the most prevalent cause [2]; however, approximately one-third of patients with parkinsonian symptoms have another disease, particularly atypical parkinsonism (APD), such as multiple-system atrophy (MSA), progressive supranuclear palsy (PSP), and dementia with Lewy bodies (DLB) [3]. There are several clinical clues that suggest APD [4, 5]. However, the differential diagnosis of parkinsonism continues to be challenging with a high misdiagnosis rate, particularly in the early stage [6], because parkinsonian patients show similar symptoms and specific symptoms do not appear in early stage [7]. It is of importance to make an accurate differential diagnosis of parkinsonism to decide on treatment regimens [8], provide a prognosis [9], investigate etiology and pathogenesis, and to develop new therapeutic strategies [10].

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Various methods have been employed to improve the accuracy of differential diagnosis in patients with parkinsonism—for example, F-18 FDG positron emission tomography (PET) [11], dual-radionuclide brain single photon emission computed tomography (SPECT) [12], and diffusion-weighted magnetic resonance imaging (MRI) [13]. Particularly, F-18 FDG PET is helpful in showing preserved or raised glucose metabolism of lentiform nucleus in IPD, while showing it is reduced in most APD [14]. Presynaptic dopamine transporter (DAT) imaging, by contrast, has not been confirmed to be as useful as F-18 FDG PET imaging in differentiating APD from PD, although it is useful in excluding essential tremor (ET), drug-induced parkinsonism (DIP), vascular parkinsonism, and Alzheimer's disease, because it reveals significant striatal DAT loss in APD as well as in PD [15, 16].

The pharmacokinetics of F-18 FP-CIT has been well established in previous studies [17–20]. Uptake of F-18 FP-CIT is rapidly increased with time in the brain cortex, as well as in the striatum, within the first 15 min. Subsequently, cortical uptake is washed out at a rate of approximately 50 %/h; by contrast, striatal radioactivity increases continuously and becomes relatively constant from 40 min onwards in normal volunteers. In IPD patients, putaminal radioactivity peaks within 30 min and shows a gradual clearance. Consequently, the specific striatal uptake reaches a plateau or increases over 100 min. We could therefore have an assumption that the main contributor to the distribution of radiotracer within the first 15 min would be relative regional cerebral perfusion, but that in the delayed phase after 120 min, it would be DAT density. Regional cerebral perfusion is usually coupled to cerebral metabolism [21]. Thus, if the early phase images reflect regional cerebral perfusion well, dual-phase F-18 FP-CIT PET imaging may be useful not only for evaluation of striatal DAT loss, but also for the differential diagnosis of atypical parkinsonism.

With this background, we investigated whether dual-phase F-18 FP-CIT PET imaging is useful in the differential diagnosis of parkinsonism.

Materials and Methods

Subjects

One hundred twenty-nine consecutive subjects who underwent dual-phase F-18 FP-CIT PET imaging for work up for parkinsonism and normal controls were included. Among these, uncertain clinical diagnosis ($n=24$), technical problem ($n=1$), and other parkinsonian disorders ($n=6$) were excluded for analysis. Five normal, seven DIP, five ET, 24 IPD, 20 MSA-parkinsonian type (MSA-P), 13 MSA-cerebella type (MSA-C), 13 PSP, and 11 DLB cases were

analyzed. The diagnosis of IPD was based on the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [22]. Patients with clinically probable MSA-P, MSA-C, PSP, and DLB were enrolled based on current diagnostic criteria [4, 23, 24]. All patients were assessed after at least a 1-year clinical follow-up by a neurologist specializing in movement disorders. Their medical records were available. The severity of motor symptoms was evaluated using the motor portion of the Unified Parkinson's Disease Rating Scale, Part III (UPDRS III) and modified Hoehn and Yahr stage. Their structural MRI was also assessed to evaluate other neurological disease, especially brain infarction.

Radiopharmaceutical Synthesis

F-18 FP-CIT was synthesized with a protic solvent (t-butanol or t-amyl alcohol) as a reaction solvent and N-[3'-(tosyloxy)propyl]-2 β -carbomethoxy-3 β -(4'iodophenyl)nortropane as a precursor [25]. The radiochemical yield [mean $\pm$ standard deviation (SD)] was 42.5 % $\pm$ 10.9 % (decay corrected), the radiochemical purity was greater than 98 % after purification by high-performance liquid chromatography, and the specific activity was 64.4 $\pm$ 4.5 GBq/ μ mol at the end of synthesis.

Positron Emission Tomography / Computed Tomography (PET/CT)

F-18 FP-CIT PET was performed using a Biograph 40 TruePoint PET/computed tomography (CT) camera (Siemens Medical Systems, USA), which provides an in-plane spatial resolution of 2.0 mm full width at half maximum at the center of the field of view. Antiparkinsonian drugs had been stopped 12 h before the scans were obtained. Image acquisition was started 5 min (early phase) and 3 h (late phase) after intravenous injection of F-18 FP-CIT (185 MBq). Emission PET data were acquired for 10 min in the 3-dimensional mode after brain CT, which was performed in the spiral mode at 120 kVp and 380 mA (reference standard) using the CARE Dose 4D program. F-18 FP-CIT PET images were reconstructed from CT data for attenuation correction using the TrueX algorithm and an all-pass filter with a 336 $\times$ 336 matrix.

Early Phase Imaging Analyses

For early phase images, visual and statistical parametric mapping (SPM) analyses were conducted. Data were analyzed for any regional-specific effects using the SPM2 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London) on MATLAB 6.5.1 for windows (The MathWorks, Inc.). After converting

the data from a DICOM file into an analysis format using MRIcro version 1.37 (Chris Rorden, Columbia, SC, USA, www.mricro.com), the images from each subject were spatially normalized into the MNI space using a perfusion PET template. The spatially normalized PET images were smoothed by an isotropic Gaussian Kernel with 8-mm full-width at half-maximum to accommodate inter-individual anatomic variability and to improve the signal-to-noise ratio.

Global count normalization was conducted in SPM. SPM analysis was performed to assess group differences in IPD vs. MSA-P, MSA-C, PSP, or DLB. Only regions that exceeded a threshold of $FDR < 0.05$ were accepted as significant.

For visual interpretation, three nuclear medicine physicians who were completely unaware of the clinical information, except for age and gender, interpreted all early phase images. They classified these images as normal, MSA-P, MSA-C, PSP, or DLB, based on previous criteria of their glucose metabolism or brain perfusion, decreased regional uptake of the putamen, pons and cerebellum in MSA-P, decreased regional uptake of the cerebellum in MSA-C, decreased regional uptake of the caudate nucleus, the thalamus, midbrain and the cingulate gyrus in PSP, and decreased regional uptake of the occipital area, posterior cingulate cortex and temporo-parietal association area in DLB [11, 22, 26–28]. The interobserver agreement and rate of correct classification were measured.

Late Phase Imaging Analyses

For late phase images, visual and quantitative analyses were conducted. For quantitative analysis, image processing was performed as described previously after the coregistration of early phase and late phase images, and also using SPM2 within MATLAB 6.5.1 for Windows and MRIcro version 1.37.

Quantitative analyses were based on volumes of interest (VOIs), which were defined based on a template in standard space. Twelve VOIs [bilateral ventral striatum, anterior caudate, posterior caudate, anterior putamen, posterior putamen (PP), and ventral putamen] of bilateral striatal subregions and one occipital VOI were drawn manually on a coregistered, spatially normalized, single T1-weighted MRI and F-18 FP-CIT template image that was made in-house from F-18 FP-CIT PET and T1-weighted MR images of 13 healthy controls (four men and nine women; 55.2 ± 9.2 years; age range, 41–70 years) by an experienced nuclear medicine physician specializing in nuclear neurology, as described previously [29].

The VOI template in the standard stereotactic space was automatically applied directly to the spatially normalized individual PET images, to analyze striatal F-18 FP-CIT binding.

The activity concentration in each VOI was calculated. The standard uptake value ratio (SUVR) was defined as follows: [mean standardized uptake value (SUV) of striatal subregional VOI – mean SUV of occipital VOI]/mean SUV of occipital VOI. The SUVR for PP was calculated and evaluated the group difference.

For visual interpretation, two nuclear medicine physicians made a consensus of diagnosis. The diagnoses were as follows: dichotomous, normal; homogenous and symmetrical striatal uptake and abnormal; asymmetrically or subregionally decreased striatal uptake.

Statistical Analyses

The SUVRs for the PP in the normal and all patient groups were compared using independent *t*-test. Age, gender, disease duration, and disease severity of all patient groups were also compared using independent *t*-test. SPSS for windows (version 12; SPSS Inc., Chicago, IL) was used for statistical analyses and *p*-values less than 0.05 were deemed to be statistically significant.

Results

The clinical characteristics of the patients with parkinsonism and healthy controls are summarized in Table 1. Patients in DIP and DLB groups were older than patients in the IPD group ($p < 0.05$ for both DIP and DLB). No significant difference was found in UPDRS III scores among the disease groups; however, compared with the IPD group, more advanced modified Hoehn and Yahr stages were shown in MSA-P, PSP, and DLB groups ($p < 0.001$, all groups).

On PET/CT images, there were no abnormalities, such as cerebral infarction, in CT images. Structural MRI was available in all patients except 14 (three normal, three DIP, three ET and five IPD). Among them, 18 subjects had cerebral infarction, but none of them had significant cortical infarctions. And there were five cerebral infarctions in the basal ganglia (one IPD, one MSA-P, two PSP and one DLB), but the lesions were too small to influence on presynaptic dopaminergic neuron, so we included them in analysis.

Late Phase Analysis

The SUVRs for PP in the IPD, MSA-P, PSP, and DLB groups were significantly lower than those in normal, DIP, ET, and MSA-C groups ($p < 0.001$) (Fig. 1). For visual interpretation, representative images are shown in Fig. 2b. F-18 FP-CIT uptake in the striatum was heterogeneously decreased and more significant in the PP in IPD, MSA-P, PSP, and DLB groups, but more homogeneous in normal, DIP, ET, and MSA-C groups, with a high level of diagnostic accuracy (Table 2).

Table 1 Clinical characteristics of subjects

Characteristics	Normal (n=5)	DIP (n=7)	ET (n=5)	IPD (n=24)	MSA-P (n=20)	MSA-C (n=13)	PSP (n=13)	DLB (n=11)
Age (years)	63.2±18.6	75.7±6.8*	54.8±14.6	60.7±12.8	61.9±9.1	57.2±7.7	68.9±5.6	73.7±6.7*
Gender (M/F)	1/4	0/7	4/1	9/15	6/15	7/6	9/4	2/9
Disease duration (years)	NA	3.8±5.4	3.2±3.8	6.3±5.2	2.8±1.8	1.9±1.0	2.7±1.3	5.4±5.4
Modified H-Y stage	NA	NA	NA	1.8±0.7	3.1±1.1 [†]	NA	3.4±1.0 [†]	2.9±0.6 [†]
UPDRS III score	NA	NA	NA	19.2±11.6	25.3±12.2	NA	26.7±12.5	22.1±11.4

* $p < 0.05$, compared with IPD.

[†] $p < 0.001$, compared with IPD.

NA not applicable

Values are reported as mean ± standard deviation (SD) unless otherwise indicated

Early Phase Analysis

Figure 3 shows the difference of regional uptake on early phase images in SPM t-maps of all patient groups compared with IPD. No difference was observed in regional uptake among normal DAT binding groups, except for the MSA-C group, which showed decreased regional uptake in the cerebella cortex. Abnormal DAT binding groups showed different regional uptake. MSA-P patients showed a decrease in regional uptake in the PP and cerebella cortex and an increase in the occipitotemporal cortex. PSP patients showed multiple areas with significantly decreased regional uptake most pronounced in the medial frontal, hypothalamus, and mid-brain. The inverse contrast showed higher relative regional uptake in the parietooccipital cortex than IPD. Finally, patients with DLB showed pronounced decreased regional uptake in the fronto-parieto-occipital cortex. The

inverse contrast did not show cortical or subcortical differences at the aforementioned thresholds.

Representative images for visual interpretation are shown in Fig. 2a. Additionally, the results of the visual analysis of early phase images are shown in Table 3. The interobserver agreement of three interpreters for the visual analysis was good (Fleiss κ coefficient, 0.668; $p < 0.05$). When discriminating APD from PD, visual interpretation of early phase images showed high diagnostic sensitivity and specificity: 75.4 % and 100 %, respectively. Regarding the ability to distinguish specific APD, sensitivities were 81 % for MSA-P, 75 % for MSA-C, 23 % for PSP, and 54.5 % for DLB.

Discussion

Several studies have tried to differentiate IPD from APD such as PSP and MSA [30, 31]; however, limitations still exist regarding differential diagnosis of parkinsonism using striatal DAT loss alone [15, 16]. Therefore, most institutions have conducted both DAT imaging and F-18 FDG PET for accurate diagnosis of parkinsonism [14].

The present study indicates that dual-phase F-18 FP-CIT PET imaging is feasible and effective in the diagnosis of neurodegenerative parkinsonism and the differential diagnosis of atypical parkinsonism, particularly in distinguishing MSA-P and MSA-C from IPD. On late phase images, we confirmed striatal DAT loss in IPD, MSA-P, PSP, and DLB groups. By contrast, DAT binding was normal in normal, ET, DIP, and MSA-C groups. On early phase images, a decrease or increase of regional uptake is shown in MSA-P, MSA-C, PSP, and DLB groups compared with the IPD group. These findings generally correspond with several previous studies that have identified characteristic DAT binding of neurodegenerative parkinsonism [32–34] and glucose metabolism patterns with IPD, MSA, PSP, and DLB [11, 23, 26, 27], respectively.

Fig. 1 Standard uptake value ratio (SUVr) of posterior putamen (PP) in all patient groups and normal subjects. SUVr for PP in IPD, MSA-P, PSP, and DLB groups were significantly lower than those in normal, DIP, ET and MSA-C groups

Fig. 2 Representative images for visual interpretation of **a** early and **b** late phase F-18 FP-CIT PET

In the present work, the regional uptake of early phase images observed in the IPD patient group was indistinguishable from that in the normal group by visual interpretation. In previous studies, although covariance analysis reveals an abnormal profile of a relatively raised resting lentiform nucleus and lowered frontal and parietotemporal metabolism [35], absolute levels in the lentiform nucleus lie within the reference range in IPD [36], like the present study.

The regional uptake pattern observed in the MSA-P group with decreased uptake in striatum and cerebellum and increased uptake in occipital cortex compared with the IPD group corresponds to earlier findings of glucose metabolism [11, 37]. However, in our and other studies using perfusion ligands, significant differences could not be demonstrated in MSA-P and IPD patients in the pons [38], a finding that is at odds with hypometabolism found in FDG PET studies. This could be related to either tracer-specific properties or perfusion/metabolism uncoupling in the pons.

In the MSA-C group, the decreased regional uptake in bilateral cerebellar cortex was pronounced. The overall correct diagnosis rate of visual analysis of early phase images was 77 % (10/

13, Table 3), which is higher than that of a previous study with F-18 FDG-PET (50 %) [37]. This could be related to tracer-specific properties of F-18 FDG that showed relatively decreased uptake in the cerebellum even in the normal group, mismatching with relatively higher perfusion in the cerebellum [39].

In the PSP group, the decreased regional uptake in medial frontal, hypothalamus, and mid-brain was observed, which corresponds to earlier findings of diminished glucose use in the frontal cortex and mid-brain [11]. Additionally, in the DLB group, the pattern of decreased regional uptake in the posterior parietal and associated temporal areas was the most discriminating finding for this analysis [38].

Visual interpretation of early phase images showed comparatively superior diagnostic accuracy for differentiating MSA-P or MSA-C from IPD, mainly in comparison with PSP and DLB, because the regional uptake pattern of the cerebral cortex was difficult to differentiate. The cause may be that, although the putaminal extraction rate and brain permeability of F-18 FP-CIT was revealed to be high in the previous study [17], the cortical extraction rate could be relatively low, due to F-18 FP-CIT not being a perfusion agent. Additionally, imaging of regional perfusion and DAT density could have been mixed up since we acquired the early phase images at 5 min after injection. Although the sensitivities for diagnosis of PSP and DLB were relatively low, considering that MSA is the most prevalent cause for misdiagnosis of IPD, the present study is meaningful for the differential diagnosis of atypical parkinsonism.

A previous study demonstrated dual-phase C-11 Pittsburgh compound B (PIB) PET imaging for investigation of neurodegenerative dementia—particularly, Alzheimer's disease [40]. In contrast to our study, C-11 PIB demonstrated a high level of first-pass extraction, K_1 . Dynamic C-11 PIB PET scans were acquired over 60 min, and they investigated functional R1 maps (relative flow delivery, K_1 region of interest/ K_1 reference region) of the first 6 min, instead of early phase images. The R1 images of C-11 PIB strongly resembled F-18 FDG uptake images, and showed very similar correlation patterns with severity of cognitive impairment. Similarly, images of the first few minutes after injection can show

Table 2 Visual interpretation of late phase F-18 FP-CIT PET images in all subjects

Clinical diagnosis	Visual diagnosis (n)	
	Normal	Abnormal
Normal (n=5)	5 (100 %)	
DIP (n=7)	6 (86 %)	1 (14 %)
ET (n=5)	5 (100 %)	0
IPD (n=24)	0	24 (100 %)
MSA-P (n=20)	0	20 (100 %)
MSA-C (n=13)	8 (62 %)	5 (38 %)
PSP (n=13)	0	13 (100 %)
DLB (n=11)	0	11 (100 %)

DIP drug-induced parkinsonism; ET essential tremor; IPD idiopathic Parkinson's disease; MSA-P multiple system atrophy-parkinson type; MSA-C multiple system atrophy-cerebellar type; PSP progressive supranuclear palsy; DLB dementia with Lewy bodies

Fig. 3 Difference of regional uptake in early phase image SPM t-maps of **a** MSA-P, **b** MSA-C, **c** PSP, and **d** DLB, compared with IPD (FDR<0.05)

distribution of the cerebral blood flow and serve as F-18 FDG PET images.

Several methodological and clinical limitations of the present study deserve mention. First, we could not investigate any objective parameter like K_1 or R1 map, because we did not perform dynamic imaging. However, in a clinical situation, obtaining dynamic images in all patients will be difficult; thus, the present study might be more appropriate clinically. Second, there was lack of kinetic evaluation of F-18 FP-CIT in this study. Although, there were several studies demonstrated kinetics of F-18 FP-CIT [17–20], they did not include full study time that we used, nor did they include the correlation with blood flow. Future study will be needed. Third, because of some limitations in the system of our center and time delay due to the move from injection room to imaging room, we

could not help starting PET scan at 5 min after injection, so there could be some mix-up of DAT binding images in early phase images. Future study that collects images including the first 10 min will be needed. Fourth, there were 18 subjects who had cerebral infarction in MRI; in particular, there were five cerebral infarctions in the basal ganglia. Although the sizes of infarctions were very small, they could change the distribution of cerebral blood flow. Finally, patients in the present study were diagnosed clinically. Therefore, misdiagnosis could have occurred because of the lack of postmortem verification [41]. Although all diagnosis was based on strict diagnostic criteria, a longer period of follow-up is needed, particularly given that overdiagnosis of IPD and underdiagnosis of APD are common [32].

Despite these limitations, the results of our study set the stage for use of dual-phase F-18 FP-CIT PET imaging for the differential diagnosis of parkinsonian disorders. We believe that at least three important points could be considered when dual-phase F-18 FP-CIT PET imaging is to be conducted in patients with parkinsonism. First, more accurate diagnosis of the specific parkinsonism is possible compared with the use of late phase imaging alone. Second, radiation exposure to patients can be decreased compared with the use of combined F-18 FP-CIT PET and F-18 FDG PET, while maintaining diagnostic accuracy. Third, patients can save time and money compared with the use of combined F-18 FP-CIT PET and F-18 FDG PET.

Conclusion

In conclusion, dual phase F-18 FP-CIT PET imaging is useful not only for demonstrating striatal DAT loss in

Table 3 Visual interpretation of early phase F-18 FP-CIT PET images in patients with IPD, MSA-P, MSA-C, PSP, and DLB

Clinical diagnosis	Visual diagnosis (n)				
	IPD	MSA-P	MSA-C	PSP	DLB
IPD (n=24)	24 (100 %)	0	0	0	0
MSA-P (n=20)	0	17 (85 %)	3 (15 %)	0	0
MSA-C (n=13)	1 (8 %)	2 (15 %)	10 (77 %)	0	0
PSP (n=13)	8 (62 %)	2 (15 %)	0	3 (23 %)	0
DLB (n=11)	5 (45 %)	0	0	0	6 (55 %)

IPD idiopathic Parkinson's disease; MSA-P multiple system atrophy-parkinson type; MSA-C multiple system atrophy-cerebellar type; PSP progressive supranuclear palsy; DLB dementia with Lewy bodies

neurodegenerative parkinsonism, but also for differentiating atypical parkinsonism, particularly MSA from PD. Future studies will be required to compare F-18 FDG PET images and early phase images of F-18 FP-CIT PET directly, and to gain more accurate early phase images of F-18 FP-CIT PET.

Conflicts of Interest The authors declare no conflict of interest

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