OPEN

Original article

Nuclear Medicine Communications

The utility of the combination of a SPECT study with [^{123}I]-FP-CIT of dopamine transporters and [^{123}I]-MIBG myocardial scintigraphy in differentiating Parkinson disease from other degenerative parkinsonian syndromes

Naoto Uyama[a], Hideki Otsuka[c], Takayoshi Shinya[a], Yoichi Otomi[a], Masafumi Harada[a], Wataru Sako[d], Yuishin Izumi[d], Ryuji Kaji[d], Yuya Watanabe[e], Satoru Takashi[b] and Yamato Kunikane[b]

Objective **Molecular imaging of nigrostriatal dopamine transporters (DAT) and sympathetic cardiac innervation with single-photon emission computed tomography (SPECT) are useful tools for differentiating idiopathic Parkinson disease (PD) from other degenerative parkinsonian syndromes (non-PD). Nevertheless, these modalities are often insufficient for achieving a definite diagnosis. The aims of this study were to evaluate the diagnostic accuracy of the combination of these tools.**

Materials and methods **The SPECT radiotracers [^{123}I]-*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)-nortropane (FP-CIT) and meta-[^{123}I]-iodobenzylguanidine (MIBG) were used to research presynaptic dopaminergic projections (DAT SPECT) and myocardial adrenergic innervation (MIBG scintigraphy), respectively. PD patients ($n = 15$; age: 61.5 ± 13.6 years) and non-PD patients ($n = 19$; age: 62.6 ± 14.2 years) who underwent both tests were enrolled in this study. Receiver-operating characteristic analyses were used to set the cutoff values of the specific binding ratio in DAT SPECT and the heart to mediastinum ratio in delayed scan in MIBG scintigraphy for differentiating PD from non-PD. We calculated the sensitivity, specificity, and test accuracy of the individual methods and also the combination of these two modalities.**

Results **When DAT SPECT and MIBG scintigraphy were used individually, they showed mild accuracy in differentiating PD from non-PD (DAT, 67.6%; MIBG, 67.6%). The combination of the two approaches using cutoff values of less than 3.24 for the specific binding ratio and less than 2.745 for the delayed heart to mediastinum ratio enabled more accurate differentiation between PD and non-PD. The accuracy of these indices in distinguishing PD from non-PD was 79.4%.**

Conclusion **These results suggested that the combination of DAT SPECT and MIBG scintigraphy may improve the diagnostic accuracy in differentiating PD from non-PD. *Nucl Med Commun* 38:487–492 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.**

Nuclear Medicine Communications 2017, **38**:487–492

Keywords: DAT SPECT, degenerative parkinsonian syndromes, MIBG myocardial scintigraphy, Parkinson disease

[a]Department of Radiology, [b]Division of Clinical Technology, Tokushima University Hospital, [c]Department of Medical Imaging/Nuclear Medicine, Institute of Biomedical Sciences, [d]Department of Clinical Neuroscience, Institute of Health Biosciences, Tokushima University Graduate School and [e]Faculty of Medicine, Radiologic Science, Tokushima University, Tokushima, Japan

Correspondence to Hideki Otsuka, MD, PhD, Department of Medical Imaging/Nuclear Medicine, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan
Tel: +81 88 6339283; fax: +81 88 6337174;
e-mail: hideki.otsuka@tokushima-u.ac.jp

Received 10 November 2016 **Revised** 14 March 2017
Accepted 24 March 2017

Introduction

Parkinson disease (PD), which is the most common neurodegenerative parkinsonian syndrome, is characterized by the degeneration of both dopaminergic and nondopaminergic neurons with neuronal intracytoplasmic inclusions known as Lewy bodies [1]. Although the clinical diagnosis of PD is often straightforward and robust in the cases with the typical cardinal symptoms and characteristic signs, the correct diagnosis can be challenging, especially in clinically mild or uncertain cases. Furthermore, it remains difficult to accurately differentiate PD from other neurodegenerative parkinsonian syndromes (non-PD), such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration. An accurate and early diagnosis is the key to correct management and prognostication.

In recent years, molecular imaging techniques using PET or single-photon emission computed tomography (SPECT) have offered a variety of tests that can improve the diagnostic

0143-3636 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc. DOI: 10.1097/MNM.0000000000000674

accuracy of PD and non-PD. Dopamine transporter (DAT) ligands [2–4] and the sympathetic innervation of the heart [1,5] have become very popular and are used widely in clinical practice. For example, imaging of DAT binding with [^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)-nortropane (FP-CIT) successfully visualizes the presynaptic dopaminergic degeneration of the nigrostriatal tract [4,6]. DAT SPECT abnormalities can help to support a diagnosis of degenerative parkinsonian syndromes by excluding patients with essential tremor [7], and psychogenic [8] and vascular parkinsonism [9] who have a normal nigrostriatal function. However, DAT imaging as a stand-alone tool cannot differentiate between the various types of degenerative parkinsonian syndromes with sufficient accuracy [10,11]. Similarly, several studies have shown the utility of meta-[^{123}I]-iodobenzylguanidine (MIBG) myocardial scintigraphy in assessing the sympathetic cardiac nerve terminals in PD patients with a decreased cardiac MIBG uptake in comparison with other parkinsonian syndrome patients in whom the MIBG uptake is normal [12]. Because these molecular imaging tools are limited in terms of their test accuracy (TA), the use of either DAT SPECT or MIBG scintigraphy alone is insufficient for distinguishing PD from non-PD [13].

In this retrospective study, we compared the results of SPECT studies of striatal DAT receptors and myocardial MIBG scintigraphy with the clinical diagnoses in 34 patients with suspected parkinsonian syndromes to evaluate the diagnostic accuracy and usefulness of combined SPECT imaging in the same patient population.

Materials and methods

Thirty-four patients (male/female: 19/15, mean age: 62.1 ± 13.7 years, age range: 31–81 years), who underwent both [^{123}I]-MIBG scintigraphy and DAT SPECT within a 4-month period for a differential diagnosis between PD and other parkinsonian syndromes were consecutively enrolled in this retrospective study, which was carried out from April 2014 until June 2016. Because many patients underwent two tests during a period ranging from 3 to 4 months at our hospital, we established a 4-month interval between the tests. The study was approved by the Institutional Ethics Committee and all procedures were in accordance with the ethical standards on human investigation and with the principles of the Declaration of Helsinki. All of the patients underwent molecular in-vivo brain and cardiac diagnostic examinations, which consisted of presynaptic striatal DAT scintigraphy with FP-CIT and the assessment of myocardial sympathetic innervation with MIBG. The final diagnosis was made by the neurologists of Tokushima University Hospital, Department of Neurology, who carefully assessed the medical history and symptoms, the possible response to dopaminergic treatment, and the diagnostic MRI findings. Fifteen patients were diagnosed with PD according to the UK Brain Bank criteria [14]. Furthermore, five patients were diagnosed with probable MSA-P according to the established criteria [15,16] and two patients fulfilled the National Institute of Neurologic Disorders and Stroke criteria for probable PSP [17].

DAT SPECT imaging and the SBR analysis

The brain SPECT scans were acquired according to the European Association of Nuclear Medicine procedure guidelines for brain neurotransmission SPECT using [^{123}I]-labeled DAT ligands (FP-CIT, DaTSCAN; Nihon Medi-Physics Co. Ltd, Tokyo, Japan) [18]. After an injection of ~167 MBq of DaTSCAN, the projection data were obtained in a 128 × 128 matrix on a ECAM, Toshiba (Toshiba Medical Systems Corp., Tochigi, Japan) (15 April 2014–14 April 2015), or Symbia T16, Siemens (Siemens Healthcare, Erlangen, Germany) (15 April 2015–30 July 2016) mounted with low-energy to medium-energy general-purpose collimators. The projection data were acquired for 28 min. The data were reconstructed using the filtered back projection method without attenuation and scatter correction from 15 April 2014 to 14 April 2015. The data were reconstructed by the ordered subset expectation maximization method (iteration 12, subset 6) using a Syngo MIVA10C with the Symbia Net software program (Siemens AG, Munich, Germany) and corrected for attenuation by computed tomography and the triple energy window scatter correction method from 15 April 2015 to 30 July 2016. The specific binding ratio (SBR) was calculated semiquantitatively using the DAT VIEW software program (Nihon Medi-Physics, Tokyo, Japan) on the basis of Bolt's method as described in detail elsewhere [19]. For the quantitative analysis, irregular regions of interest (ROIs) were drawn on single-slice views in areas corresponding to the left and right striata on either side. Although DAT SPECT in PD typically shows an asymmetric loss of DAT binding (most prominent in the putamen), the tracer uptake is more symmetric in MSA [20] and PSP [21]. In one report of pathology-confirmed PD and MSA cases with a similar disease duration [22,23], visual inspection and a semiquantitative analysis with DAT SPECT detected a bilateral reduction in striatal DAT binding in all patients, but the trend toward greater asymmetric binding was greater in MSA than in PD. For this study, we adopted the average value of the right and left SBRs as the SBR.

Cardiac imaging: [^{123}I]-MIBG myocardial scintigraphy

After the patient had rested for 15 min in the supine position, 111 MBq of [^{123}I]-MIBG (MyoMIBG; Fuji RI Pharma, Tokyo, Japan) was injected intravenously. Early and delayed SPECT were performed at 15 min and 3 h after the injection, respectively. Planar imaging for 5 min in the anterior projection was performed automatically during SPECT. Planar scanning and SPECT were performed using a dual-head gamma camera equipped with a low-energy to medium-energy general purpose parallel-hole collimator (Toshiba ECAM). The relative organ uptake was determined by setting the ROI on the anterior view.

The heart to mediastinum (H/M) ratio was calculated by dividing the count density of the left ventricular ROI by that of the mediastinal ROI, according to the standard method, which has been described previously [23, 24]. The H/M ratios calculated from the ROI counts obtained by delayed SPECT were used for the comparison study because delayed scans show the neuronal uptake of MIBG more explicitly [24].

Statistical analysis

The values were expressed as mean ± SD and were analyzed using Student's *t*-test and χ^2-test. *P* values of less than 0.05 were considered to indicate a statistically significant difference between PD and non-PD groups. The sensitivity and specificity of the respective diagnostic index (H/M ratios of the MIBG uptake in the delayed phase, SBR on DAT SPECT, and combined DAT SPECT and MIBG myocardial scintigraphy) for differentiation between PD and non-PD were assessed using a receiver-operating characteristic (ROC) analysis. For the combined use of DAT SPECT and MIBG myocardial scintigraphy, the cutoff delayed-phase H/M and SBR values were 2.745 and 3.24, respectively. The statistical analyses were carried out using the SPSS software program (IBM SPSS Statistics, version 23; IBM Corp., Armonk, New York, USA). The group data are presented as mean ± SD. The normality of the data distribution was assessed using the Shapiro–Wilk test. The Mann–Whitney *U*-test was used for the comparison of non-normally distributed data. Differences with a *P* value of less than 0.05 were considered to be biologically significant. The analysis of the descriptive statistics and basic comparisons were carried out using the SPSS software program.

The sensitivity and specificity of the respective diagnostic index (the H/M ratios of the MIBG uptake in the delayed phase, SBR on DAT SPECT, and combined DAT SPECT and MIBG myocardial scintigraphy) for the differentiation between PD and non-PD were assessed in a ROC analysis. We also calculated the specificity, sensitivity, positive predictive value, negative predictive value, and TA of the combination of the two methods using the cutoff value for their combination.

Results

Table 1 shows the characteristics of the patients. Although there was no significant difference in the age of the patients in the two groups, a statistically significant difference was observed in the male-to-female ratio.

The mean H/M ratio of the MIBG uptake in the delayed phase (2.19 ± 0.55 vs. 2.44 ± 0.80, cutoff = 2.745, $P = 0.025$) was significantly lower in the PD patients than in the non-PD patients; however, the mean SBR (2.46 ± 0.87 vs. 2.94 ± 1.40, cutoff = 3.24, $P = 0.08$) did not differ to a statistically significant extent (Table 1 and Fig. 1). ROC analyses were used to set the cutoff SBR value (in DAT SPECT) and the H/M ratio (in delayed scanning) in MIBG scintigraphy for differentiating PD from non-PD (Fig. 2). In the comparison with the separate use of the SBR and the delayed H/M ratio, the combined use of the two semiquantitative analyses using cutoff values of less than 3.24 and less than 2.745, respectively, allowed for more accurate differentiation between PD and non-PD. The sensitivity and specificity of SBR were 86.7 and 52.6%, respectively (Table 2). The sensitivity and specificity of the delayed H/M ratio on MIBG scintigraphy were 93 and 47%, respectively. The accuracy of these analyses in differentiating between PD and non-PD was the same using each of the molecular methods (DAT SPECT, 67.6%; MIBG scintigraphy, 67.6%). In comparison with the SBR and delayed H/M ratio, the combined use of two semiquantitative analyses enabled PD and non-PD to be differentiated more accurately (cutoff values: SBR < 3.24; delayed H/M ratio < 2.745). These indices distinguished PD from non-PD with a sensitivity of 86.7%, a specificity of 73.7%, an accuracy of 79.4%, a positive predictive value of 72.2%, and a negative predictive value of 87.5% (Table 2).

Table 1 The demographic and clinical features of the PD and non-PD patients

	PD	Non-PD	*P* value
N	15	19	
Age (years)	61.5 ± 13.6	62.6 ± 14.2	0.471[a]
Male : female	6 : 9	13 : 6	0.047[b]
Age (range) (years)	34–80	31–81	
Delayed H/M	2.19 ± 0.55	2.44 ± 0.80	0.025[a]
SBR	2.46 ± 0.87	2.94 ± 1.40	0.08[a]

H/M, heart to mediastinum ratio in MIBG scintigraphy; non-PD, degenerative parkinsonian syndrome other than PD; PD, Parkinson's disease; SBR, specific binding ratio.
[a]Student's *t*-test.
[b]χ^2-test.

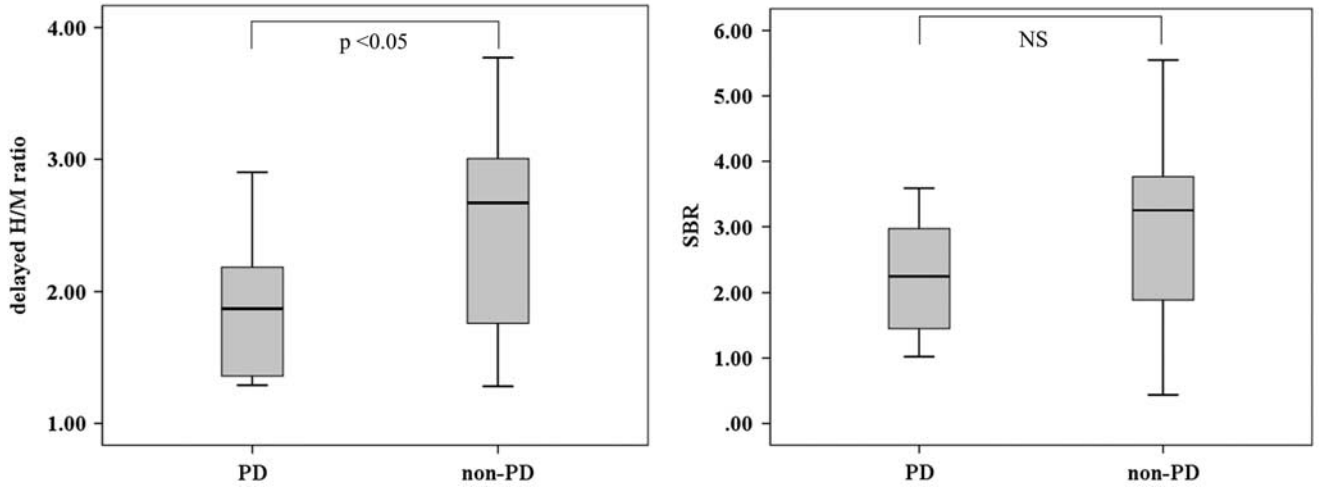
Discussion

This retrospective study investigated the extent to which the combined use of MIBG scintigraphy and DAT SPECT may improve diagnostic accuracy in differentiation between PD and non-PD. The analysis showed that the individual molecular approaches had a mild TA in differentiating between PD and non-PD (MIBG scintigraphy, 62%; FP-CIT SPECT, 69%). In agreement with previous studies [25,26], we confirmed that the combined use of DAT SPECT and MIBG scintigraphy was more useful for differentiating between PD from non-PD in comparison with the use of either method alone.

Striatal DAT SPECT

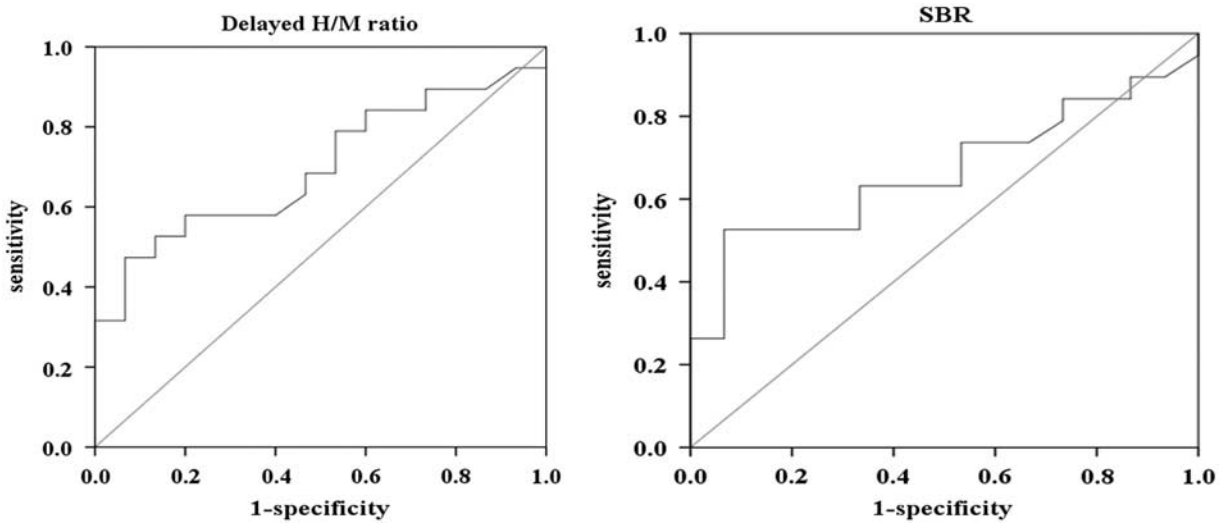
Presynaptic DAT imaging can be evaluated by many SPECT and PET tracers [3,27]. DAT SPECT is therefore very popular in the clinical setting and enables highly accurate differentiation between degenerative parkinsonian syndromes and movement disorders that are not associated with a dopamine deficit [7–9]. According to

Fig. 1



Box plots of the striatal FP-CIT and cardiac delayed MIBG accumulation in the PD and non-PD patients. The box plots show the striatal FP-CIT and cardiac delayed MIBG accumulation in the PD and non-PD patients. The bold lines represent the median values. Whiskers represent the minimum and maximum values. There was a statistically significant difference in the delayed H/M ratios of the PD and non-PD groups. The SBR values of the two groups did not differ to a statistically significant extent. FP-CIT, *N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)-nortropane; H/M, heart to mediastinum ratio; MIBG, meta-[^{123}I]-iodobenzylguanidine; non-PD, degenerative parkinsonian syndrome other than PD; PD, Parkinson's disease; SBR, specific binding ratio.

Fig. 2



The receiver-operating characteristic curves of the delayed H/M ratio and SBR. Delayed H/M ratio: AUC = 0.698; cutoff value = 2.745; sensitivity = 0.93; specificity = 0.47. SBR: AUC = 0.667; cutoff value = 3.24; sensitivity = 0.867; specificity = 0.526. AUC, area under the curve; H/M, heart to mediastinum ratio; SBR, specific binding ratio.

Plotkin, the resulting accuracy, sensitivity, and specificity of FP-CIT SPECT in the detection of PD and non-PD were 94, 93, and 100%, respectively [28]. However, the loss of dopaminergic neurons in the substantia nigra and the reduction of striatal dopamine projections are histopathological characteristics that are common to the degenerative parkinsonian syndromes and the low accumulation of striatal DAT shows a moderate TA in differentiating PD from non-PD. DAT SPECT imaging does not help to differentiate between the neurodegenerative

Table 2 The statistical parameters that were evaluated when investigating the combined use of FP-CIT SPECT and MIBG scintigraphy in differentiating PD from non-PD

	PD ($n=15$)	Non-PD ($n=19$)	Total
Delayed H/M ratio ≥ 2.745	1	9	10
Delayed H/M ratio < 2.745	14	10	24
Total	15	19	34
Sensitivity	9/10 = 0.9	–	–
Specificity	14/24 = 0.583	–	–
Positive predictive value	14/15 = 0.93	–	–
Negative predictive value	9/19 = 0.47	–	–
Test accuracy	(14 + 9)/34 = 23/34 = 0.676	–	–
SBR ≥ 3.24	2	10	12
SBR < 3.24	13	9	22
Total	15	19	34
Sensitivity	10/12 = 0.833	–	–
Specificity	13/22 = 0.591	–	–
Positive predictive value	13/15 = 0.867	–	–
Negative predictive value	10/19 = 0.526	–	–
Test accuracy	(13 + 10)/34 = 23/34 = 0.676	–	–
Other than the following	2	14	16
SBR < 3.24 and delayed H/M < 2.745	13	5	18
Total	15	19	34
Sensitivity	4/16 = 0.875	–	–
Specificity	13/18 = 0.722	–	–
Positive predictive value	13/15 = 0.867	–	–
Negative predictive value	14/19 = 0.737	–	–
Test accuracy	(13 + 14)/34 = 27/34 = 0.794	–	–

FP-CIT, *N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)-nortropane; H/M, heart to mediastinum ratio; MIBG, meta-[^{123}I]-iodobenzylguanidine; non-PD, degenerative parkinsonian syndrome other than PD; PD, Parkinson's disease; SBR, specific binding ratio; SPECT, single-photon emission computed tomography.

parkinsonian disorders [3]. The sensitivity (86.7%) and specificity (52.6%) that were observed in the present study were consistent with previous studies [10,20,29,30].

The cardiac MIBG uptake

In our study, the sensitivity and specificity in differentiating PD from non-PD using the H/M ratio of the MIBG uptake were 93 and 47%, respectively. The usefulness of MIBG myocardial scintigraphy in the diagnosis of DLB was suggested recently in a meta-analysis. The sensitivity and specificity of MIBG scintigraphy in the differential diagnosis between PD and other parkinsonian syndromes ranged from 71 to 100% and from 50 to 100%, respectively, with pooled estimates of 88% (95% confidence interval: 86–90%) and 85% (95% confidence interval: 81–88%) [5]. The specificity observed in the present study was lower than expected. In terms of the diagnostic performance, MIBG scintigraphy is usually a sensitive, but not specific, test for PD [5]. There might be several reasons for this. As the myocardial [^{123}I]-MIBG uptake in patients with non-PD (especially in patients with MSA and PSP) is often found to be slightly reduced in comparison with healthy controls [31], [^{123}I]-MIBG scintigraphy may yield some false-positive results in patients with MSA and PSP. The myocardial sympathetic nervous system of MSA patients typically shows mild degeneration [32]; thus, false-positive results may account for this scintigraphic finding. In addition to LBD-related postganglionic sympathetic degeneration, false-positive results on [^{123}I]-MIBG scintigraphy may also occur because of age-related degeneration because the myocardial [^{123}I]-MIBG uptake has been reported to decrease significantly with age [30,33].

The investigation of the combined use of striatal DAT SPECT and cardiac MIBG uptake

The combination of dopaminergic and sympathetic scintigraphic imaging tests for differentiating between PD and non-PD has been explored by other authors [25,26,28,30,34]. Some studies showed the complementary role of [^{123}I]-MIBG scintigraphy and DAT SPECT in the differential diagnosis between PD and non-PD [25,34]. A recent study showed that [^{123}I]-FP-CIT SPECT presents high sensitivity in the diagnosis of Lewy body disease; thus, [^{123}I]-MIBG scintigraphy may play a complementary role in the differential diagnosis between PD and other parkinsonism [30]. In the present study, we therefore explored the extent to which the combination of these two tracers would improve the TA. Our data show that by combining FP-CIT SPECT and MIBG scintigraphy, the TA can be increased to 79.4%. Our data are in agreement with the results of previous studies [25,26,28,30,34].

Limitations

This study is associated with several critical limitations. First, this study was carried out in a single university hospital; thus, the study population was small. Second, the clinical diagnosis was used as the gold standard in our study because of the absence of histopathological confirmation; thus, the clinical diagnosis may have been incorrect in some cases. Third, before a molecular examination is performed, it is necessary to establish an appropriate withdrawal period in which to cease the

administration of interfering drugs – by considering their biological half-lives. We did not cease the administration of these interfering drugs.

Conclusion

The combination of DAT SPECT and MIBG myocardial scintigraphy may improve the sensitivity of the diagnosis of PD. In particular, this approach is based on commercially available radiotracers and can therefore be used in clinical practice without short-lived PET tracers. The sample size of the present study was small and the study was carried out in a single center. The results should therefore be confirmed in a multicenter study with a large population of pathologically diagnosed patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Orimo S, Suzuki M, Inaba A, Mizusawa H. 123 I-MIBG myocardial scintigraphy for differentiating Parkinson's disease from other neurodegenerative parkinsonism: a systematic review and meta-analysis. *Parkinsonism Relat Disord* 2012; **18**:494–500.

2 Raffel DM, Koeppe RA, Little R, Wang CN, Liu S, Junck L, *et al*. PET measurement of cardiac and nigrostriatal denervation in Parkinsonian syndromes. *J Nucl Med* 2006; **47**:1769–1777.

3 Kägi G, Bhatia KP, Tolosa E. The role of DAT-SPECT in movement disorders. *J Neurol Neurosurg Psychiatry* 2010; **81**:5–12.

4 Seibyl JP, Marek K, Sheff K, Zoghbi S, Baldwin RM, Charney DS, *et al*. Iodine-123-beta-CIT and iodine-123-FPCIT SPECT measurement of dopamine transporters in healthy subjects and Parkinson's patients. *J Nucl Med* 1998; **39**:1500–1508.

5 Chung EJ, Kim SJ. (123)I-metaiodobenzylguanidine myocardial scintigraphy in lewy body-related disorders: a literature review. *J Mov Disord* 2015; **8**:55–66.

6 Tissingh G, Booij J, Bergmans P, Winogrodzka A, Janssen AG, van Royen EA, *et al*. Iodine-123-N-omega-fluoropropyl-2beta-carbomethoxy-3beta-(4-iodophenyl)tropane SPECT in healthy controls and early-stage, drug-naive Parkinson's disease. *J Nucl Med* 1998; **39**:1143–1148.

7 Benamer TS, Patterson J, Grosset DG, Booij J, de Bruin K, van Royen E, *et al*. Accurate differentiation of parkinsonism and essential tremor using visual assessment of [^{123}I]-FP-CIT SPECT imaging: the [^{123}I]-FP-CIT study group. *Mov Disord* 2000; **15**:503–510.

8 Booij J, Speelman JD, Horstink MW, Wolters EC. The clinical benefit of imaging striatal dopamine transporters with [^{123}I]FP-CIT SPET in differentiating patients with presynaptic parkinsonism from those with other forms of parkinsonism. *Eur J Nucl Med* 2001; **28**:266–272.

9 Lorberboym M, Djaldetti R, Melamed E, Sadeh M, Lampl Y. ^{123}I-FP-CIT SPECT imaging of dopamine transporters in patients with cerebrovascular disease and clinical diagnosis of vascular parkinsonism. *J Nucl Med* 2004; **45**:1688–1693.

10 Pirker W, Asenbaum S, Bencsits G, Prayer D, Gerschlager W, Deecke L, *et al*. [^{123}I]beta-CIT SPECT in multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration. *Mov Disord* 2000; **15**:1158–1167.

11 Orimo S, Ozawa E, Nakade S, Sugimoto T, Mizusawa H. ^{123}I-metaiodobenzylguanidine myocardial scintigraphy in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1999; **67**:189–194.

12 Lee PH, Kim JS, Shin DH, Yoon SN, Huh K. Cardiac 123I-MIBG scintigraphy in patients with drug induced parkinsonism. *J Neurol Neurosurg Psychiatry* 2006; **77**:372–374.

13 Suchowersky O, Reich S, Perlmutter J, Zesiewicz T, Gronseth G, Weiner WJ. Quality Standards Subcommittee of the American Academy of Neurology. Practice Parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006; **66**:968–975.

14 Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992; **55**:181–184.

15 Gilman S, Low PA, Quinn N, Albanese A, Ben-Shlomo Y, Fowler CJ, *et al*. Consensus statement on the diagnosis of multiple system atrophy. *J Neurol Sci* 1999; **163**:94–98.

16 Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, *et al*. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* 2008; **71**:670–676.

17 Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, *et al*. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology* 1996; **47**:1–9.

18 Darcourt J, Booij J, Tatsch K, Varrone A, Vander Borght T, Kapucu OL, *et al*. EANM procedure guidelines for brain neurotransmission SPECT using (123) I-labelled dopamine transporter ligands, version 2. *Eur J Nucl Med Mol Imaging* 2010; **37**:443–450.

19 Tossici-Bolt L, Hoffmann SM, Kemp PM, Mehta RL, Fleming JS. Quantification of [^{123}I]FP-CIT SPECT brain images: an accurate technique for measurement of the specific binding ratio. *Eur J Nucl Med Mol Imaging* 2006; **33**:1491–1499.

20 Varrone A, Marek KL, Jennings D, Innis RB, Seibyl JP. [(123)I]beta-CIT SPECT imaging demonstrates reduced density of striatal dopamine transporters in Parkinson's disease and multiple system atrophy. *Mov Disord* 2001; **16**:1023–1032.

21 Filippi L, Manni C, Pierantozzi M, Brusa L, Danieli R, Stanzione P, *et al*. ^{123}I-FP-CIT in progressive supranuclear palsy and in Parkinson's disease: a SPECT semiquantitative study. *Nucl Med Commun* 2006; **27**:381–386.

22 Perju-Dumbrava LD, Kovacs GG, Pirker S, Jellinger K, Hoffmann M, Asenbaum S, *et al*. Dopamine transporter imaging in autopsy-confirmed Parkinson's disease and multiple system atrophy. *Mov Disord* 2012; **27**:65–71.

23 Yoshita M, Taki J, Yamada M. A clinical role for [(123)I]MIBG myocardial scintigraphy in the distinction between dementia of the Alzheimer's-type and dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry* 2001; **71**:583–588.

24 Braune S, Reinhardt M, Schnitzer R, Riedel A, Lücking CH. Cardiac uptake of [^{123}I]MIBG separates Parkinson's disease from multiple system atrophy. *Neurology* 1999; **53**:1020–1025.

25 Südmeyer M, Antke C, Zizek T, Beu M, Nikolaus S, Wojtecki L, *et al*. Diagnostic accuracy of combined FP-CIT, IBZM, and MIBG scintigraphy in the differential diagnosis of degenerative parkinsonism: a multidimensional statistical approach. *J Nucl Med* 2011; **52**:733–740.

26 Spiegel J, Möllers MO, Jost WH, Fuss G, Samnick S, Dillmann U, *et al*. FP-CIT and MIBG scintigraphy in early Parkinson's disease. *Mov Disord* 2005; **20**:552–561.

27 Ba F, Martin WR. Dopamine transporter imaging as a diagnostic tool for parkinsonism and related disorders in clinical practice. *Parkinsonism Relat Disord* 2015; **21**:87–94.

28 Plotkin M, Amthauer H, Klaffke S, Kühn A, Lüdemann L, Arnold G, *et al*. Combined ^{123}I-FP-CIT and ^{123}I-IBZM SPECT for the diagnosis of parkinsonian syndromes: study on 72 patients. *J Neural Transm (Vienna)* 2005; **112**:677–692.

29 [No authors listed]. A multicenter assessment of dopamine transporter imaging with DOPASCAN/SPECT in parkinsonism. Parkinson Study Group. *Neurology* 2000; **55**:1540–1547.

30 Treglia G, Cason E, Cortelli P, Gabellini A, Liguori R, Bagnato A, *et al*. Iodine-123 metaiodobenzylguanidine scintigraphy and iodine-123 ioflupane single photon emission computed tomography in Lewy body diseases: complementary or alternative techniques? *J Neuroimaging* 2014; **24**:149–154.

31 Yoshita M. Differentiation of idiopathic Parkinson's disease from striatonigral degeneration and progressive supranuclear palsy using iodine-123 meta-iodobenzylguanidine myocardial scintigraphy. *J Neurol Sci* 1998; **155**:60–67.

32 Orimo S, Kanazawa T, Nakamura A, Uchihara T, Mori F, Kakita A, *et al*. Degeneration of cardiac sympathetic nerve can occur in multiple system atrophy. *Acta Neuropathol* 2007; **113**:81–86.

33 Estorch M, Carrió I, Berná L, López-Pousa J, Torres G. Myocardial iodine-labeled metaiodobenzylguanidine 123 uptake relates to age. *J Nucl Cardiol* 1995; **2**:126–132.

34 Novellino F, Arabia G, Bagnato A, Cascini GL, Salsone M, Nicoletti G, *et al*. Combined use of DAT-SPECT and cardiac MIBG scintigraphy in mixed tremors. *Mov Disord* 2009; **24**:2242–2248.