Original Article

Anosmia in Parkinson’s Disease in Pakistan: A Matched Case – Control Study

Shahid Mukhtar1, Ijaz Hussain Wadd2, Arsalan Haider3, Mohsin Zaheer2, Rashid Imran2
Department of Neurology, 1Lahore General Hospital (LGH), 2Punjab Institute of Neurosciences (PINS), 3Shareef Medical City Hospital, Lahore.

ABSTRACT

Objective: To assess olfactory dysfunction in Parkinson’s disease (PD) patients in Pakistan utilizing an autochthonous smell test.

Setting: Tertiary care center, single-center study.

Materials and Methods: Eighty-seven non-demented patients with PD, who fulfilled Queen Square Brain Bank Criteria were enrolled at the Movement Disorder Clinic, Lahore General Hospital (LGH), Lahore. Fifty-eight controls matched by gender, age, and place of residence were enrolled among patients and visitors attending other hospital clinics. Both groups underwent olfactory testing using the Pakistani Smell Identification test (PKSIT). The participants were required to identify the smell from a set of choices and were scored out of 10.

Results: Among patients in the study group, the mean duration of disease was 4.7 years (range 6 months to 19 years). The PD onset mean age was 52.15 ± 13.02 years among patients. The mean number of smell test items accurately recognized by the PD patients was 4.55 ± 2.4. A multiple linear regression demonstrated that age (P < 0.05) but not disease duration (P = 0.899) was a significant determinant of the smell test result in PD and control groups. The mean number of smell test items appropriately recognized by the controls was 7.33 ± 1.69. Logistic regression showed that the PKSIT had 73.2% sensitivity and 84.3% specificity to distinguish PD from control.

Conclusion: PKSIT being easily available, cheap, and more convenient to use in the Pakistani population, can be used in the evaluation of olfactory dysfunction in PD subjects.

Keywords: Parkinson’s disease (PD), anosmia, Pakistani smell identification test (PKSIT).

INTRODUCTION

During the early nineteenth century, a novel disease was described by James Parkinson in the shape of “shaking palsy” which is currently
recognized as PD (Parkinson’s Disease).\(^1\) PD is one of the world’s fastest-growing neurological disorders\(^2\) and has affected almost ten million people globally. The amount of patients with PD is anticipated to twofold by 2030 because of the elderly populace that is becoming an important national burden among several countries.\(^3\)

After Alzheimer’s disease, PD has believed to be the 2nd most prevalent neuro-degenerative syndrome.\(^4,5\) The Parkinson’s disease has two types, familial; hereditarily inherited in either an autosomal prevailing/recessive way and idiopathic (sporadic); believed to progress from interactions of gene-environment.\(^6\) It is due to numerous motor as well as non-motor symptoms (NMSs).\(^7\) The PD key motor symptoms are bradykinesia, resting tremor postural reflex problem, and rigidity.\(^8\) In addition to such dopaminergic motor indications, non-motor indications also progress due to cholinergic, noradrenergic, serotonergic as well as autonomic nervous system immersion,\(^9\) including cognitive damage, neuropsychiatric indications, olfactory dysfunction (OD), and sleep problems, a few of which could precede motor dysfunction development. Furthermore, PD non-motor symptoms could have an important impact on life quality than the motor indications and are considerably related to decreased well-being.\(^10\)

Olfactory dysfunction is a well-established NMS of Parkinson’s disease.\(^11\) It is the dysfunction that could be from a mildly reduced sense of the smell (hyposmia) to entire smell loss (anosmia).\(^12\) Anosmia is commonly observed in the PD,\(^13\) although it is also quite common in older age\(^14\) and mostly takes place early during the period of the disease. Among PD patients, smell impairment recorded rates ranges from 75 – 95 percent as compared to 25 percent among the normal populace. The olfactory impairment could be related to 10 percent enhanced risk of PD in the future. Therefore, the loss of olfactory is believed a significant criterion regarding PD diagnosis.\(^15\)

Numerous smell tests are available to screen the olfactory dysfunction, including tests of odor adaptation, detection, discrimination, memory, identification, and supra-threshold intensity scaling.\(^16\) Of various olfactory testing kits available, the UPSIT (University of Pennsylvania Smell Identification Test) and Sniffin-sticks are much popular and widely utilized for screening olfaction in idiopathic PD patients.\(^17,18\) Smell tests are heavily influenced by cultural factors. No published studies are available for formal olfactory testing among patients with PD in Pakistan. The current study aims at finding the level of olfactory dysfunction among patients with PD in our country with culturally appropriate smells. We have applied the Pakistani Smell Identification test (PKSIT) to 87 PD Pakistani patients and 58 matched controls.

**MATERIALS AND METHODS**

**Study Type**
Case-control study.

**Setting**
This study is carried out among PD patients visiting Movement Disorder Clinic, LGH, Lahore from Aug. 2019 to Dec. 31, 2020. The study was carried out after approval from Hospital Ethical Committee.

**Inclusion Criteria**
Eighty-seven non-demented Parkinson’s disease patients fulfilling Queen Square Brain Bank criteria were enrolled.

**Exclusion Criteria**
Patients with a history of head trauma, SOL brain, dementia (DSM-IVR), deviated nasal septum,
nasal polyps, chronic sinusitis, and upper respiratory tract infections (within 1 week) were excluded from the study.

**Data Collection**

All respondents provided written informed consent as determined by the local ethics committee. Fifty–eight controls matched by gender, age, and place of residence were recruited among visitors and patients attending other clinics from the hospital with similar exclusion criteria. Socio-demographic variables collected included gender, age, age of onset, and disease duration.

PKSIT was administered in a well-ventilated room. Both the patient and examiner were blind to the name of smell. We used odorants that are common and familiar in our day-to-day life. The 10 odorants used in the PKSIT are cardamom, thinner, clove, rose-water, kewra, mint, mango, chocolate, lemon, and coffee. They are commercially available as food essences in the market. The smells were placed 1 cm from one nostril while the patient inhaled with the other nostril closed. The same was repeated with another nostril. The subjects were given four choices to identify the correct smell. The response was recorded as 1 for correct and 0 for the wrong answer.

To calculate sample size, we used power analysis on G-power Statistical software version 3.1. We used a one-sample t-test and assumed "smell test items appropriately recognized by patients with PD" as an outcome variable. The mean number of smell test items appropriately recognized by patients with PD was considered 6.2 ± 2.5.\(^\text{19}\) We calculated the effect size & power (1-β) to be 0.28 & 0.95, respectively. A total of 140 samples were required to justify the effect of the smell test in PD patients. However, the study was conducted on 145 individuals.

**Statistical Analysis**

All the data entered in SPSS (Statistical package for social science) version 22.0 was analyzed with the same software. The mean rank of skewed smell test scores was calculated for numerical variables. Frequencies and %ages were calculated for qualitative variables. The percentage of controls and PD patients, who answered each item accurately, was compared by Chi-square test. To find out the difference concerning age and gender, the Mann-Whitney U test and Kruskal Wallis tests were applied. To assess if the duration of disease affected PKSIT score in PD, we carried out multiple linear regression analyses that demonstrated a significant effect over PKSIT in control regression. Logistic regression was also carried out to see the predictive relationship that affected the smell test in controls. A p-value < 0.05 was taken as statistically significant.

**RESULTS**

**Gender Distribution**

Among 145 registered patients, 108 (74.5%) were males and 37 (25.5%) were females.

**Age Distribution**

Male patients’ mean age was 55.7 ± 11.3 years while for female patients was 55 ± 12.9 years. For PD and control groups, the mean age was 56.9 ± 12.20 and 55.38 ± 10.79 years, respectively (Table 1). The mean age of disease onset in PD patients was 52.15 ± 13.02 years. Disease duration in PD patients was 4.77 ± 3.87 years.

**Statistical Analysis**

The mean number of smell test items accurately recognized by patients with PD was 4.55 ± 2.45. The mean number of smell test items accurately recognized by control was 7.33 ± 1.69 (Table 2). There was no significant difference (p-value 0.336) between male and female subjects.
regarding smell test scores. It was observed that the mean rank of smell test scores was significantly decreased as age increased (p < 0.001) (Table 3). Disease duration (p-value 0.899) was not a significant determinant of the smell test result in the PD group. Association between the control group and patient group participants who identified the smell was significant in all items (p<0.05). All the odorants showed significant ability to differentiate between PD and control groups (Table 4). Figure-2 indicates the correct replies percentage for each of 10 odorants in both PD and control groups. Clove yielded the highest percentage of correct answers 63.2% in the PD group and 87.9% in the control group. Coffee and thinner yielded the lowest percentage in PD and control groups respectively. All the odorants showed a significant ability to differentiate between both groups (p<0.05). Furthermore, the regression analysis showed that the cardamom and lemon were significantly less likely to be identified (OR = 0.19, p = 0.001; OR = 0.25, p = 0.009) respectively. The analysis also revealed that the mango and coffee had non-significantly higher chances of being identified than other smells (OR = 1.16, p = 0.728; OR = 1.51, p = 0.369) (Table 5). Logistic

![Figure 1: Group – Wise Gender Distribution of Patients.](image)

| Table 1: Descriptive Statistics. |
|----------------------------------|
| **Grouping** | **Control Group** | **Patient Group** | **Mean Age (Years)** | **Total** |
| Gender | Count | % within Group | Count | % within Group | 55.7 ± 11.3 | 74.5% | 37 |
| Male | 37 | 63.8% | 71 | 81.6% | 74.5% | 37 |
| Female | 21 | 36.2% | 16 | 18.4% | 25.5% | 37 |
| Mean age in Groups (Years) | 55.38 ± 10.79 | 56.9 ± 12.20 |
| Total | 58 | 100.0% | 87 | 100.0% | 145 |

| Table 2: Difference of Smell Test Scores in Both Groups. |
|---------------------------------------------------------|
| **Control Group** | **Patient Group** |
| Age of disease onset | 52.15 ± 13.02 years |
| Disease duration at the time of study | 4.77 ± 3.87 years |
| Smell test items correctly identified (n) | 7.33 ± 1.69 | 4.55 ± 2.45 |

| Table 3: Difference of Smell Test Scores Concerning Gender and Age (N = 145). |
|---------------------------------|
| **Parameters** | **n** | **Mean Rank** | **p-value** |
| Gender | | | |
| Male | 108 | 71.05 | 0.336** |
| Female | 37 | 78.69 | |
| < 40 years | 13 | 86.92 | |
| Age | | | |
| 40 – 60 years | 84 | 82.4 | < 0.001* |
| > 60 years | 48 | 52.78 | |

**Non-Significant p-value calculated by Mann Whitney U test.**

*Significant p-value was calculated by Kruskal Wallis H test.
regression showed that the PKSIT had 73.2% sensitivity and 84.3% specificity to differentiate PD from control.

**DISCUSSION**

Parkinson’s disease is a neurodegenerative syndrome that is linked with a wide range of motor & non-motor indications. Olfactory dysfunction is a well-established NMS of
Parkinson’s disease. Identification of Odor is an easy, however, valuable instrument that helps in differentiating Parkinson’s disease from other parkinsonism causes. Though smells are based on cultural differences, thus test methods have to be modified to regional circumstances as well as habits in which they are envisioned for utilize. Therefore, the current study was carried out to know the extent of olfactory dysfunction in Parkinson’s disease patients in our country with the smells that are culturally appropriate and to know the olfactory dysfunction in PD patients in Pakistan utilizing an autochthonous smell test. To acquire appropriate outcomes, a total of one hundred and forty – five registered patients were included in the study and found that most of the patients (74.5%) were male while only 25.5% were female patients with mean age 55.7 ± 11.3 and 55 ± 12.9 years, respectively. The study further indicated that the mean age for PD and control groups was 56.9 ± 12.20 and 55.38 ± 10.79 years, respectively. The mean duration of disease among patients was 4.77 ± 3.87 years. A similar study carried out by George and teammates (2013) demonstrated that among 53 PD patients and 50 controls, no significant difference was found regarding age and gender. The mean age was 58.5 ± 13.1 and 55.8 ± 7.4 years for PD patients and controls, respectively. The majority of the participants 71.7% and 62.0% were males in the patient and control groups, respectively. Among patients, the mean duration of disease was 7.1 years.

In our study, olfaction was assessed by a self-made smell test utilizing commonly used items that are pertinent to our culture. We have named it PKSIT (Pakistani Smell Identification test). Literature shows that the outcome of smell identification tests usually depends on country, culture, age, sex, and smoking status. In our study when male and female subjects are compared, we see that there is no significant difference between the two groups (p-value 0.336). There is mixed data in the literature on this matter. The UPSIT is affected by gender however other studies that involved large samples of participants showed that olfactory identification is similar in both sexes.

In our study, most of the smells used were common kitchen smells (food essences) and females were expected to perform better than males. Studies show that in general females have a better sense of smell as compared to males. It is shown that females have higher grey matter concentration within orbitofrontal lobes including Brodmann’s areas 10, 11 & 25, and bilateral hippocampus, right amygdala, and left basal insular cortex.

Our study showed that advanced age adversely affects olfaction (p < 0.001). This is in agreement with international studies. Increasing age is associated with severe non-motor symptoms and these patients also show rapid progression of the disease process. Multiple factors play part in an age-related loss in olfaction including damage to olfactory mucosa from viral and environmental agents, ossification of lamina cribrosa, alteration in neuromodulation systems, and expression of intracellular inclusion bodies that are pathological hallmarks of several neurodegenerative disorders.

Data obtained from our study showed that olfaction is not affected by the age of onset and disease duration. It is mainly due to fact that olfaction is affected early in the disease process before full-blown motor symptoms kick in. The earliest pathological changes take place in the anterior olfactory nucleus and olfactory bulb while substantia nigra is not engaged yet.

Utilizing PKSIT, the control group showed the percentage of correct responses ranging from 87.9% (Clove) to 58.6% (coffee). In the study group percentage of correct answers ranged from 63.2% (clove) to 36.8% (Thinner). Better response with clove is mainly due to clove being the common ingredient of Pakistani cuisine.

PKSIT showed a sensitivity of 73.2% and specificity of 84.3% to differentiate PD from other neurodegenerative diseases.
control. Studies done across the globe report sensitivity of smell tests ranging from 71.4% to 93% and specificity to be 68% to 99% depending on different olfaction kits used in each study. Further studies may improve the sensitivity and specificity of PKSIT.

Until now, there is no smell identification test specifically made for the Pakistani populace. This is the first study done in Pakistan so far. Diagnosing PD on basis of PKSIT can be fruitful in the future as the test is very simple, easy and quick to administer, and cost-effective as well. The findings of our study show olfactory dysfunction in PD patients in Pakistan consistent with studies done in other parts of the world.

Since PKSIT utilized over-the-counter food essences as test smells so their intensities can be different depending on manufacturers etc. so test-retest reliability needs to be studied in future researches. Future studies are required to compare PKSIT with other well-known smell identification tests (SIT) like odorant Sniffin-sticks® test and UPSIT. There is a need to develop a standard smell test designed specifically for our population that can be used in future studies.

CONCLUSION
PKSIT can predict olfactory loss in patients with idiopathic PD. Being low-cost and culturally appropriate, PKSIT can be employed to test olfaction in PD patients in Pakistan. Given the increasing interest in olfactory dysfunction in movement disorders, additional research is warranted to establish the clinical utility of PKSIT in our country. Future studies can also help to make necessary amendments in PKSIT to improve the test-retest reliability as well as its sensitivity and specificity.

Strengths and Limitations of the Study
- The first study in Pakistan on this subject.
- Culturally appropriate smells are used rather than imported smell tests.
- One limitation was related to the lack of standardization of smell test items.

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Additional Information
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Human Subjects: Consent was obtained by all patients/participants in this study.
Conflicts of Interest:
In compliance with the ICMJE uniform disclosure form, all authors declare the following:
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AUTHORS CONTRIBUTIONS

| Sr.# | Author’s Full Name | Intellectual Contribution to Paper in Terms of: |
|------|-------------------|-----------------------------------------------|
| 1.   | Shahid Mukhtar    | 1. Study design and methodology.              |
| 2.   | Ijaz Hussain Wadd | 2. Paper writing and data calculations.       |
| 3.   | Arsalan Haider    | 3. Data collection and calculations.          |
| 4.   | Mohsin Zaheer     | 4. Analysis of data and interpretation of results quality insurer etc. |
| 5.   | Rashid Imran      | 5. Literature review and referencing.         |