Combined Use of 123i-fp-cit Spect and 123i-mibg Scintigraphy for Differentiation of Progressive Supranuclear Palsy Subtypes and Parkinson's Disease

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Abstract

Background:

This study was undertaken to investigate the utility of $^{123}$I-ioflupane ($^{123}$I-FP-CIT) single photon emission computed tomography (SPECT), $^{123}$I-metaiodobenzylguanidine ($^{123}$I-MIBG) scintigraphy and both of these to differentiate among progressive supranuclear palsy (PSP), including typical cases and other subtypes, and Parkinson’s disease (PD).

Methods:

Twenty-five patients with typical PSP (Richardson’s syndrome; PSP-RS), 14 atypical ones (PSP-variants; PSP-V) and 42 PD who underwent both $^{23}$I-FP-CIT SPECT and $^{123}$I-MIBG scintigraphy within short intervals were enrolled. Specific binding ratio (SBR) of the striatum and midbrain and anteroposterior and asymmetry ratio of the striatal SBR on $^{123}$I-FP-CIT SPECT and heart-to-mediastinum (H/M) ratio and washout rate (WR) on $^{123}$I-MIBG scintigraphy were used as quantitative measures. The classifier performance based on adaptive boosting was evaluated using five-fold cross-validation for these measures.

Results:

Midbrain SBR and the striatal anteroposterior ratio were statistically lower in PSP-RS than PD. On the other hand, there were no significant differences in any other quantitative measures among PSP-RS, PSP-V and PD. Striatal and midbrain SBRs and anteroposterior ratio of PSP-V were approximately in-between those of PSP-RS and PD. PD showed the lowest early and delayed H/M ratios and highest WR of any group. The combination of $^{123}$I-FP-CIT and $^{123}$I-MIBG was useful in discriminating PSP-RS and PSP-V from PD, while $^{123}$I-FP-CIT was superior to $^{123}$I-MIBG in differentiating PSP-RS from PSP-V.

Conclusion:

The combination of $^{123}$I-FP-CIT SPECT and $^{123}$I-MIBG scintigraphy, rather than either alone, may be a useful differential diagnostic tool to differentiate patients with PSP-RS, PSP-V and PD.

Background

Progressive supranuclear palsy (PSP) is a distinctive neurodegenerative disease characterized by various neurological symptoms including progressive vertical gaze palsy, prominent postural instability, akinesia, axial rigidity, frontal cognitive dysfunction and a poor response to levodopa therapy. However, these classical symptoms of PSP are not always observed in all cases with pathologically confirmed PSP. Recently, it has been recognized that PSP comprises both typical cases and various clinical subtypes with atypical clinical courses such as levodopa-responsive parkinsonism, pure akinesia with gait freezing, corticobasal syndrome, and non-fluent aphasia [1]. Although the accurate diagnosis of this disorder is
important for deciding on treatments and management, accurate differentiation between PSP clinical subtypes other than the typical Richardson's syndrome and Parkinson's disease (PD) is often difficult because of the similarities in their neurological symptoms and lack of reliable disease-specific biomarkers in the early stages [2, 3, 4]. Because appropriate clinical distinction among typical PSP, other PSP subtypes and PD has implications for prognosis, disease progression, and caregiver burden, it is valuable to attempt a differentiation among typical PSP, other PSP subtypes and PD based on objective methods other than the neurological symptoms and findings alone [5].

The lack of specific structural imaging findings such as midbrain atrophy in the field of imaging diagnosis, especially in cases with early stage PSP, highlights the need for sensitive functional imaging techniques to improve the diagnostic accuracy. Indeed, dopamine transporter (DAT) and serotonin transporter (SERT) imaging on single photon emission computed tomography (SPECT) is already being performed to differentiate PSP from PD [6, 7, 8, 9, 10]. These techniques delineate different aspects of the neurodegeneration and add some value to diagnose PSP including its subtypes [11, 12]. However, presynaptic nigrostriatal degeneration is not a specific pathological change. Therefore, DAT imaging is of limited value in differentiating between PSP and PD [13]. On the other hand, more specific techniques including $^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy, which can detect degeneration of the cardiac sympathetic system, are necessary to differentiate PSP from PD [14]. Similarly, the usefulness of the combination of DAT and cardiac sympathetic imaging has been reported in patients with parkinsonian syndrome [15, 16]. Nevertheless, the utility of combination of DAT and cardiac sympathetic imaging has not been evaluated in PSP subtypes and PD patients. Considering the inhomogeneous and misleading neurological symptoms associated with the diverse pathological tau burden and distribution in the substantia nigra in PSP, it is plausible to hypothesize that the combination of DAT, SERT and cardiac sympathetic imaging would be useful in differentiating typical PSP, other clinical subtypes and PD. The aim of the present study was to investigate whether the combination of DAT, SERT and cardiac sympathetic imaging using $^{123}$I-ioflupane ($^{123}$I-FP-CIT) SPECT and $^{123}$I-MIBG scintigraphy can offer useful clues to differentiate among PSP, including typical cases and other subtypes, and PD.

**Materials And Methods**

**Subjects**

This was a retrospective study that evaluated the diagnostic value of $^{123}$I-FP-CIT SPECT for differentiating PSP, including stereotype and subtypes, and PD patients. This study used data obtained at a single medical center, and was approved by our Institutional Review Board (IRB). The retrospective nature of this study made it difficult to acquire informed consent from all patients. Therefore, with the permission of IRB, we provided an opportunity for these patients to opt out. The privacy of all patients was completely protected.

Patient backgrounds were standardized by applying the following inclusion criteria: (1) diagnoses of PSP and PD at the Department of Neurology and (2) the acquisition of both $^{123}$I-FP-CIT SPECT and $^{123}$I-MIBG.
scintigraphy within a short interval (less than two weeks for most patients). The diagnosis of PSP including typical cases (Richardson's syndrome; PSP-RS) and other subtypes (PSP-variants; PSP-V) was based on the current diagnostic criteria [1, 17, 18, 19]. PD patients were diagnosed on the basis of the criteria set by the United Kingdom Parkinson's Disease Society Brain Bank [20]. Exclusion criteria were insufficient quality of the $^{123}$I-FP-CIT SPECT images and failure of image analyses due to the presence of significantly abnormal findings (e.g., large cerebral infarctions or hemorrhages). All patients were evaluated clinically, tested for L-dopa responses, and examined with SPECT between April 2014 and March 2017. Thirty-nine PSP (mean age, 73 ± 7 years; 28 men and 11 women) and 42 PD (mean age, 75 ± 7 years; 19 men and 23 women) patients were enrolled.

$^{123}$I-FP-CIT SPECT imaging and volume of interest analysis

SPECT imaging was performed four hours after an intravenous injection of 167 MBq $^{123}$I-FP-CIT (DaTSCAN®; Nihon Medi-Physics, Tokyo, Japan) on a dual-head gamma camera system PRISM-AXIS (SHIMADZU Co., Kyoto, Japan), equipped with low-energy, high-resolution, and parallel-hole collimators. Energy windows were set at 140 keV ± 20%, and 90 views were obtained throughout 360 degrees of rotation (128 × 128 matrix, 3.0 mm/pixel). Data processing was performed on an ODYSSEY FX PRISM-AXIS (SHIMADZU Co., Kyoto, Japan). All images were reconstructed using OSEM (iteration 3, subset 15) and then 3D smoothed with a Butterworth filter (order 8, cut-off 0.3 cycles/pixel). The brain volume was resliced after reorienting the axial planes along the anterior-posterior commissural line, and axial sections of 3.0 mm in thickness were produced.

To perform the volume of interest (VOI) analyses, image processing was performed with Statistical Parametric Mapping (SPM) 8 (Welcome Department of Cognitive Neurology, University College, London, UK) implemented in MATLAB version R2010a (The MathWorks, Inc., Natick, MA). $^{123}$I-FP-CIT SPECT images of all PSP and PD patients were spatially normalized onto this in-house-made $^{123}$I-FP-CIT SPECT template, as described previously, in the Montreal Neurological Institute (MNI) space [21]. The final image format was 16-bit, with a size of 79 × 95 × 68 and voxel size of 2 × 2 × 2 mm.

To evaluate the striatal binding, bilateral striatal VOIs were created using an in-house-made $^{123}$I-FP-CIT SPECT template and MRICron (https://www.nitrc.org/projects/mricron). Considering previous studies that reported posterior dominant binding reduction in PD and uniform binding reduction in PSP, bilateral striatal VOIs were divided into anterior and posterior VOIs [22]. According to studies that reported lower SERT midbrain binding in PSP patients, the midbrain VOI was obtained with WFU PickAtlas tool in SPM8 [8, 9, 23]. Additionally, the bilateral occipital lobes were selected as a reference region. After spatial normalization and VOI placement, the presence of misregistration was visually evaluated. Specific–to–nonspecific binding ratios (SBR) in the targeting region (i.e., striatum and midbrain) were defined as (mean counts of targeting region – mean counts of occipital lobe)/(mean counts of occipital lobe) [24]. Additionally, the anterior-to-posterior striatal ratio (StAP), which represented anterior striatal counts/posterior striatal counts, and asymmetry striatal ratio (StAS), which represented the less affected
side striatal counts/more affected side striatal counts, were also calculated to evaluate the anteroposterior and asymmetry indices of the striatum according to the previously reported method.

**123 I-MIBG myocardial scintigraphy and region of interest analysis**

Early and delayed static images with a 128 x 128 matrix were obtained at 20 minutes and 4 hours after intravenous injection of 111 MBq of 123I-MIBG, respectively. Planar images were obtained using the same dual-head gamma camera system, equipped with low-energy, general-purpose, and parallel-hole collimators. Regions of interest (ROI) were drawn manually around the whole heart and mediastinum. According to the standard method described previously, the heart-to-mediastinum (H/M) ratio was calculated from the average counts per pixel in the heart and mediastinum [25]. The washout rate (WR), which is an index of the rate at which MIBG is washed out between the early and delayed images, was also calculated according to the following formula: WR = [(early heart counts – early mediastinal counts) – (delayed heart counts – delayed mediastinal counts)]/(early heart counts – early mediastinal counts) x 100. For the comparison study, early and delayed H/M ratios and WR were used for analysis.

**Machine Learning**

All machine learning processes and statistical analyses were performed in the Python environment (version 3.7.3) by using the scikit-learn (version 0.19.1) and SciPy (version 1.2.1) [26]. A classifier algorithm based on adaptive boosting (called AdaBoost) was trained to evaluate the ability to discriminate between each type of pathological condition [27]. The AdaBoost classifier is a decision stump-based ensemble classifier that has advantages of algorithm transparency, robust discrimination ability, and a built-in feature selection process. The algorithm adaptively seeks the optimal combination of weak classifiers and weights assigned to each weak classifier. During each iteration, the algorithm selects weak classifiers to minimize the training error (sum of the misclassified sample weights) and down-weights correctly classified samples. Subsequently, the algorithm selects weak classifiers sensitive to misclassified samples during previous iterations based on sample weights until the performance of the classifier reaches a plateau. Based on the result of our experimental studies, the parameter of the classifier was used as n_estimators = 100.

**Classification Performance Evaluation**

A patient-stratified five-fold cross-validation scheme was repeated 100 times to mitigate bias towards a particular class and selection and classifier training bias. Predictive performance of the classifier and stability was evaluated by area under the receiver operator curve (AUC) and 95% confidence interval (CI), respectively. AUCs were compared with Mann-Whitney/Wilcoxon U statistics with Bonferroni adjustments.

**Statistical analysis**
Statistical analyses were performed using IBM SPSS statistics 21 (IBM SPSS Inc, Chicago, IL). The Kruskal-Wallis and Mann-Whitney U test for non-normally distributed data (age, gender, disease duration, Hohen-Yahr stage and H/M ratio) and one-way analysis of variance and unpaired $t$-test for normally distributed data (SBR) were performed for comparisons among patient groups. Comparisons of SBR among PSP-RS, PSP-V and PD patients were also performed. When a significant level was found in multiple comparisons, the Mann-Whitney U test or unpaired $t$-test was also performed. After Bonferroni corrections for multiple comparisons, differences were considered significant when $p < 0.016$.

## Results

### Patient backgrounds

Patient characteristics are summarized in Table 1. Of the PSP patients there were 25 with PSP-RS and 14 with PSP-V including eight with progressive gait freezing (PSP-PGF), three with cerebellar ataxia (PSP-C), two with predominant parkinsonism (PSP-P) and one with predominant corticobasal syndrome (PSP-CBS). Of note, PSP related pathological changes were verified in four patients including three PSP-RS and one PSP-CBS cases. No significant differences were observed in age or gender among the PSP-RS, PSP-V, PD groups. There were also no differences in the disease duration among the PSP-RS, PSP-V and PD patients. However, disease severity (Hohen-Yahr stage) of the PSP-RS and PSP-V patients was worse than that of the PD ones ($4.0 \pm 0.9$ for PSP-RS patients vs. $3.1 \pm 1.1$ for PD patients and $3.9 \pm 0.7$ for PSP-V patients vs. $3.1 \pm 1.1$ for PD patients; $p = .0011$ and $p = .0091$, respectively). Typical images of $^{123}$I-FP-CIT SPECT and $^{123}$I-MIBG myocardial scintigraphy in patients with PSP-RS, PSP-V and PD were presented in Fig. 1.

|                      | PSP-RS | PSP-V | PD    | $p$ value |
|----------------------|--------|-------|-------|-----------|
| **Number**           | 25     | 14    | 42    | NA        |
| **Age (years)**      | 73 ± 7.7 | 71 ± 7.1 | 75 ± 7.1 | 0.11      |
| **Male/Female**      | 18/7   | 10/4  | 19/23 | 0.06      |
| **Disease duration at imaging (years)** | 5.1 ± 2.2 | 5.9 ± 5.1 | 7.0 ± 4.5 | 0.32      |
| **Hohen-Yahr stage at imaging** | 4.0 ± 0.9* | 3.9 ± 0.7** | 3.1 ± 1.1 | 0.0011** |

Data are shown as absolute numbers or the mean ± standard deviation.

**Note:**
- NA = not applicable
- PD = Parkinson’s disease
- PSP = progressive supranuclear palsy
- RS = Richardson’s syndrome
- V = variants

**Annotations:**
- *Kruskal-Wallis test
- *$p=0.0011$ vs. PD by Mann-Whitney U test
- **$p=0.0091$ vs. PD by Mann-Whitney U test

Due to Bonferroni’s multiple group comparisons, differences were considered significant when $p < 0.016$. 

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VOI and ROI analyses results

The results of the VOI and ROI analyses are shown in Table 2 and Fig. 2. Despite the low striatal SBR of the PSP-RS patients, there was no significant difference among the PSP-RS, PSP-V and PD patients. Compared with PD, the striatal anteroposterior ratio in PSP-RS was lower (0.92 ± 0.07 in PSP-RS patients vs. 0.98 ± 0.08 in PD patients; \( p = .007 \)). On the other hand, there was no significant difference between the PSP-RS and PSP-V patients (0.92 ± 0.07 in PSP-RS vs. 0.96 ± 0.08 in PSP-V patients; \( p = .11 \)). Similarly, there were no significant differences between PSP-V and PD (PSP-V vs. PD; \( p = .60 \)). There was no significant difference in striatal asymmetry ratio among PSP-RS, PSP-V and PD patients (1.07 ± 0.06 in PSP-RS patients vs. 1.07 ± 0.04 in PSP-V patients vs 1.08 ± 0.06 in PD patients; \( p = .63 \)). The striatal SBR and anteroposterior ratio of PSP-V showed values approximately in-between those of the PSP-RS and PD patients. The midbrain SBR of PSP-RS was lower than that of PD (0.0008 ± 0.10 in PSP-RS patients vs. 0.10 ± 0.12 in PD patients; \( p = .001 \)). Despite the low midbrain SBR in PSP-RS patients, there was no significant difference between PSP-RS and PSP-V (0.0008 ± 0.11 in PSP-RS patients vs. 0.06 ± 0.07 in PSP-V patients; \( p = .033 \)). As well as the striatal SBR and anteroposterior ratio, the midbrain SBR of PSP-V was approximately in-between that of the PSP-RS and PD patients. Early H/M ratio of \(^{123}\)I-MIBG uptake was lowest in the PD patients (1.6 ± 0.3 in PD patients vs. 2.3 ± 0.3 in PSP-RS patients and 1.6 ± 0.3 in PD patients vs. 2.4 ± 0.3 in PSP-V patients; \( p < .0001 \) and \( p < .0001 \), respectively). Delayed H/M ratio of \(^{123}\)I-MIBG uptake was also the lowest in PD patients (1.4 ± 0.2 in PD patients vs. 2.2 ± 0.4 in PSP-RS patients and 1.4 ± 0.2 in PD patients vs. 2.4 ± 0.2 in PSP-V patients; \( p < .0001 \) and \( p < .0001 \), respectively). Furthermore, PD patients revealed the highest WR in all patient groups (33.7 ± 23.6 in PSP-RS patients vs. 32.3 ± 11.3 in PSP-V patients vs 65.3 ± 13.0 in PD patients; \( p < .0001 \)).

![Table 2. Comparison of \(^{123}\)I-FP-CIT and \(^{123}\)I-MIBG indices](image)
Machine learning results

For each pair-wise comparison, three different models were constructed and applied: FP-CIT model using $^{123}$I-FP-CIT imaging metrics only; MIBG model using $^{123}$I-MIBG metrics only; and FP-CIT-MIBG model using both $^{123}$I-FP-CIT and $^{123}$I-MIBG metrics. The diagnostic performance is detailed in Table 3 and Fig. 3.

An excellent ability to distinguish PSP-RS from PD was attained by the FP-CIT-MIBG model with AUC of 0.950 (95% CI, 0.945–0.954). This was followed by the MIBG model with AUC of 0.913 (95% CI, 0.908–0.919) and FP-CIT model with AUC of 0.530 (95% CI, 0.519–0.540). The diagnostic performance of the FP-CIT-MIBG model was superior to that of FP-CIT model ($p < .001$) and MIBG model ($p < .001$). No statistical difference was observed between the performances of FP-CIT-MIBG model and MIBG model. The highest discriminatory ability to distinguish PSP-RS and PSP-V was achieved by FP-CIT model with AUC of 0.721 (95% CI, 0.707–0.736), followed by MIBG model with AUC of 0.617 (95% CI, 0.599–0.636), and FP-CIT-MIBG model with AUC of 0.625 (95% CI, 0.611–0.639). The diagnostic performance of FP-CIT model was superior to that of MIBG model ($p < .05$) and FP-CIT-MIBG model ($p < .001$).

|                         | FP-CIT Model | MIBG Model | FP-CIT-MIBG model |
|-------------------------|--------------|------------|-------------------|
| PSP-RS vs PD            | 0.530 [0.519, 0.540] | 0.913 [0.908, 0.919] | 0.950 [0.945, 0.954] |
| PSP-V vs PD             | 0.570 [0.554, 0.586] | 0.987 [0.983, 0.992] | 0.984 [0.978, 0.990] |
| PSP-RS vs PSP-V         | 0.721 [0.707, 0.736] | 0.617 [0.599, 0.636] | 0.625 [0.611, 0.639] |

| Sensitivity             |             |            |                   |
|-------------------------|--------------|------------|-------------------|
| PSP-RS vs PD            | 0.652 [0.642, 0.661] | 0.900 [0.891, 0.903] | 0.950 [0.945, 0.954] |
| PSP-V vs PD             | 0.212 [0.194, 0.228] | 0.933 [0.925, 0.950] | 0.977 [0.967, 0.987] |
| PSP-RS vs PSP-V         | 0.515 [0.494, 0.536] | 0.453 [0.433, 0.478] | 0.392 [0.372, 0.413] |

| Specificity             |             |            |                   |
|-------------------------|--------------|------------|-------------------|
| PSP-RS vs PD            | 0.390 [0.373, 0.405] | 0.788 [0.780, 0.800] | 0.807 [0.797, 0.817] |
| PSP-V vs PD             | 0.827 [0.817, 0.837] | 0.991 [0.983, 0.992] | 0.991 [0.987, 0.994] |
| PSP-RS vs PSP-V         | 0.797 [0.785, 0.796] | 0.710 [0.694, 0.727] | 0.713 [0.611, 0.639] |

Note. —PD = Parkinson’s disease, PSP = progressive supranuclear palsy, RS = Richardson’s syndrome, V = variants.
Feature metrics were ranked using the best performance classifiers for each pair-wise discrimination (Table 4). These features included 4 FP-CIT features for the comparison between PSP-RS and PSP-V, 4 FP-CIT and 3 MIBG features for the comparison between PD and PSP-RS, and 3 MIBG features for the comparison between PD and PSP-V. Feature importance was normalized with respect to the best predictor.

### Table 4. Important features selected by the machine learning-based models with best performance for each classification analysis

#### PSP-RS vs PD

| Feature Names     | Normalized Gini Importance | 95% Confidence Interval |
|-------------------|-----------------------------|-------------------------|
| Delayed H/M ratio | 0.910                       | 0.900, 0.920            |
| Midbrain SBR      | 0.571                       | 0.552, 0.590            |
| Washout rate      | 0.350                       | 0.375, 0.414            |
| Early H/M ratio   | 0.367                       | 0.349, 0.384            |
| StAS ratio        | 0.295                       | 0.277, 0.312            |
| SIA ratio         | 0.293                       | 0.274, 0.311            |
| Striatal SBR      | 0.241                       | 0.225, 0.257            |

#### PSP-V vs PD

| Feature Names     | Normalized Gini Importance | 95% Confidence Interval |
|-------------------|-----------------------------|-------------------------|
| Delayed H/M ratio | 0.948                       | 0.930, 0.966            |
| Washout rate      | 0.042                       | 0.026, 0.058            |
| Early H/M ratio   | 0.010                       | 0.001, 0.012            |

#### PSP-RS vs PSP-V

| Feature Names     | Normalized Gini Importance | 95% Confidence Interval |
|-------------------|-----------------------------|-------------------------|
| StAP ratio        | 0.894                       | 0.882, 0.906            |
| Striatal SBR      | 0.783                       | 0.770, 0.796            |
| SIA ratio         | 0.700                       | 0.694, 0.708            |
| Midbrain SBR      | 0.610                       | 0.597, 0.624            |

Note.—Feature importance was calculated by averaging normalized Gini importance over 100 trials.

H/M = heart-to-mediasthm, PD = Parkinson's disease, PSP = progressive supranuclear palsy, RS = Richardson's syndrome, V = variants, SBR = specific binding ratio, StAP = striatal anteroposterior, SIA = striatal asymmetry.

### Discussion

This is the first study to evaluate the utility of the combined use of $^{123}$I-FP-CIT SPECT and $^{123}$I-MIBG scintigraphy to differentiate among PSP including various subtypes other than typical Richardson's
syndrome and PD. We found that the combination of $^{123}\text{I}}$-FP-CIT SPECT and $^{123}\text{I}}$-MIBG scintigraphy could offer a valuable clue to differentiate PSP including both PSP-RS and PSP-V from PD. On the other hand, even with the use of VOI analyses results including statistically lower midbrain SBR and striatal anteroposterior ratio, $^{123}\text{I}}$-FP-CIT SPECT exhibited a low discrimination power (FP-CIT model with AUC of 0.530) to differentiate between PSP-RS and PD. Similarly, the discrimination power to differentiate PSP-V from PD was also insufficient (FP-CIT model with AUC of 0.570). These results reconfirm the difficulty in reliably distinguishing PD from other parkinsonian syndromes including PSP on the basis of the DAT imaging results alone [13].

Regarding PSP-RS, the results of the VOI analyses, namely a lower striatal anteroposterior ratio and midbrain SBR as compared with PD, were consistent with those of previous studies [6, 8, 9]. PSP-RS tends to have a more anterior dominant and profound low striatal SBR than that of PD [6]. The reduced midbrain SBR in PSP-RS is another well-known imaging finding [8, 9]. These differences are surmised to reflect a more widespread decline of monoaminergic neurotransmitter systems due to PSP related neuropathologic changes in the brainstem areas containing SERT, DAT or noradrenergic transporter bearing neurons, such as the substantia nigra, locus ceruleus, and raphe nuclei [28, 29, 30].

On the other hand, compared with PSP-RS, PSP-V reveal relatively mild reduction of striatal and midbrain SBR and striatal anteroposterior ratio. To the best of our knowledge, no studies have evaluated the difference in the midbrain SBR between PSP-RS and PSP-V patients. Despite a lack of statistical difference, PSP-RS patients tended to have a lower midbrain SBR than PSP-V patients. Differences in the pathological severity have been recognized to affect both the clinical and radiological findings in PSP patients [31]. Considering the more severe pathological changes of the brainstem noted in PSP-RS than in other subtypes, the assumption of a relatively lower midbrain SBR in PSP-RS patients is reasonable. In contrast to the two studies that reported lower caudate DAT activity impairment to be the key point to differentiate PSP subtypes including PSP-P and PSP-PGF from PD, no statistical differences were apparent between PSP-V and PD in our study [11, 12]. This result would seem to be inconsistent with our VOI analyses. We assumed the major reason for this inconsistency to be the non-uniformity of the PSP subtypes including not only PSP-P and PSP-PGF but also PSP-CBS and PSP-C in this study.

Even with the use of machine learning, to improve the low discrimination power of DAT imaging, it is necessary to use more specific functional imaging techniques to more accurately differentiate PSP from PD [32]. Some studies combining DAT and D2 receptor SPECT have shown that PD can be differentiated from PSP, whereas others have demonstrated otherwise [33, 34, 35]. Taking into account the disease-specificity, a more promising technique would be cardiac sympathetic imaging with $^{123}\text{I}}$-MIBG scintigraphy, which can detect the myocardial adrenergic denervation caused by PD. A previous study combining DAT, D2 receptor and cardiac sympathetic imaging has reported a positive predictive value of 89%, and a negative predictive value of 97% to differentiate degenerative parkinsonism [36].

In this study, the importance of various features was suggested based on the results of the AdaBoost classifier algorithm. Delayed H/M ratio was found to be the most valuable of these in discriminating PSP
from PD. Considering the degeneration of the cardiac sympathetic system in PD patients, it is reasonable to suggest that delayed H/M ratio on $^{123}$I-MIBG scintigraphy is more useful than other indices on $^{123}$I-FP-CIT SPECT to differentiate PSP including both PSP-RS and PSP-V from PD patients [37]. Meanwhile, midbrain SBR is of secondary usefulness in differentiating PSP-RS from PD. This result is also consistent with that of a previous study, in which a marked reduction of SERT in typical PSP patients compared to PD was confirmed [9]. For the differentiation between PSP-RS and PSP-V, striatal anteroposterior and asymmetry ratio and SBR of the striatum and midbrain on $^{123}$I-FP-CIT SPECT have been shown to be of high normalized Gini importance. Previous studies evaluating PSP-V have reported a lower striatal uptake and higher asymmetric index in PSP-P and slightly higher caudate SBR in PSP-PGF than PSP-RS patients [11, 12]. It has recently become apparent that the degree of neuropathological changes is inconsistent in PSP patients. Therefore, it is plausible to ascribe the different distribution of radiotracer uptake on $^{123}$I-FP-CIT SPECT to differences in the degree of neurodegeneration of DAT and SERT in PSP-RS and PSP-V.

The relatively small number of patients, especially PSP clinical subtypes other than PSP-RS, is a limitation of the present study. Due to this, it was difficult to perform statistical analyses in each PSP clinical subtype. Therefore, PSP patients other than PSP-RS were grouped into a single entity as PSP-V. This may have affected the results of the VOI analyses and machine learning. Furthermore, our study may also have been limited by the absence of pathological diagnoses in most cases excluding three PSP-RS and one of the PSP-CBS patients. Considering these limitations, it will be necessary to investigate more cases with PSP clinical subtypes to further clarify the diagnostic value of the combined use of $^{123}$I-FP-CIT SPECT and $^{123}$I-MIBG scintigraphy for the differentiation among PSP-RS, PSP-V and PD patients.

**Conclusion**

Considering the difficulty to differentiate PSP-V from PD and different clinical outcome between PSP-V and PSP-RS, it is important to make an accurate antemortem diagnosis. When it is difficult to differentiate patients with PSP-RS, PSP-V and PD, the combination of $^{123}$I-FP-CIT SPECT and $^{123}$I-MIBG scintigraphy, rather than either of these modalities alone, may be a useful differential diagnostic tool.

**Declarations**

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**Authors’ contributions**

IA, KS and IS designed the study. US, SS, RH, IA and AI contributed to data
acquisition. KS and IS contributed to the data analysis and interpretation. KS performed the statistical analysis. IA, KS and IS contributed to drafting of the manuscript together. The authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

We declare that all human and animal studies have been approved by the Institutional Review Board (IRB) for Clinical Research of the Higashi Nagoya National Hospital, and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The retrospective nature of this study made it difficult to acquire informed consent from all patients. Therefore, with the permission of IRB, we provided an opportunity for these patients to opt out. The privacy of all patients was completely protected.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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Figures
Figure 1

Typical images of 123I-FP-CIT SPECT and delayed 123I-MIBG scintigraphy in patients with PSP-RS, PSP-V and PD (a-c) A 70-year-old man with PSP-RS. Severely decreased uptake of the bilateral striatum (arrowheads, a) and midbrain (arrow, b) on 123I-FP-CIT SPECT and normal myocardial uptake on 123I-MIBG scintigraphy (arrow, c) eight years after the symptom onset. (d-f) A 74-year-old man with PSP-C. Compared with PSP-RS, the degree of bilateral striatum (arrowheads, d) and midbrain (arrow, e) decrease was relatively mild on 123I-FP-CIT SPECT. 123I-MIBG scintigraphy showed normal myocardial uptake (arrow, f) two years after the symptom onset. (g-i) A 79-year-old man with PD. 123I-FP-CIT SPECT showed relatively mild decreased uptake of the bilateral striatum (arrowheads, g) and preserved midbrain (arrow, h). On the other hand, 123I-MIBG scintigraphy revealed severely decreased myocardial uptake (arrow, i) seven years after onset.
Figure 2

Boxplots of 123I-FP-CIT VOI (a-d) and 123I-MIBG ROI (e-g) analyses results. Striatal specific binding ratio (SBR), striatal anteroposterior ratio, striatal asymmetry ratio and midbrain SBR on 123I-FP-CIT SPECT, and early and delayed heart-to-mediastinum ratio and washout rate on 123I-MIBG scintigraphy were compared among PSP-RS, PSP-V and PD patients. The box contains the median values (represented by a horizontal line within the box), 25th and 75th percentiles, and whiskers representing the minimum and maximum data.

Figure 3

Receiver operating characteristic curves for the differentiation among PSP-RS, PSP-V and PD with the use of 123I-FP-CIT SPECT, 123I-MIBG scintigraphy and their combination: (a) PSP-RS vs PD, (b) PSP-V vs PD, (c) PSP-RS vs PSP-V.