The diagnostic value of dopamine transporter imaging and olfactory testing in patients with parkinsonian syndromes

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ABSTRACT

Purpose: To compare the efficacy of olfactory testing and presynaptic dopamine imaging in diagnosing Parkinson's disease (PD) and Atypical Parkinsonian Syndromes (APS); to evaluate if the combination of these two diagnostic tools can improve their diagnostic value.

Methods: A prospective investigation of 24 PD patients, 16 APS patients and 15 patients with non-parkinsonian syndromes was performed during an 18-month period. Single Photon Emission Computed Tomography with the presynaptic radioligand ^{123}I-FP-CIT (DaTSCAN®) and olfactory testing with the Brief 12-item Smell Identification Test (B-SIT) were performed in all patients. DaTSCAN was analysed semi-quantitatively, by calculating two different striatal uptake ratios, and visually according to a predefined ranking scale.

Results: B-SIT score was significantly lower for PD patients, but not significantly different between APS and Non-parkinsonism. The visual assessment of DaTSCAN had higher sensitivity, specificity and diagnostic accuracy compared to olfactory testing. Most PD patients (75%) had visually predominant dopamine depletion in putamen, while most APS patients (56%) had visually severe dopamine depletion both in putamen and in caudate nucleus. The combination of DaTSCAN and B-SIT led to a higher rate of correctly classified patients.

Conclusions: Olfactory testing can distinguish PD from Non-parkinsonism, but not PD from APS or APS from Non-parkinsonism. DaTSCAN is more efficient than olfactory testing and can be valuable in differentiating PD from APS. However, combining olfactory testing and DaTSCAN imaging has a higher predictive value than these two methods separately.

Keywords: Parkinson's disease, Atypical Parkinsonism, Parkinsonian syndromes, olfaction, ^{123}I-FP-CIT SPECT

INTRODUCTION

The clinical diagnosis of Parkinson's disease (PD) is currently based on the presence of cardinal motor features and positive response to dopaminergic therapy [1]. However, it can be difficult to differentiate PD from other parkinsonian syndromes with similar signs and symptoms, especially in the early stages of the disease. Diseases that can imitate the clinical image of PD are grouped as Atypical Parkinsonian Syndromes (APS) or Secondary Parkinsonism (SP) [2] . Despite the similar clinical image of PD and other parkinsonian syndromes in the early stages, prognosis differs significantly [3]. Therefore, a reliable method that can differentiate PD from other parkinsonian syndromes is essential.

In recent years, single photon emission computed tomography (SPECT) with the presynaptic radiotracer ioflupane, also known as DaTSCAN®, has been widely used as a diagnostic test to detect loss of functional dopaminergic neuron terminals in striatum [4]. DaTSCAN imaging has high diagnostic performance in separating patients with PD from patients with non-parkinsonian syndromes [5, 6]. However, the efficacy of DaTSCAN imaging in separating PD from APS has been a matter of controversy [4, 7-10].

Olfactory dysfunction in patients with PD has been confirmed since several years; it occurs in the early stages of the disease and is independent of treatment or age at onset [11-16]. Olfactory function can vary from normal to strongly impaired in APS [17-19]. Olfactory testing is officially recommended by the European Federation of Neurological Societies and the Movement Disorder Society in order to differentiate PD from other parkinsonian disorders [20].

The main objective of this study was to compare DaTSCAN imaging and simple olfactory testing in terms of accuracy and efficacy in diagnosing parkinsonian syndromes. We analysed DaTSCAN SPECT with two different approaches: semi-quantification and visual assessment of DaTSCAN uptake. Moreover, we wanted to assess the diagnostic contribution of the combined results from DaTSCAN imaging and olfactory testing in separating PD from APS.

MATERIALS AND METHODS

This study was conducted in accordance with the current revision of the Declaration of Helsinki and was approved by the Regional Ethical Review Board in Linköping, Sweden (registration number 2011/415-31).

Patients

All patients who were referred to the Department of Nuclear Medicine for DaTSCAN SPECT, during an 18-month period, were asked for inclusion in the study. Patients were referred and followed-up by neurologists and geriatricians from the Southeast region of Sweden. Written consent was obtained by all patients who agreed to participate. Co-morbid medical conditions, such as severe head injury, intracranial surgery, surgery in the nasal cavity, seasonal allergies, sinusitis or other current respiratory infection, as well as current smoking served as exclusion criteria.

The following diagnosis groups were defined in this study:

i. PD: patients diagnosed with idiopathic Parkinson's Disease
ii. APS: patients with Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP), Dementia with Lewy Bodies (DLB) or unspecified APS syndrome
iii. Secondary Parkinsonism (SP): patients with vascular parkinsonism or drug-induced parkinsonism
iv. Non-parkinsonism: patients with essential tremor, postural tremor or other pathology that was not related to the basal ganglia.

Olfactory Evaluation

In order to simulate clinical practice, where time-efficiency matters, we chose to use the Brief 12-item Smell Identification Test (B-SIT, Sensonics, Inc., New Jersey, USA), among the various available testing paradigms. This test consists of a booklet with 12 different microencapsulated odorants. In each page, there is a multiple-choice question with four alternative responses and one odorant embedded in a microcapsule at the bottom of the page. Each odorant is released by scratching the microcapsule, and the patient is then required to choose the alternative that corresponds to the odorant. The performance of each patient is presented as B-SIT score, which has a range from 0 to 12.

An examiner, blind to participants' clinical status, explained the test beforehand and helped all patients by scratching the booklets and marking their answers. We used the norms provided by the manufacturer in order to classify the patients as normosmic, hyposmic or anosmic in accordance to their sex and age. Prior to the B-SIT examination, all participants were asked to self-evaluate their olfactory ability as impaired or normal.

DaTSCAN®

The iodine-labelled ligand ioflupane (^{123}I-FP-CIT) was employed for DaTSCAN SPECT (GE Healthcare, Eindhoven, the Netherlands). Ioflupane is a presynaptic radioligand with affinity to the presynaptic dopamine transporter protein, in the striatal dopaminergic terminals. Image acquisition, processing and automated semi-quantitative evaluation were performed as previously described by our group [7]. We used EXINI DAT (EXINI Diagnostics AB, Lund, Sweden) for the quantification of our data. EXINI DAT is CE-approved software, which allows automated, supervised quantification of DaTSCAN SPECT, including partial volume effect correction. The specific ligand binding to putamen and caudate nucleus was calculated, with the occipital lobe serving as reference for non-specific binding. Two ratios were calculated: the ratio between the uptake in striatum and that in the occipital lobe, hereinafter mentioned as striatum ratio, and the ratio between the uptake in putamen and that in caudate nucleus, hereinafter mentioned as putamen/caudate ratio.

An experienced nuclear medicine technician and an experienced physician, both blinded to patients' clinical status, performed individually visual assessment of all transaxial SPECT images. The uptake pattern of the ligand was classified in five different stages, as previously proposed by Kahraman et al. [8] and as shown in Figure 1. These five stages are listed below:

1. Burst striatum: severe bilateral reduction, with almost no uptake in putamen or caudate nucleus.
2. Egg shape: bilateral uptake reduction in both putamina and normal or borderline normal uptake from caudate nucleus, creating an oval shape.
3. Mixed type: asymmetrical ioflupane uptake, with reduced uptake in the putamen of one side.
4. Eagle wing: borderline normal, symmetrical ioflupane uptake, with only discrete reduction in one or both putamina, creating the shape of a wing.
5. Normal: symmetrical ioflupane uptake in putamen and caudate nucleus bilaterally.

Statistical analysis

Kruskal-Wallis one-way ANOVA was employed to investigate potential differences in age and illness duration among groups. Fisher's exact test was used to investigate potential differences in sex among groups. Pearson's Chi-square test was used to compare the results of visual assessment of DaTSCAN. In order to identify potential differences in the B-SIT score and the semi-quantitative analysis, we used non-parametric Kruskal-Wallis one-way ANOVA, with Mann-Whitney U Test as post hoc test for pairwise comparisons; for significant differences, the p-value from Mann-Whitney U Test is presented. The analysis of the B-SIT score was cross-examined for possible confounders with ANCOVA, by using age as covariate and sex as additional factor. Correlation was

assessed by Pearson coefficient (r). Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated for the B-SIT score and the visual evaluation. The semi-quantitative analysis of DaTSCAN produces two striatal uptake ratios for each patient, one for each hemisphere of the brain; the lower of these two ratios was used in the statistical analysis. The results of semi-quantification depend on the type of camera, collimator, acquisition and reconstruction parameters, and are, therefore, not easily comparable within different SPECT systems [21]. Hence, we did not to calculate the sensitivity, specificity, positive predictive value and negative predictive value for the semi-quantitative analysis of DaTSCAN. Binary logistic regression was employed in order to estimate the predictive value of B-SIT and of the visual assessment of DaTSCAN. Statistical analysis was performed using IBM® SPSS® Statistics v22. For all tests, $p<0.05$ was considered statistically significant. All results are presented in the form median value with lower and upper 95% confidence intervals (CI). The abbreviation df will be hereinafter used to state the degrees of freedom.

RESULTS

Patients

In total 67 patients were recruited in the study. One patient was excluded from data analysis due to previous intracranial surgery and another patient was excluded because of previous surgery in the nasal cavity. One patient died of cancer before receiving a diagnosis regarding his parkinsonism, and he was, therefore, excluded. One patient could not complete the DaTSCAN examination due to claustrophobia and was also excluded. Three patients had to be excluded due to uncertain diagnosis several months after recruitment. The remaining 60 patients were divided into four groups, according to their diagnosis: PD (24 patients), APS (16 patients), SP (5 patients), Non-parkinsonism (15 patients). Among the patients with APS, 6 were diagnosed with MSA, 4 with PSP, 1 with DLB and 5 with unspecified form of APS. Among the patients with SP, 3 were diagnosed with vascular parkinsonism and 2 with drug-induced parkinsonism. The SP group was too small to be included in the statistical comparisons among groups; it was however included in the comparisons between parkinsonism (all PD, APS and SP patients) and Non-parkinsonism. The demographics of each group, including age, sex, illness duration and medication at the time of the study are presented in Table 1. Kruskal-Wallis one-way ANOVA showed no significant difference regarding age and illness duration among groups. Fisher's exact test showed no significant difference regarding sex among groups.

Olfactory self-evaluation

In the PD group 50% of the patients were aware of some smell impairment vs. 38% in the APS group and 20% in the Non-parkinsonism group. Pearson's Chi-square showed no significant difference between groups. There was a weak positive correlation between smell self-evaluation and B-SIT score in PD patients (Pearson correlation r=0.458, p=0.024), but no significant correlation in the APS or Non-parkinsonism group.

Olfactory evaluation with B-SIT

The median value of B-SIT score in the PD group was 4.0 (95% CI: 3 and 4.5) vs. 6.0 (95% CI: 4 and 9) in the APS group and 8.0 (95% CI: 7 and 9) in the Non-parkinsonism group. Kruskal-Wallis one-way ANOVA, with Mann-Whitney U test as post hoc test, showed significant difference between PD and Non-parkinsonism ($p<0.001$, 3 df), but no significant difference between PD and APS or APS and Non-parkinsonism. After using age as a covariate and sex as an additional factor (ANCOVA), there was still significant difference between PD and Non-parkinsonism ($p<0.001$, 3 df). There was no significant correlation between B-SIT score and illness duration in PD, APS or Non-parkinsonism. Based on the B-SIT norms provided with the test, 71% of PD patients were anosmic and 21% were hyposmic vs. 31% anosmic and 38% hyposmic APS patients (Table 2). Anosmic patients were compared against the combination of normosmic and hyposmic, with Pearson's Chi-square test; there were significantly more anosmic PD patients than anosmic APS patients ($p=0.016$, 1 df).

Patients with impaired olfaction (anosmic and hyposmic) were grouped together and were compared to normosmic patients in terms of sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy for B-SIT. The sensitivity of B-SIT in distinguishing parkinsonism (all PD, APS and SP patients included) from Non-parkinsonism was 80%, the specificity 40%, the positive predictive value 80%, the negative predictive value 40% and the diagnostic accuracy 70%. By focusing only on PD (PD vs. Non-parkinsonism) the sensitivity was 92%, the specificity 40%, the positive predictive value 71%, the negative predictive value 75% and the diagnostic accuracy 72%.

DaTSCAN®

The striatal uptake for all patients was visually categorized in 5 different patterns, as proposed by Kahraman et al. [8] ; the results for each diagnostic group are presented in Table 2. All PD patients had abnormal striatal uptake pattern (Grades 1-3), while one APS patient had normal striatal uptake pattern (Grade 5). In the PD group, 21% of the patients were classified as Grade 1 "burst striatum" vs. 56% in the APS group. Moreover, 75% of PD patients were classified as Grade 2 "egg shape" vs. 19% for the APS group. Grade 1 was compared against the

combination of all other grades for PD and APS with Pearson's Chi-square. Similarly, Grade 2 was compared against all other grades. There was significant difference between PD and APS for Grade 1 ($p=0.025$, 1 df) and Grade 2 ($p=0.001$, 1 df), as illustrated in Figure 2. The majority (80%) of Non-parkinsonism patients were classified as normal (Grade 5). However, 13% were classified as Grade 4 and 7% as Grade 3.

Patients with abnormal striatal uptake of DaTSCAN (Grades 1-4) were grouped together and were compared to patients with normal striatal uptake (Grade 5) in terms of sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy. The sensitivity of DaTSCAN in distinguishing parkinsonism (all PD, APS and SP patients included) from Non-parkinsonism was 96%, the specificity 80%, the positive predictive value 93%, the negative predictive value 86% and the diagnostic accuracy 92%.

The semi-quantitative results of DaTSCAN were analysed with Kruskal-Wallis one-way ANOVA with Mann Whitney U Test as post hoc. There was no significant difference in the striatum uptake ratio between PD (median 2.18, 95% CI 1.91 and 2.47) and APS (median 2.12, 95% CI 1.81 and 2.51). However, there was a significant difference ($p<0.001$, 3 df) between PD and Non-parkinsonism (median 4.79, 95% CI 4.27 and 5.47) as well as between APS and Non-parkinsonism ($p<0.001$, 3 df, Figure 3a). The putamen/caudate uptake ratio in PD (median 0.730, 95% CI 0.714 and 0.748) was significantly lower ($p=0.006$, 3 df) compared to APS (median 0.793, 95% CI 0.768 and 0.800) and significantly lower ($p<0.001$, 3 df) than Non-parkinsonism (median 0.819, 95% CI 0.807 and 0.847), as shown in Figure 3b.

There was a strong positive correlation (Pearson correlation $r=0.697$, $p<0.001$) between B-SIT and the striatum uptake ratio for the PD group. A weak positive correlation between B-SIT and the striatum uptake ratio was shown even for the APS (Pearson correlation $r=0.352$, $p=0.181$) and Non-parkinsonism groups (Pearson correlation $r=0.408$, $p=0.131$). There was no correlation between B-SIT and the putamen/caudate ratio for any of the diagnostic groups.

As the majority of APS patients were classified as Grade 1 and the majority of PD patients were classified as Grade 2, we employed binary logistic regression to evaluate if the combination of B-SIT and Grade 1 or Grade 2 can increase the predictive value for PD and APS. Regression analysis for the other grades of visual assessment was not performed due to insufficient amount of data. The correct classification for APS was 43.8% when solely using B-SIT, 56.3% when solely using Grade 1 uptake pattern, and 62.5% when combining these two methods. Similarly, the overall classification for both PD and APS was improved by the combination of B-SIT and Grade 1 or Grade 2, as shown in Table 3.

DISCUSSION

The main findings of this study illustrate that DaTSCAN has better diagnostic value than olfactory testing in discriminating parkinsonism from Non-parkinsonism. Moreover, DaTSCAN offers prospect of differentiating PD from APS. However, the combination of DaTSCAN and olfactory testing can increase their predictive value.

Olfaction

According to this study, olfactory testing can successfully distinguish PD patients from Non-parkinsonism, which is in line with previous studies [22-25]. However, olfactory testing fails in distinguishing PD from APS or APS from Non-parkinsonism. Olfactory function can vary in APS from preserved to differentially impaired. It can be significantly impaired in DLB, mildly impaired in MSA, but within normal range in PSP [26, 27], explaining why the olfactory test cannot differentiate APS from PD or Non-parkinsonism. Other studies indicate that testing the olfactory function may be helpful in distinguishing PD from vascular parkinsonism or drug-induced parkinsonism [28, 29]. In this study, we could not recruit enough patients to these two subgroups in order to validate this argument.

The B-SIT score had a sensitivity of 80% for discriminating parkinsonism from Non-parkinsonism and an even higher sensitivity of 92% for discriminating PD from Non-parkinsonism. However, its specificity was poor (40%) in both cases. These results are comparable to Deeb et al. [22] , but not in accordance with other studies where sensitivity and specificity were nearly on the same level [25, 30]. A potential explanation for this divergence could depend on cultural biases and odour familiarity. Even though the B-SIT test is a cross-cultural brief smell test, the Swedish population is not familiar with some of the included odours (i.e. wintergreen and lime in this study), resulting in a lower score even for normosmic patients. None of the participants of this study managed to get a perfect score (12 out of 12). In the present study, we chose not to focus on specific odours that may identify PD more effectively. Selective olfactory loss in PD has been controversial; according to Hahner et al. selective hyposmia is not a reliable method to distinguish PD from Non-parkinsonism [31].

Olfactory loss is among the most common non-motor symptoms in PD patients in the 2- to 10-year period prior to motors symptom [32]. Olfactory testing has been used as a supporting diagnostic tool for several years. Our study can confirm the efficacy of olfactory testing in discriminating PD from Non-parkinsonism; however, olfactory testing has a limited efficacy in differentiating the different types of parkinsonism.

DaTSCAN

Following the five uptake patterns suggested by Kahraman et al., we found that most PD patients had a Grade 2 (egg-shape) uptake reduction, meaning that dopamine depletion in most PD patients is prominent in putamen, while caudate nucleus retains normal or almost normal function. On the other hand, most APS patients showed a Grade 1 (burst striatum) uptake reduction, suggesting more severe dopamine depletion both in putamen and in caudate nucleus in APS. Both Kahraman et al. and Davidsson et al. have previously published similar results to these findings [7, 8]. Compared to the B-SIT test, the visual assessment of DaTSCAN was more efficient in discriminating parkinsonism from Non-parkinsonism in terms of sensitivity (96%), specificity (80%) and diagnostic accuracy (92%). These results contradict Deeb et al., who suggested that a basic smell test is as sensitive as DaTSCAN [22], but are in accordance with Hong et al. who, by comparing the Cross-Cultural Smell Identification Test and dopamine transporter Positron Emission Tomography (PET), proved that the olfactory test alone has little power in detecting dopaminergic depletion [33].

The semi-quantitative analysis of DaTSCAN showed that the striatum ratio is accurate to differentiate PD from Non-parkinsonism, as well as APS from Non-parkinsonism, but it cannot differentiate PD from APS. These results are in accordance with one meta-analysis on the diagnostic accuracy of DaTSCAN [9] and two previously published studies on the same topic [10, 34]. However, the putamen/caudate ratio is greater in APS than in PD, suggesting a more uniform dopamine depletion both in putamen and in caudate nucleus in APS patients; this result concurs with the previously discussed visual assessment. Two more studies verify that there is more symmetric loss of dopaminergic nerve terminals in MSA [35] and in PSP [36] compared to PD. This finding could depend on higher severity of clinical symptoms in APS patients at the time of the first clinical evaluation.

There was a strong correlation between B-SIT and the striatum ratio in PD patients, indicating that a lower striatum ratio in a PD patient signals a more severely impaired olfaction. The aforementioned studies by Deeb et al [22]. and Hong et al. [33] also found strong correlation between the score of smell identification test and the DaTSCAN uptake in PD patients. Moreover, binary logistic regression analysis showed that the combination of B-SIT and DaTSCAN has better predictive value, with a higher overall rate of correctly classified PD and APS patients, compared to when these two methods are used separately. As shown in Table 3, the combination of Grade 1 uptake pattern and olfactory testing is a significantly better diagnostic model than Grade 1 alone. The addition of olfactory testing in Grade 2 uptake pattern also leads to a higher rate of correctly classified patients, but this improvement is not statistically significant. In conclusion, B-SIT can be a useful supplementary

diagnostic tool, despite its lower diagnostic accuracy compared to DaTSCAN, especially for Grade 1 uptake pattern, which is dominated by APS patients.

Discordant results

As seen in Table 4, seven patients had discordant results. Two normosmic PD patients had abnormal DaTSCAN. According to previously published data, 26% of PD patients had an olfactory test score within the normal range [11]. This finding is in line with the low specificity of smell test in detecting parkinsonism. One APS patient with clearly impaired olfaction had normal DaTSCAN and can, therefore, be classified as Scans Without Evidence of Dopaminergic Deficit (SWEDD). This patient was receiving dopaminergic medication at the time of examination and was diagnosed with MSA after DaTSCAN; hence, the possible interference of dopaminergic medication cannot be eliminated in that case. Also, one normosmic patient with vascular parkinsonism can be classified as SWEDD. A recently published study compared the clinical and imaging characteristics between SWEDD patients and patients with abnormal DaTSCAN during a 22-month follow-up, and concluded that SWEDD patients had minimal evidence of clinical or imaging progression, suggesting that SWEDD patients are unlikely to have parkinsonism [37]. Three patients received a diagnosis different than parkinsonism, despite abnormal DaTSCAN and impaired olfaction, implying incorrect diagnosis. Dopaminergic deficit has been previously documented in some patients with essential tremor, hinting at a possible association between essential tremor and PD [38]. However, olfaction is normal in the vast majority of patients with essential tremor, or in some cases slightly abnormal [39]. As suggested by a multicentre study, a second DaTSCAN two years after clinical observation can reduce diagnostic uncertainty in patients with inconclusive diagnosis [6].

Limitations of the study

Our cohort is of a prospective nature and therefore no long-term follow-up data is available. In addition, most of the patients included in the study were not drug-naïve to dopaminergic medication, which could potentially affect the results of DaTSCAN SPECT. As with all the studies on the same topic, there is no gold standard for the diagnosis of parkinsonism, apart from a post-mortem examination of the brain. Finally, information about UPDRS and Hoehn and Yahr scale was not documented in the medical journals of all patients since it is not standard practice; analysis of covariance based on this classification was consequently not possible. However, the results of this study are in line with other previously published studies, which underlines the validity of the findings presented here.

Conclusions

In conclusion, the semi-quantitative analysis of DaTSCAN SPECT is an accurate diagnostic tool to differentiate parkinsonism from Non-parkinsonism. Additionally, the visual assessment of DaTSCAN together with the uptake ratio between putamen and caudate nucleus can offer valuable aid in differentiating PD from APS. On the other hand, a smell identification test has lower diagnostic value than DaTSCAN in differentiating parkinsonism from Non-parkinsonism. Olfactory testing is efficient in detecting PD, but it cannot successfully detect APS, and its specificity is low. Nonetheless, the combination of olfactory testing and DaTSCAN imaging has a higher predictive value than these two methods separately, especially for Grade 1 uptake pattern. Therefore olfactory tests may be used as a complementary diagnostic tool in parkinsonian syndromes.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical Standards

This study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments, and was approved by the Regional Ethical Review Board in Linköping, Sweden (registration number 2011/415-31). Informed consent was obtained from all individual participants included in the study.

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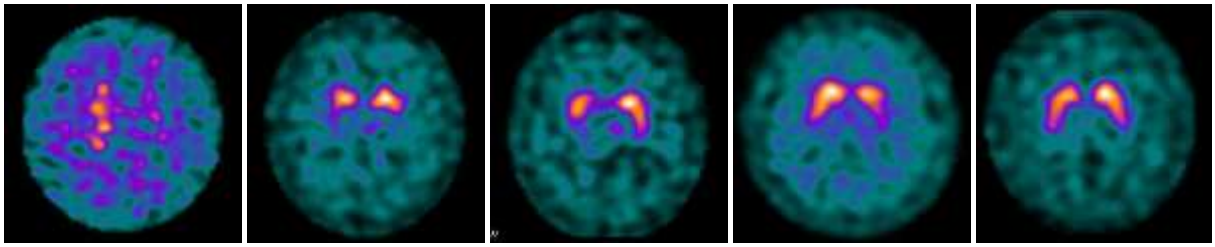
FIGURES

Fig.1 Classification of DaTSCAN uptake. The visual assessment of DaTSCAN SPECT was based on these five striatal uptake patterns of DaTSCAN, as previously proposed by Kahraman et al. [8]



Grade 1 (burst striatum)	Grade 2 (egg shape)	Grade 3 (mixed type)	Grade 4 (eagle wing)	Grade 5 (normal)

Fig.2 Distribution of PD and APS patients in five striatal uptake grades. All patients were classified in five different uptake patterns (as previously proposed by Kahraman et al.), after visual assessment of DaTSCAN imaging. Significant differences were detected between PD and APS for Grade 1 (p=0.025) and Grade 2 (p=0.001). PD: Parkinson's disease, APS: Atypical Parkinsonism, * if p<0.05, ** if p<0.01 [8]

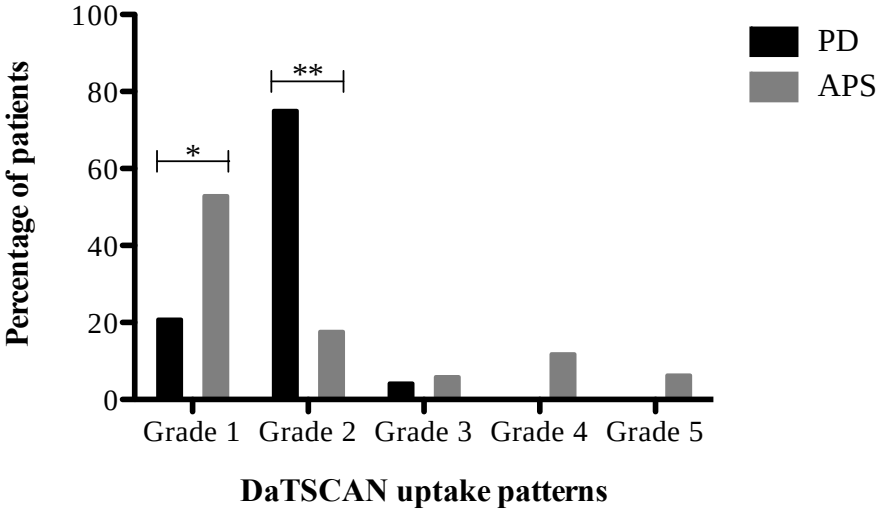
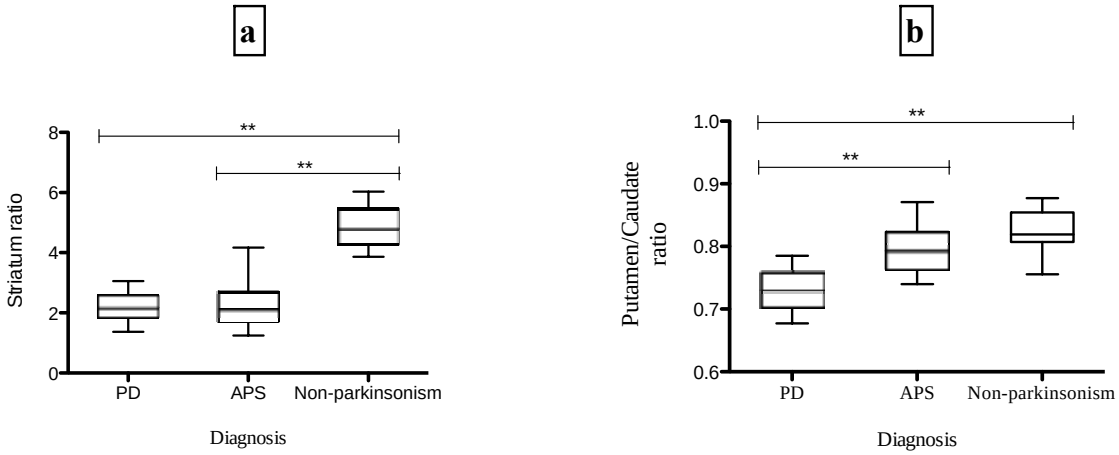


Fig.3 DaTSCAN uptake ratios for PD, APS and Non-parkinsonism. The box plots represent the two different uptake ratios, which were calculated using the 3D EXINI DAT software (EXINI Diagnostics AB, Lund, Sweden). The box horizontal upper and lower limits represent the 75th and 25th percentiles, respectively, and the horizontal line within each box represents the median. **a)** The striatum ratio was significantly lower ($p<0.001$) both for PD and APS compared to Non-parkinsonism. **b)** The Putamen/Caudate ratio was significantly lower for PD compared to APS ($p=0.006$) and Non-parkinsonism ($p<0.001$); there was no significant difference between APS and Non-parkinsonism. PD: Parkinson's disease, APS: Atypical Parkinsonism, Non-p: Non-parkinsonian syndromes, ** if $p<0.01$



The diagnostic value of dopamine transporter imaging and olfactory testing in patients with parkinsonian syndromes

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Table 1: Demography and medication of patients at the time of examination. Age and illness duration are presented in the form median value with lower and upper 95% confidence intervals (CI) in parentheses. Kruskal-Wallis one-way ANOVA (3 df) showed no significant difference in age and illness duration among the four patient groups. Fisher's exact test (3 df) showed no significant difference in sex among the four patient groups; PD: Parkinson's Disease; APS: Atypical parkinsonism; SP: Secondary parkinsonism; MAO: Monoamine Oxidase; SSRI: Selective Serotonin Reuptake Inhibitor; NaSSA: Noradrenergic and Specific Serotonergic Antidepressants; SNRI: Serotonin and Noradrenalin Reuptake Inhibitors.

	PD	**APS**	**SP**	**Non-parkinsonism**	**p**
Number of patients	24	16	5	15	
Age (years)	70.5 (95% CI: 67 and 73)	65.5 (95% CI: 61 and 72)	77 (95% CI: 47 and 80)	66 (95% CI: 60 and 71)	0.257
Sex (male/female)	13/11	9/7	5/0	7/8	0.226
Illness duration (years)	3.5 (95% CI: 2 and 4)	4 (95% CI: 2 and 6.5)	4 (95% CI: 3 and 7)	6 (95% CI: 3.5 and 13)	0.260
Levodopa	16	10	0	2	
Dopamine Agonist	7	1	0	1	
MAO inhibitor	3	1	0	0	
Benzodiazepine	2	2	1	3	
Antiepileptic	3	2	2	3	
SSRI	0	1	1	1	
Tricyclic Antidepressants	0	0	0	1	
NaSSA	2	1	1	1	
SNRI	1	2	0	1	
Serotonin Receptor Agonist	1	0	0	0	
Antipsychotic	0	1	1	0	
No medication	5	2	1	8	

Table 2: Distribution of patients into three olfactory groups based on their performance on B-SIT and into five different uptake patterns of DaTSCAN SPECT. Olfactory evaluation was based on the norms provided by the manufacturer of the B-SIT test. The visual assessment was performed in accordance with the evaluation model proposed by Kahraman et al. [8]. Normosmic and hyposmic patients were combined and were compared against anosmic patients for PD and APS, with Pearson's Chi-square test; there were significantly more anosmic patients in the PD group than in the APS group (p=0.016, 1 df). Likewise, Grade 1 was compared against the combination of the remaining grades for PD and APS, with Pearson's Chi-square test. Similarly, Grade 2 was compared against the combination of the remaining grades for PD and APS. There were significantly more PD patients with Grade 2 uptake pattern (p=0.025, 1 df) and significantly more APS patients with Grade 1 uptake pattern (p=0.001, 1 df). The percentages within each diagnostic group are presented in parentheses; B-SIT: Brief Smell Identification Test; PD: Parkinson's disease; APS: Atypical parkinsonism; SP: Secondary parkinsonism.

		PD (n=24)	**APS** (n=16)	**SP** (n=5)	**Non-parkinsonism** (n=15)
B-SIT	Normosmic	2 (8%)	5 (31%)	2 (40%)	6 (40%)
	Hyposmic	5 (21%)	6 (38%)	1 (20%)	8 (53%)
	Anosmic	17 (71%)	5 (31%)	2 (40%)	1 (7%)
Visual assessment of DaTSCAN SPECT	Grade 1 "Burst Striatum"	5 (21%)	9 (56%)	1 (20%)	0
	Grade 2 "Egg shape"	18 (75%)	3 (19%)	2 (40%)	0
	Grade 3 "Mixed type"	1 (4%)	1 (6%)	1 (20%)	1 (7%)
	Grade 4 "Eagle wing"	0	2 (13%)	0	2 (13%)
	Grade 5 "Normal"	0	1 (6%)	1 (20%)	12 (80%)

Table 3: Predictive value of B-SIT, Grade 1 and Grade 2 uptake patterns, both exclusively and combined. Binary logistic regression analysis of diagnosis, using B-SIT and visual assessment of DaTSCAN as independent variables, shows that the combination of these two diagnostic methods results in a higher overall number of correctly classified patients. The predictive value of these two methods was calculated only for PD and APS patients. The dependent variable in this analysis is diagnosis, coded so that 0=PD and 1=APS. The five models were compared with each other with Wald test (1df per comparison). PD: Parkinson's disease; APS: Atypical parkinsonism; B-SIT: Brief Smell Identification Test; B: coefficient for the constant; S.E: Standard Error of the coefficient for the constant; O.R: Odds Ratio.

Model		Model comparison	Log likelihood	Nagelkerke R^2	Overall correctly classified		B	S.E.	O.R.	p
1	**B-SIT**		47.339	0.203	70%		0.317	0.136	1.373	0.020
2	**Grade 1 uptake pattern of DaTSCAN**		48.539	0.168	70%		1.586	0.712	4.967	0.026
3	**Grade 2 uptake pattern of DaTSCAN**		40.924	0.373	77.5%		-2.565	0.795	0.077	0.001
4	**Combination of B-SIT and Grade 1 uptake pattern**	$p<0.02$ [1]	41.718	0.353	72.5%	**B-SIT**	0.348	0.147	1.417	0.018
		$p<0.001$ [2]				**Grade 1**	1.800	0.800	6.048	0.025
5	**Combination of B-SIT and Grade 2 uptake pattern**	$p<0.002$ [1]	37.166	0.461	82.5%	**B-SIT**	0.284	0.155	1.328	0.067
		$p>0.05$ [3]				**Grade 2**	-2.448	0.841	0.086	0.004

[1] Comparison with Model 1 (Wald test)
[2] Comparison with Model 2 (Wald test)
[3] Comparison with Model 3 (Wald test)

Table 4: Characteristics of patients with discordant test results; B-SIT: Brief Smell Identification Test; PD: Parkinson's disease; APS: Atypical parkinsonism; SP: Secondary parkinsonism.

Patient	**Age**	**Sex**	**Diagnosis**	**Symptom Duration**	**DaTSCAN**	**Visual Assessment Grade**	**B-SIT score/12**
P1	32	Male	PD	2 years	Abnormal	3	11
P2	70	Female	PD	2 years	Abnormal	2	9
P3	61	Male	APS	1 year	Normal	5	5
P4	75	Male	SP	4 years	Normal	5	10
P5	57	Male	Non-parkinsonism	9 years	Abnormal	4	8
P6	70	Male	Non-parkinsonism	2 years	Abnormal	4	8
P7	69	Male	Non-parkinsonism	24 years	Abnormal	3	6