



Original Article

# Olfactory dysfunction in Parkinson-plus syndromes: A comparison among themselves and controls

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## ABSTRACT

**Objective:** Smell dysfunction may be a feature of Parkinson-plus syndromes such as multiple system atrophy and progressive supranuclear palsy. This study assessed the smell function of patients with Parkinson-plus syndromes and compared them with each other and their controls.

**Materials and Methods:** Utilizing the University of Pennsylvania Smell Identification Test (UPSIT) kits, the authors studied the olfaction of 30 Parkinson-plus syndrome patients (14 with multiple system atrophy [MSA] and 16 with progressive supranuclear palsy [PSP]) and 30 age- and sex-matched healthy controls in both nostrils and assessed whether the duration of disease influences these scores.

**Results:** The mean total UPSIT score of MSA was  $13.00 \pm 3.96$  (right) and  $13.00 \pm 3.68$  (left), and that of PSP was  $12.00 \pm 5.07$  (right) and  $12.06 \pm 5.04$  (left), while it was  $29.73 \pm 3.23$  (right) and  $29.90 \pm 3.45$  (left), with significant *P*-values ( $<0.001$ ) between patients and controls and non-significant *P*-values between MSA and PSP. Overall, MSA patients had a lower ability to identify menthol, motor oil, mint, banana, clove, coconut, onion, licorice, cinnamon, gasoline, strawberry, gingerbread, lilac, turpentine, peach, pineapple, lime, orange, watermelon, paint thinner, grass, smoke, lemon, soap, and rose, while PSP patients could not identify bubble gum, cherry, dill pickle, natural gas, and peanut in either nostril. However, disease duration did not affect the patient scores.

**Conclusion:** Contrary to popular belief, patients with PSP and MSA have significantly impaired olfaction compared to controls, but the differences between PSP and MSA may not be significant.

**Keywords:** Multiple system atrophy, Olfaction, Progressive supranuclear palsy, Smell, University of Pennsylvania smell identification test

## INTRODUCTION

Neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease (PD), often exhibit smell dysfunction even in their early stages.<sup>[1]</sup> In fact, it helps differentiate PD from other Parkinson's plus syndromes, such as progressive supranuclear palsy (PSP).<sup>[2]</sup> In addition, smell testing is useful in recognizing PD even in its preclinical stages, and patients are oblivious to smell dysfunction until they undergo formal testing.<sup>[2,3]</sup> In PD, Lewy bodies accumulate in the olfactory pathway, from the olfactory bulb to the higher olfactory centers, resulting in olfactory dysfunction.<sup>[4]</sup> Another reason for olfactory dysfunction in PD is alpha-synuclein aggregation in different regions of the brain.<sup>[5]</sup> Multiple system atrophy (MSA), a synucleinopathy, can cause smell dysfunctions.<sup>[6]</sup> In PSP, degeneration also occurs in the insular region of the primary olfactory

region.<sup>[7]</sup> Hence, smell dysfunction may occur in patients with PSP.

There are numerous methods of testing olfaction in humans, like the University of Pennsylvania Smell Identification Test (UPSIT), the Brief-Smell Identification Test, the Indian Smell Identification Test, and the Sniffin' 12 and Sniffin' 16 odor identification tests.<sup>[8,9]</sup> Although the results of smell testing may vary among individuals depending on the language and place of residence,<sup>[10]</sup> UPSIT is quite sensitive and specific<sup>[11]</sup> and is valid for testing neurological patients.<sup>[8]</sup> As per previous records, UPSIT is also valuable for the regional population.<sup>[12]</sup>

In this study, the authors assessed patients with Parkinson-plus syndromes to evaluate smell dysfunction, if any, and compared them with their age- and sex-matched healthy controls.

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## MATERIALS AND METHODS

In this observational study, the clinicians studied patients with Parkinson-plus syndrome coming outdoors as well as age- and sex-matched healthy controls (who gave their consent for the study) in the Department of Neurology of the institute from August 2020 to October 2023. For this study, the controls were patient attendants.

### Case selection

Here, the study participants included 30 cases and 30 controls.

### Inclusion criteria

For this study, our inclusion criteria were patients with Parkinson-plus syndrome (multiple system atrophy and progressive supranuclear palsy) aged more than 30 years and with education not below the 8<sup>th</sup> standard who consented to this study and we included 30 age- and sex-matched healthy controls who consented to the study. Since, in our setup, very few patients with corticobasal degeneration (CBD) or dementia with Lewy bodies (DLBs) visit, we did not include these patients.

### Exclusion criteria

In addition, we did not include people with any history of head injury, space-occupying lesions of the brain, history of known psychiatric illness, use of any drugs, or addictive substances that might affect smell, upper respiratory tract infections, sinusitis, or local pathology in the nose, dementia (Mini-Mental State Examination <21), or a history of olfactory hallucinations, diabetes mellitus, smoking, asthma, or allergies.

### Procedure

Using UPSIT kits, we tested olfaction in 30 patients with PSP or MSA. To select patients with MSA, we used the second consensus statement on the diagnosis of multiple system atrophy criteria and included those with probable MSA<sup>[13]</sup>. Furthermore, we selected those who fulfilled the Movement Disorder Society criteria for PSP<sup>[14]</sup>. To rule out the exclusion criteria, we took patient histories and examined them including the Unified Multiple System Atrophy Rating Scale, the modified Progressive Supranuclear Palsy Rating Scale, or mPSPRS, and the Unified Parkinson's Disease Rating Scale. We then conducted routine laboratory tests, such as hemograms, renal function tests, liver function tests, fasting and postprandial blood sugar levels, and a magnetic resonance imaging head.

Thereafter, clinicians tested olfaction using the UPSIT kit. The UPSIT kit contains 40 microencapsulated odorants in a standardized booklet, which the examiner may scratch

with a pencil to release the odors. The patients then closed their eyes, closed one nostril, took a single sniff of one odor, identified the odor, and then repeated the same test by occluding the other nostril and using both nostrils. Before introducing the second odor, the person sniffed normal air. Using the standard scoring of the UPSIT, we then scored their results, as the UPSIT contains 40 questions with four options, with the scoring key containing the correct answers.

Since PSP and MSA patients mostly belong to an elderly age group and elderly healthy people may have an impaired sense of smell as compared to their younger counterparts, we included 30 age- and sex-matched healthy controls to eliminate this bias. The ethics committee of our institute has approved this study.

### Statistical analysis

#### *Sample size calculation*

Approximately 200 people with Parkinson-plus syndrome attended the outdoors of the institute for 6 months. Therefore, at a confidence interval of 95% and a margin of error of 15, we needed 36 patients. However, after screening around 50 patients, we were able to get only 30 patients who fulfilled the inclusion criteria.

Using Microsoft IBM Statistical Package for the Social Sciences version 20, we analyzed data for different smells in both nostrils together and separately in cases and controls and calculated the mean UPSIT scores of different odors and the mean total scores of the right and left nostrils. The investigators tested the age, sex, and education status for normality using the Shapiro–Wilk test. For continuous variables, the results were expressed as means with standard deviations. In addition, the independent samples *t*-tests gave us *P*-values between MSA and PSP, MSA and controls, and PSP and controls and we considered  $P < 0.05$ , to be significant. We also investigated the relationship between the duration of the disease and the UPSIT scores of the patients using regression coefficients.

#### *Outcome measures*

In the present study, our outcome measures relate to the different odors tested and the degree of impairment of smell found in Parkinson-plus syndrome patients as compared to their healthy counterparts, according to the UPSIT.

## RESULTS

Table 1 depicts the demographic and clinical parameters of the Parkinson-plus syndrome patients and the controls. The investigators tested the age, sex, and education status for normality using the Shapiro–Wilk test and found skewness and kurtosis of  $-0.162$  and  $-1.337$ , respectively, for age,  $2.295$  and  $3.792$ , respectively, for sex and  $-0.487$  peanut and  $-0.226$ , respectively, for education in patients with MSA. The

similar values for the PSP patients were 0.710 and  $-0.159$ , respectively, for age, 0.571 and  $-1.934$ , respectively, for sex and 0.197 and  $-0.373$ , respectively, for education.

The mean total UPSIT score of the right side was  $13.00 \pm 3.96$  for MSA patients and  $12.00 \pm 5.07$  for PSP patients, while it was  $29.73 \pm 3.23$  for the controls, and p-value between MSA and controls as well as that between PSP and controls was  $<0.001$ . However, the P-value between MSA and PSP was 0.770. For the left side, the mean total UPSIT score was  $13.00 \pm 3.68$  for MSA patients,  $12.06 \pm 5.04$  for PSP patients, and  $29.90 \pm 3.45$  for the controls and p-value between MSA and controls, and that between PSP and controls was  $<0.001$ . p-value between MSA and PSP on the left side was 0.796. Table 2 depicts the values of different odors on the right side and the comparison between MSA and PSP and between cases and controls. Table 3 shows similar values on the left-hand side.

For MSA patients, the relationship between disease duration and UPSIT score gave a beta value of  $-0.565$  and a P-value of 0.035 on the right side and a beta value of  $-0.635$  and a P-value of 0.015 on the left side. Similar values for people with PSP were a beta of  $-0.299$  and P-value of 0.261 on the right side and a beta of  $-0.264$  and P-value of 0.323 on the left side.

Among different odors, MSA as well as PSP patients were not able to significantly identify many odors in both nostrils compared to healthy controls [Tables 2 and 3].

## DISCUSSION

The mean UPSIT scores of patients with both MSA and PSP were significantly higher than those of the age- and sex-matched controls, indicating that these disorders impair an individual's ability to smell. This is in contrast to previously reported literature, which suggests that normosmia, or very little impairment of smell, is a characteristic feature of PSP.<sup>[15-18]</sup> Nevertheless, some previous researchers have reported smell dysfunction in PSP, similar to our observations.<sup>[19,20]</sup> Similar to PSP, MSA patients do not conventionally suffer from olfactory dysfunction, contrary to what we observed in the present study.<sup>[21,22]</sup>

In our study, we did not observe significant differences in the mean UPSIT scores of patients with MSA and PSP, in contrast to some previous studies that observed that MSA may alter smell detection ability more often than PSP.<sup>[23,24]</sup> However, some studies have identified no significant differences in olfaction between MSA and PSP.<sup>[21]</sup>

Although rare, these findings led a previous study to conclude that olfactory testing may not be an accurate biomarker for differentiating between PD and atypical Parkinsonism.<sup>[25]</sup>

Among different odors, MSA patients were not able to significantly identify many odors in both the nostrils compared

**Table 1:** Demographic and clinical parameters of patients and controls

S. No.	Parameter	Cases	Controls
1.	Sex		
	Males	22 (72.33%)	20 (66.67%)
	Females	8 (26.67%)	10 (33.33%)
2.	Age		
	41-60 years	16 (53.33%)	15 (50%)
	61-80 years	13 (43.33%)	15 (50%)
	>80 years	1 (3.33%)	0 (0%)
3.	Education		
	Class tenth	2 (6.67%)	2 (6.67%)
	Class twelfth	8 (26.67%)	7 (23.33%)
	Graduation	16 (53.33%)	17 (56.67%)
	Postgraduation	4 (13.33%)	4 (13.33%)
4.	Mean duration of disease (years)	1.75±0.954	-
5.	Mean UPDRS*±SD <sup>1</sup> score	57.37±12.824	-
6.	Mean MMSE <sup>#</sup> ±SD <sup>1</sup> score	23.17±2.086	28.57±1.006
7.	Mean global UPSIT <sup>^</sup> score (of both the nostrils)	12.77±4.408	30.23±3.256

\*UPDRS: Unified Parkinson's Disease Rating Scale  
<sup>#</sup>MMSE: Mini-Mental State Examination  
<sup>^</sup>UPSIT: University of Pennsylvania Smell Identification Test  
<sup>1</sup>SD: Standard deviation

to healthy controls and the ability to identify many odors was conspicuously less in PSP patients as compared to the control population [Tables 2 and 3]. Although we do not have values of Parkinson-plus syndrome patients for similar comparison, previous studies on PD patients found similar results with the difference of some odors (menthol, orange, and coconut to be the most differentiating and turpentine, grape, and grass were the least discriminating in one study, and bubble gum, menthol, mint, banana, clove, coconut, onion, grape, powder, coffee, cinnamon, strawberry, petrol, cedar, apple, orange, watermelon, grass, smoke, pine, raspberry, soap, natural gas, and rose to be the most differentiating in another study) that our patients could identify.<sup>[12,26]</sup> Although PSP patients could not identify most of the odors that MSA patients were unable to identify, they were able to identify a few more smells such as those of bubble gum, cherry, dill pickle, natural gas, and peanuts. Therefore, there may be some differences between MSA and PSP patients with regard to the number and type of smells that these two groups of patients can recognize.

In previous studies, the mean UPSIT score for controls was 24–28 and the mean score for PD was 14–20, and our study had a more or less similar value for controls ( $29.73 \pm 3.23$ ) and the value for MSA in our study was  $13.00 \pm 3.96$ , and that for PSP was  $12.00 \pm 5.07$ . These values showed significant impairment

**Table 2:** Mean UPSIT<sup>^</sup> scores of patients of MSA<sup>#</sup>, PSP\* and controls of the right nostril for different odors tested and comparison amongst them

Odor tested	Mean±SD <sup>‡</sup> UPSIT <sup>^</sup> score for MSA <sup>#</sup>	Mean±SD <sup>‡</sup> UPSIT <sup>^</sup> score for PSP*	Mean±SD <sup>‡</sup> UPSIT <sup>^</sup> score for controls	p-value between MSA <sup>#</sup> and controls	p-value between PSP* and controls	p-value between MSA <sup>#</sup> and PSP*
Pizza	0.21±0.426	0.31±0.479	0.57±0.504	0.069	0.211	0.843
Bubble gum	0.43±0.514	0.13±0.342	0.60±0.498	0.496	0.005	0.185
Menthol	0.21±0.426	0.38±0.500	0.93±0.254	<0.001	<0.001	0.473
Cherry	0.43±0.514	0.38±0.500	0.73±0.450	0.129	0.048	0.950
Motor oil	0.43±0.514	0.50±0.516	1.00±0.000	<0.001	<0.001	0.852
Mint	0.36±0.497	0.19±0.403	1.00±0.000	<0.001	<0.001	0.312
Banana	0.36±0.497	0.19±0.403	0.90±0.305	<0.001	<0.001	0.452
Clove	0.50±0.519	0.69±0.479	1.00±0.000	<0.001	0.015	0.314
Leather	0.57±0.514	0.50±0.516	0.90±0.305	0.050	0.009	0.889
Coconut	0.29±0.469	0.13±0.342	0.83±0.379	<0.001	<0.001	0.506
Onion	0.43±0.514	0.19±0.403	0.87±0.346	0.004	<0.001	0.242
Fruit punch	0.21±0.426	0.13±0.342	0.10±0.305	0.566	0.970	0.761
Licorice	0.43±0.514	0.31±0.479	0.87±0.346	0.007	<0.001	0.738
Cheddar cheese	0.07±0.267	0.06±0.250	0.23±0.430	0.346	0.276	0.997
Cinnamon	0.36±0.497	0.50±0.516	1.00±0.000	<0.001	<0.001	0.520
Gasoline	0.43±0.514	0.63±0.500	1.00±0.000	<0.001	0.003	0.293
Strawberry	0.29±0.469	0.19±0.403	0.67±0.479	0.034	0.004	0.828
Cedar	0.07±0.267	0.00±0.000	0.23±0.430	0.296	0.069	0.827
Chocolate	0.43±0.514	0.19±0.403	0.70±0.466	0.174	0.002	0.335
Ginger bread	0.43±0.514	0.50±0.516	0.87±0.346	0.008	0.024	0.896
Lilac	0.50±0.519	0.69±0.479	1.00±0.000	<0.001	0.015	0.314
Turpentine	0.36±0.497	0.75±0.447	0.97±0.183	<0.001	0.043	0.043
Peach	0.21±0.426	0.19±0.403	0.87±0.346	<0.001	<0.001	0.980
Root beer	0.21±0.426	0.00±0.000	0.17±0.397	0.901	0.258	0.203
Dill pickle	0.43±0.514	0.06±0.250	0.47±0.507	0.964	0.016	0.081
Pine apple	0.29±0.469	0.31±0.479	0.97±0.183	<0.001	<0.001	0.977
Lime	0.14±0.363	0.06±0.250	0.83±0.379	<0.001	<0.001	0.802
Orange	0.29±0.469	0.38±0.500	1.00±0.000	<0.001	<0.001	0.755
Wintergreen	0.21±0.426	0.13±0.342	0.17±0.379	0.921	0.934	0.799
Watermelon	0.21±0.426	0.13±0.342	0.83±0.379	<0.001	<0.001	0.799
Thinner	0.64±0.497	0.50±0.516	1.00±0.000	0.008	<0.001	0.520
Grass	0.21±0.426	0.25±0.447	0.77±0.430	0.001	0.001	0.972
Smoke	0.07±0.267	0.31±0.479	0.97±0.183	<0.001	<0.001	0.088
Pine	0.07±0.267	0.13±0.342	0.00±0.000	0.569	0.159	0.779
Grape	0.00±0.000	0.06±0.250	0.07±0.254	0.625	0.998	0.723
Lemon	0.14±0.363	0.31±0.479	0.83±0.379	<0.001	<0.001	0.490
Soap	0.36±0.497	0.31±0.479	1.00±0.000	<0.001	<0.001	0.932

<sup>^</sup>UPSIT: University of Pennsylvania Smell Identification Test

<sup>#</sup>MSA: Multiple System Atrophy

\*PSP: Progressive Supranuclear Palsy

<sup>‡</sup>SD: Standard deviation

**Table 3:** Mean UPSIT<sup>^</sup> scores of patients of MSA<sup>#</sup>, PSP\* and controls of the left nostril for different odors tested and comparison amongst them

Odors tested	Mean±SD <sup>‡</sup> UPSIT <sup>^</sup> score for MSA <sup>#</sup>	Mean±SD <sup>‡</sup> UPSIT <sup>^</sup> score for PSP*	Mean±SD <sup>‡</sup> UPSIT <sup>^</sup> score for controls	p-value between MSA <sup>#</sup> and controls	p-value between PSP* and controls	p-value between MSA <sup>#</sup> and PSP*
Pizza	0.21±0.426	0.31±0.479	0.57±0.504	0.069	0.211	0.843
Bubble gum	0.43±0.514	0.13±0.342	0.63±0.490	0.363	0.002	0.180
Menthol	0.29±0.469	0.38±0.500	0.93±0.254	<0.001	<0.001	0.803
Cherry	0.43±0.514	0.31±0.479	0.73±0.450	0.123	0.015	0.781
Motor oil	0.50±0.519	0.56±0.512	1.00±0.000	<0.001	0.001	0.884
Mint	0.36±0.497	0.31±0.479	1.00±0.000	<0.001	<0.001	0.932
Banana	0.36±0.497	0.25±0.447	0.90±0.305	<0.001	<0.001	0.741
Clove	0.43±0.514	0.63±0.500	1.00±0.000	<0.001	0.003	0.293
Leather	0.57±0.514	0.50±0.516	0.83±0.379	0.181	0.052	0.902
Coconut	0.29±0.469	0.19±0.403	0.87±0.346	<0.001	<0.001	0.773
Onion	0.43±0.514	0.19±0.403	0.87±0.346	0.004	<0.001	0.242
Fruit punch	0.21±0.426	0.13±0.342	0.13±0.346	0.773	0.997	0.782
Licorice	0.43±0.514	0.31±0.479	0.87±0.346	0.007	<0.001	0.738
Cheddar cheese	0.07±0.267	0.06±0.250	0.27±0.450	0.238	0.182	0.998
Cinnamon	0.36±0.497	0.44±0.512	1.00±0.000	<0.001	<0.001	0.810
Gasoline	0.50±0.519	0.63±0.500	1.00±0.000	<0.001	0.004	0.606
Strawberry	0.29±0.469	0.19±0.403	0.70±0.466	0.017	0.002	0.823
Cedar	0.07±0.267	0.00±0.000	0.23±0.430	0.296	0.069	0.827
Chocolate	0.43±0.514	0.19±0.403	0.73±0.450	0.104	0.001	0.322
Ginger bread	0.43±0.514	0.38±0.500	0.87±0.346	0.008	0.002	0.939
Lilac	0.50±0.519	0.69±0.479	0.97±0.183	0.001	0.048	0.360
Turpentine	0.36±0.497	0.75±0.447	1.00±0.000	<0.001	0.046	0.005
Peach	0.21±0.426	0.19±0.403	0.80±0.407	<0.001	<0.001	0.983
Root beer	0.21±0.426	0.06±0.250	0.23±0.430	0.988	0.340	0.540
Dill pickle	0.43±0.514	0.13±0.342	0.47±0.507	0.966	0.058	0.192
Pine apple	0.29±0.469	0.31±0.479	0.93±0.254	<0.001	<0.001	0.980
Lime	0.14±0.363	0.00±0.000	0.83±0.379	<0.001	<0.001	0.449
Orange	0.29±0.469	0.38±0.500	1.00±0.000	<0.001	<0.001	0.755
Wintergreen	0.21±0.426	0.13±0.342	0.23±0.430	0.989	0.668	0.822
Watermelon	0.21±0.426	0.13±0.342	0.83±0.379	<0.001	<0.001	0.799
Paint thinner	0.64±0.497	0.50±0.516	1.00±0.000	0.008	<0.001	0.520
Grass	0.21±0.426	0.25±0.447	0.80±0.407	0.001	0.001	0.971
Smoke	0.07±0.267	0.31±0.479	0.97±0.183	<0.001	<0.001	0.088
Pine	0.07±0.267	0.13±0.342	0.10±0.305	0.956	0.963	0.883
Grape	0.00±0.000	0.06±0.250	0.10±0.305	0.445	0.881	0.778
Lemon	0.14±0.363	0.31±0.479	0.83±0.379	<0.001	<0.001	0.490

<sup>^</sup>UPSIT: University of Pennsylvania Smell Identification Test<sup>#</sup>MSA: Multiple System Atrophy<sup>\*</sup>PSP: Progressive Supranuclear Palsy<sup>‡</sup>SD: Standard deviation

in our MSA and PSP patients, similar to those found in PD patients in previous studies.<sup>[12,27,28]</sup> These values showed greater impairment in smell identification in our patients with MSA and PSP compared to those of PD patients in previous studies.

The duration of the disease did not significantly alter the mean UPSIT scores of patients with PSP and MSA in the present study, similar to a previous study on PSP.<sup>[19]</sup> In PD, the disease duration does not affect the results of smell testing.<sup>[9]</sup>

### Limitations

Due to a lack of funds, the study investigators were able to recruit only 30 patients with Parkinson-plus syndromes; hence, the lack of a larger number of patients is a limitation of this study. Moreover, in our setup, most of the patients presented with either MSA or PSP and DLB and CBD were very infrequently seen; hence, we could not compare these patients. The lack of a pathologically confirmed diagnosis and a comparison group with PD are other limitations of this study.

### CONCLUSION

Hence, patients suffering from Parkinson-plus syndromes (PSP and MSA) have significantly impaired olfaction compared to age- and sex-matched healthy controls, but the differences between the PSP and MSA groups may not be significant. In addition, disease duration did not affect the UPSIT scores of patients with MSA and PSP. These findings may thereby help in differentiating Parkinson-plus patients and controls based on their olfaction but not to that extent between MSA and PSP. Also, the smell dysfunction in these patients may be independent of the duration of disease in these patients.

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**Ethical approval:** The Institutional Review Board at Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, number 2019-194-IMP-113, dated 21/02/2020, approved the study.

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