Comparison of the Performances of ^{18}F -FP-CIT Brain PET/MR and Simultaneous PET/CT: a Preliminary Study

SangDon Kwon¹ · KyungAh Chun¹ · EunJung Kong¹ · IhnHo Cho¹

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Abstract

Purpose ^{18}F -FP-CIT [^{18}F -fluorinated *N*-3-fluoropropyl-2-beta-carboxymethoxy-3-beta-(4-iodophenyl) nortropane] has been well established and used for the differential diagnosis of atypical parkinsonian disorders. Recently, combined positron emission tomography (PET)/magnetic resonance (MR) was proposed as a viable alternative to PET/computed tomography (CT). The aim of this study was to compare the performances of conventional ^{18}F -FP-CIT brain PET/CT and simultaneous PET/MR by visual inspection and quantitative analysis.

Methods Fifteen consecutive patients clinically suspected of having Parkinson's disease were recruited for the study. ^{18}F -FP-CIT PET was performed during PET/CT and PET/MR. PET/CT image acquisition was started 90 min after intravenous injection of ^{18}F -FP-CIT and then PET/MR images were acquired. Dopamine transporter (DAT) density in bilateral striatal subregions was assessed visually. Quantitative analyses were performed on bilateral striatal volumes of interest (VOIs) using average standardized uptake values (SUVmeans). Intraclass correlation coefficients (ICCs) and their 95 % confidence intervals (CIs) were assessed to compare PET/CT and PET/MR data. Bland–Altman plots were drawn to perform method-comparisons.

Results All subjects showed a preferential decrease in DAT binding in the posterior putamen (PP), with relative sparing of the ventral putamen (VP). Bilateral striatal subregional

binding ratio (BR) determined PET/CT and PET/MR demonstrated close interequipment correspondence (BR_{right caudate} - ICC, 0.944; 95 % CI, 0.835–0.981, BR_{left caudate} - ICC, 0.917; 95 % CI, 0.753–0.972, BR_{right putamen} - ICC, 0.976; 95 % CI, 0.929–0.992 and BR_{left putamen} - ICC, 0.970; 95 % CI, 0.911–0.990, respectively), and Bland–Altman plots showed interequipment agreement between the two modalities.

Conclusions It is known that MR provides more information about anatomical changes associated with brain diseases and to enable the anatomical allocations of subregions than CT, though this was not observed in the present study. Although the subregional BR of simultaneous PET/MR was comparable to that of PET/CT in Parkinson's disease, our isocontouring method could make bias. A future automated method using standard template study or manual segmentation of putamen/caudate based on MR or CT is needed.

Keywords Dopamine transporter · ^{18}F -FP-CIT · PET/CT · PET/MR

Introduction

Parkinsonian disorder is among the most common neurodegenerative diseases in elderly individuals with Alzheimer's disease [1, 2]. Its main clinical symptoms are akinesia, rigidity, resting tremor, and poor balance (postural instability) [3]. The cause of parkinsonian disorder is not known, but idiopathic Parkinson's disease is the most common cause. Furthermore, the clinical symptoms of Parkinson's disease are associated with lesions in the substantia nigra. Atypical parkinsonian disorders, such as, multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy, and dementia with Lewy bodies, also account for a large percentage of parkinsonian disorder cases [4].

Many studies have been performed to improve the accuracy of differential diagnosis in patients with parkinsonian

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✉ KyungAh Chun
cka52@yumail.ac.kr

¹ Department of Nuclear Medicine, Yeungnam University Hospital, Namgu Daemyung 5-dong 317-1, 705-717 Daegu, South Korea

disorder, these include studies on 2-deoxy-2- ^{18}F fluoro-D-glucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT), dual-radionuclide dopamine transporter (DAT) and brain perfusion single photon emission computed tomography (SPECT), and diffusion-weighted magnetic resonance imaging (MRI) [5–7].

Recently F-18 fluorinated-N-3-fluoropropyl-2-b-carboxymethoxy-3-b-(4-iodophenyl) nortropane (^{18}F -FP-CIT) PET/CT became available for use in parkinsonian disorder for DAT imaging. ^{18}F -FP-CIT PET/CT makes it possible to evaluate regional DAT densities in the brain and to differentiate parkinsonian disorders into subtypes [8, 9].

However, CT imaging of the brain is limited by lack of soft tissue differentiation, and recently a whole-body fully integrated PET/MR scanner was introduced [10–12], and for brain lesions, it has been suggested the higher soft tissue contrast of MRI could provide more information about brain anatomical changes [13, 14].

Given this background, the purpose of the present study was to compare the performances of conventional ^{18}F -FP-CIT brain PET/CT and simultaneous PET/MR.

Materials and Methods

Subjects

Fifteen patients (five men, ten women; mean age 65.1 ± 10.4 years; age range, 48–79 years) were recruited consecutively (Table 1). All study subjects were clinically suspected of having Parkinson's disease due to akinesia, rigidity, and resting tremor or postural instability by an experienced neurologist, and all provided informed consent. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, and was approved by the Institutional Review Board of Yeungnam University Hospital (IRB no. YUH-13-0430-O57).

Data Acquisition

^{18}F -FP-CIT PET was performed using a PET/CT (Discovery VCT, GE Medical Systems, Milwaukee, WI, USA) and a PET/MR unit (Biograph mMR, Siemens Medical Solution, Hoffman Estates, Knoxville, TN, USA). All patients underwent emission scan after injecting 185 MBq (5 mCi) of ^{18}F -FP-CIT — antiparkinsonian drugs were stopped 12 h before scans were performed.

PET/CT image acquisition was started 90 min after the intravenous injection of ^{18}F -FP-CIT. Brain CT was performed in helical mode at auto mAs (50–200 mAs) and 120 kVp. ^{18}F -FP-CIT PET images were acquired in the 3-dimensional (3D) mode for 10 min. The protocols for reconstruction were iterative reconstruction with 20 subsets/2 iterations. The matrix size for attenuation

correction was 128×128 , and a 2.57 mm gaussian filter and a fully 3D iterative algorithm (VUE Point HD) were applied.

Subsequently PET/MR with T1-weighted magnetization prepared rapid gradient echo (MPRAGE) and diffusion sequences including a ultrashort echo-time (UTE) sequence was performed (mean time interval between PET/CT and PET/MR 37.3 ± 20.1 min; range 19–87 min). The PET/MR imaging acquisition protocols were as follows; iterative reconstruction with 21 subsets/5 iterations, matrix size 344×344 , and a 4 mm gaussian post reconstruction filter was used. All patients underwent MR imaging with an UTE sequence, conducted with a repetition time of 11.94 ms, echo time 1 of 0.07 ms, echo time 2 of 2.46 ms, field of view 300×300 mm, matrix size 192×192 , and flip angle 10° . PET data were acquired over a single bed position of 30 cm covering the head and neck for 20 min. Syngo MR VB20P software was used for all patients. PET/MR systems used segmentation-based attenuation correction (AC) based on an attenuation map derived from MR images.

Data Analysis

PET images were interpreted by visual inspection and quantitative analysis. DAT densities in bilateral striatal subregions were performed visually. Quantitative analyses were based on bilateral striatal volumes of interest (VOIs) using average standardized uptake values (SUVmeans) and standardized uptake values (SUV) is commonly used as a relative measure of FDG uptake. SUV is a mathematically derived ratio of tissue radioactivity concentration at a point in time and the injected dose of radioactivity per kilogram of the patient's body weight.

Four VOIs of bilateral striatal subregions (bilateral caudate nucleus and putamen) and one cerebellar VOI (from just below the inferior margin of the occipital lobe to the lower margin of the cerebellum) were drawn manually on respective PET scans by an experienced nuclear medicine physician specializing in nuclear neurology (Fig. 1). Three-dimensional iso-contouring VOIs of 40 % max-threshold were created to calculate mean SUVs as in previous oncologic studies [15, 16]. Activity concentrations were calculated for VOIs. Binding ratio (BR) was defined as follows: (SUVmean of striatal subregional VOI – SUVmean of cerebellar VOI)/SUVmean of cerebellar VOI [17]. BRs of bilateral striatal subregions were calculated ($\text{BR}_{\text{right caudate}}$, $\text{BR}_{\text{left caudate}}$, $\text{BR}_{\text{right putamen}}$ and $\text{BR}_{\text{left putamen}}$). The analysis procedure was conducted on a dedicated workstation using commercial software (PET/CT - Advantage Workstation version 4.6, GE; and PET/MR - Syngo MMWP and Syngo TrueD, Siemens Medical Solutions, respectively).

Statistical Analysis

The analysis was performed using SPSS for windows (SPSS, Chicago, IL, USA). All continuous values are presented as means and standard deviations. The nonparametric Wilcoxon

Table 1 Patients characteristics

No.	Age (years)	Gender	Disease duration (months)	H & Y stage	Visual analysis of DAT density
1	48	F	36	NA	Decreased in both putamen
2	64	F	60	3	Decreased in both putamen and right caudate nucleus
3	74	F	3	1	Decreased in left putamen
4	79	M	10	NA	Decreased in both putamen
5	50	F	5	NA	Decreased in both putamen
6	76	M	24	NA	Decreased in both putamen and right caudate nucleus
7	59	F	2	3	Decreased in both putamen
8	69	F	24	2	Decreased in both putamen
9	75	F	NA	NA	Decreased in both putamen
10	73	F	3	2.5	Decreased in both putamen
11	56	M	12	3	Decreased in both putamen
12	63	F	72	NA	Decreased in both putamen and both caudate nucleus
13	55	M	8	1.5	Decreased in both putamen
14	77	M	72	3	Decreased in both putamen
15	58	F	2	1	Decreased in both putamen

NA not available

H & Y Hoehn and Yahr

DAT dopamine transporter

Fig. 1 Illustration of manual placements of volumes of interest (VOIs). Three-dimensional iso-contouring VOIs were constructed manually on PET/CT (a) and PET/MR (b) images (transaxial, coronal, and sagittal views) in areas corresponding to the caudate nucleus and putamen bilaterally

matched-pairs signed rank test was used to calculate overall statistical differences in measured SUVs and BRs. BRs obtained by PET/CT and PET/MR data were directly compared, and levels interequipment agreement were evaluated using intraclass correlation coefficients (ICCs). In addition, ICCs and their 95 % confidence intervals (CIs) were used to compare PET/CT and PET/MR data. ICC values were interpreted as follows: slight (0.04–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and almost perfect (0.81–1.00) [18, 19]. Bland-Altman plots were also drawn to compare the two modalities, as previously described [20, 21]. Probability values of less than 0.05 were considered statistically significant.

Results

Visual Assessment

Visual inspection of ^{18}F -FP-CIT PET scans showed 14 of the 15 subjects exhibited decreased DAT density on bilateral striata. The other subject showed decreased DAT density on unilateral striatum. Both PET/CT and PET/MR showed reduced DAT densities in bilateral or unilateral striata (particularly in the posterior putamen, “rabbit hip” sign on maximum-

intensity-projection images). Visual evaluations made by ^{18}F -FP-CIT brain PET/MR and simultaneous ^{18}F -FP-CIT PET/CT agreed. All subjects were visually diagnosed with Parkinson's disease by common consent (Fig. 2). No patient showed acute infarction and one had an old lacunar infarction in both basal ganglia.

Quantitative Assessment

SUVmeans of the four bilateral subregions and cerebellum were measured in PET/CT and PET/MR images. Overall, average regional PET/CT SUVs were significantly higher than PET/MR SUVs (average SUVmeans right caudate 5.41 ± 1.54 , left caudate 5.61 ± 1.34 , right putamen 5.03 ± 1.58 , left putamen 4.93 ± 1.31 , and cerebellum 1.03 ± 0.17 for PET/CT; and right caudate 3.87 ± 1.17 , left caudate 4.00 ± 1.02 , right putamen 3.59 ± 1.22 , left putamen 3.49 ± 1.02 , and cerebellum 0.73 ± 0.11 for PET/MR, $p < 0.001$, respectively) (Table 2). Overall the SUVmean of the bilateral striatal subregion showed excellent interequipment agreement in ICCs between PET/CT and PET/MR (Fig. 3).

BRs obtained by PET/CT and PET/MR were not significantly different (Table 2). Bilateral striatal subregion BRs determined by PET/CT and PET/MR demonstrated excellent

Fig. 2 PET/CT (a,b) and PET/MR (c,d) images of 55-year-old male patient who showed decreased DAT binding in the posterior putamina, though the left side was more affected. The quality of the PET/MR image

was similar to that of the respective PET scan of PET/CT. PET/CT (e,f) and PET/MR (g,h) images of 78-year-old male patient who showed symmetrically decreased (DAT) binding in posterior putamina

Table 2 SUVmeans and BR values determined by ^{18}F -FP-CIT PET/CT and PET/MR

Anatomic region	PET/CT		PET/MR		<i>P</i> -value	
	SUV means	BR	SUV means	BR	SUV means	BR
Right caudate	5.41 ± 1.54	4.38 ± 1.84	3.87 ± 1.17	4.31 ± 1.67	<0.001	0.842
Left caudate	5.61 ± 1.34	4.54 ± 1.56	4.00 ± 1.02	4.50 ± 1.50	<0.001	0.910
Right putamen	5.03 ± 1.58	4.00 ± 1.88	3.59 ± 1.22	3.95 ± 1.84	<0.001	0.570
Left putamen	4.93 ± 1.31	3.88 ± 1.62	3.49 ± 1.02	3.82 ± 1.57	<0.001	0.496
Cerebellum	1.03 ± 0.17		0.73 ± 0.11		<0.001	

SUVmeans average standardized uptake values

BR binding ratio

Fig. 3 Relationship between PET/CT and subsequent PET/MR as determined using SUVmean values. The PET/CT SUVmeans were significantly higher than the PET/MR SUVmeans. ICCs of bilateral caudate nucleus and putamen represented excellent interequipment agreement (SUV

in right caudate nucleus - ICC, 0.964; 95 % CI, 0.892–0.988, SUV in left caudate nucleus - ICC, 0.942; 95 % CI, 0.828–0.981, SUV in right putamen - ICC, 0.963; 95 % CI, 0.889–0.988 and SUV in left putamen - ICC, 0.950; 95 % CI, 0.850–0.983, respectively)

interequipment agreement in ICCs. To estimate the reliability between both PET/CT and PET/MR, we also designed Bland-Altman plots. BRs in Bland-Altman plots showed that most dots were contained within the CIs. BR of caudate nucleus shows more variable than those of putamen and BR on PET/MR was lower than BR on PET/CT (right caudate 0.073 ± 1.58 , left caudate 0.044 ± 1.65 , right putamen 0.054 ± 1.11 , left putamen 0.066 ± 1.06 , respectively) (Fig. 4).

Discussion

Parkinson's disease and atypical parkinsonism (such as multiple system atrophy and progressive supranuclear palsy) exhibit significantly decreased striatal DAT density and each disorder shows different preferential subregional DAT binding values when examined by FP-CIT SPECT and PET [22–24]. The recent introduction of ^{18}F -FP-CIT PET/CT enables

Fig. 4 DAT BR values of PET/CT and PET/MR for striatal subdivisions. **a** The bilateral striatal subregion of BR demonstrated interequipment correspondence and the BR of caudate nucleus and putamen did not show significant difference from PET/CT and PET/MR. BR of caudate nucleus and putamen represented excellent interequipment agreement ($\text{BR}_{\text{right caudate}}$ - ICC, 0.944; 95 % CI, 0.835–0.981, $\text{BR}_{\text{left caudate}}$ - ICC, 0.917; 95 % CI, 0.753–0.972, $\text{BR}_{\text{right putamen}}$ - ICC, 0.976; 95 % CI,

0.929–0.992 and $\text{BR}_{\text{left putamen}}$ - ICC, 0.970; 95 % CI, 0.911–0.990, respectively). **b** Bland-Altman plots showing interequipment agreement between the two modalities. Most dots were contained within the CIs in bilateral striatal subregions (right caudate 0.073 ± 1.58 , left caudate 0.044 ± 1.65 , right putamen 0.054 ± 1.11 , left putamen 0.066 ± 1.06 , respectively)

Fig. 4 (continued)

presynaptic DAT imaging in parkinsonian disorder, and it is also possible to evaluate regional DAT densities in the brain [8, 9].

However, CT imaging of the brain is limited by a lack of soft tissue differentiation. In brain lesions, the higher soft tissue contrast of MRI could provide more information about brain anatomical changes [12–14], and recently a fully integrated PET/MR scanner was introduced [10–12].

Although brain PET/MR has several advantages in terms of brain tissue segmentation and anatomic information over PET/CT, controversy continues as whether PET/CT and PET/MR data are replaceable [25]. The present study indicates ^{18}F -

FP-CIT brain PET/MR is feasible and has a performance comparable to that of simultaneous brain PET/CT. No definite differences were observed between visual analyses of ^{18}F -FP-CIT brain PET scan results obtained by PET/CT and PET/MR. Furthermore, PET/MR images were of similar quality to PET/CT images and all study population was visually diagnosed in Parkinson's disease [decrease in DAT binding in the posterior putamen (PP), with relative sparing of the ventral putamen (VP)]. Previous oncologic PET studies have also indicated that there is no significant difference between the PET data obtained by PET/MR and PET/CT with respect to image quality [26, 27].

Quantification of ^{18}F -FP-CIT has been considered an important issue in clinical brain PET studies [28, 29]. It is essential to achieve accurate quantification for ^{18}F -FP-CIT PET for clinical applications given the development of quantitative imaging based biomarkers. In particular, DAT imaging have been regarded as a biomarker of nigrostriatal dopaminergic pathway dysfunction. In this context, spatially and temporally coregistered PET/MR may have advantages in terms of accurately defining structures for quantification [17].

In previous studies, binding potentials calculated from striatal regional ratios were found to be useful when ^{18}F -FP-CIT reaches equilibrium binding in the brain [30, 31]. For quantitative analysis, we calculated DAT BRs from PET/MR and PET/CT based on manually drawn VOIs and as a preliminary report, simple and fast striatum segmentation method was employed. This simple method could provide acceptable quantification for DAT binding of ^{18}F -FP-CIT [32]. The BRs of bilateral striata showed interequipment reliability in the present study (BR_{right caudate} - ICC, 0.944; 95 % CI, 0.835–0.981, BR_{left caudate} - ICC, 0.917; 95 % CI, 0.753–0.972, BR_{right putamen} - ICC, 0.976; 95 % CI, 0.929–0.992 and BR_{left putamen} - ICC, 0.970; 95 % CI, 0.911–0.990, respectively), although average regional SUVs were higher for PET/CT than PET/MR. The lower SUVs of the second PET scans (PET/MR) were probably due to the use of different scanners from different manufacturers, the dynamic changes (FP-CIT kinetics) of ^{18}F -FP-CIT. Previous reports on the pharmacokinetics of ^{18}F -FP-CIT have shown putaminal radioactivity peaks within 30 min and then gradually diminishes in idiopathic Parkinson's disease (IPD) patients [33]. This finding agrees with a previous report issued by Choi et al. [17], who compared BRs using PET template and performed statistical probabilistic anatomic mapping derived from ^{18}F -FP-CIT brain PET data using the PET/MR and PET/CT approaches. They found that BRs of caudate and putamen showed excellent interequipment agreements when non-AC data from PET/MR and PET/CT were used. Nevertheless, DAT BR in the caudate nucleus was significantly underestimated by PET/MR, compared with PET/CT because of spatial bias of attenuation map. Our results showed excellent interequipment agreements when AC data from PET/MR and PET/CT were used. It is not clear about this difference but in the present study, we used the isocontouring method which may not fully include the caudate nucleus and the bias of our quantification method could make this difference.

Our study has several limitations. The first limitation is that only a small number of patients were included. Second, we used PET/MR (Biograph mMR, Siemens Medical Solution) and PET/CT (Discovery VCT, GE Medical Systems) scanners from different manufacturers; Delso G et al. showed that even when PET/CT and PET/MR scanners from the same vendor were used, PET detectors were significantly different [34]. Third, we examined only two regions (caudate nucleus and

putamen), and thus, further studies on more segmented subregions (anterior caudate, posterior caudate, anterior putamen, posterior putamen, and ventral putamen) are needed as previous studies [35]. Fourth, the study is limited by the use of serial PET protocols and by PET/MR acquisition after PET/CT. Moreover, scan acquisition times and times between PET/CT and PET/MR scans were not standardized (mean time between PET/CT and PET/MR 37.3 ± 20.1 min; interval range 19–87 min). Accordingly, a study is required that takes into account possible dynamic changes in the binding potential of ^{18}F -FP-CIT for PET/CT and PET/MR. Furthermore, reconstruction protocols differed for PET/CT and PET/MR, and this could have affected the quantification of PET data. But smoothing with a Gaussian filter could help comparability between PET images with different matrix size [36, 37]. Fifth, the isocontour approach have a lot of limitations, such as underestimation of SUV [38] and the tracer uptake heterogeneity can influence the delineation results [15]. To obtain more accurate quantification, automated method using standard template study or manual segmentation of putamen/caudate based on MR or CT is needed.

Conclusion

In spite of a later imaging time-point, PET image qualities of PET/CT and PET/MR were found to be comparable in terms of discriminating parkinsonian disorders. Although the subregional BR of simultaneous PET/MR was comparable to that of PET/CT in this study, isocontouring method using max-threshold could make serious bias. An additional, larger-scale prospective study and automated method using standard template study or manual segmentation of putamen/caudate based on MR or CT is needed that includes image quality analysis.

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Compliance with Ethical Standards

Conflict of Interest SangDon Kwon, Eunjung Kong, KyungAh Chun and IhnHo Cho declare that they have no conflict of interest.

Ethical Statement All procedures performed in the study involving human participant were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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