Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 193 – 202
Received 25 April 2021; Accepted 08 May 2021.

Quantifiable Olfactory Dysfunction as a Diagnostic marker in Parkinson's disease: A study from Central Kerala

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Date of Submission: 31/03/2021

ABSTRACT

Olfactory dysfunction which may precede motor dysfunction in Parkinson's disease (PD) is often neglected in the clinical care setting. The present study aimed at assessing and quantitating olfactory function in PD patients and comparing olfactory function between patients with young-onset Parkinson's disease (YOPD) and those with the later-onset disease. Patients diagnosed with PD had their olfactory function tested and compared with controls; tested olfactory parameters included Olfactory Recognition Threshold, Olfactory Identification Score and Olfactory Discrimination Score. 32 PD patients and 63 healthy controls were recruited for olfactory function assessment after obtaining informed consent. Our results revealed a statistically significant loss of olfactory function among PD patients compared to age-matched controls (p-value <0.001). The correlation analysis showed a statistically significant negative correlation between olfactory scores with a duration of PD (p-value =0.029 and <0.001).Olfactory function was impaired in YOPD compared to controls but not as severely affected as in elderly PD patients. We conclude that olfactory dysfunction can be used as an easily tested, reliable, quantifiable and inexpensive biomarker for Parkinson's disease.

Keywords: Olfaction, Hyposmia, Parkinson's disease.

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Received 25 April 2021; Accepted 08 May 2021.

INTRODUCTION

Parkinson's disease (PD) is a slowly progressing neurodegenerative disorder that affects nearly 1% of the population above 60 years (Alexander, 2004).Although the motor signs of PD are well- recognized since the time of their initial description by James Parkinson in 1819,non-motor symptoms have been less appreciated till relatively recently. Among these non-motor symptoms is olfactory and gustatory dysfunction, which may precede motor involvement in PD but are often missed due to non-awareness of the patient and clinician (Doty, 2012).The olfactory sense affects appetite and guides food preference; it is intricately interconnected with memory, mood and emotion (Mouly et al., 2010).Odorous chemicals acting as pheromones can influence sexual behaviour and well-being, while noxious odours occasionally warn of danger. Olfactory impairment can be an early sign of neurodegenerative disorders, particularly synucleinopathies, including PD. Hyposmia can serve as a biomarker to differentiate PD from 'Parkinson's - plus' or atypical Parkinsonian syndromes and improve diagnostic accuracy (Doty,2012, Rodriguez–violante et al., 2017, Haehner et al.,2011).Hyposmia and hypogeusia may also predispose to nutritional deficiencies that can affect the quality of life and lead to disease exacerbation. However, olfactory and gustatory assessment is often neglected by clinicians as they are inconvenient and cumbersome to perform in an outpatient setting. The testing of these functions is also hindered by the lack of easily available, culturally appropriate, structured and validated tools (Huttenbrink et al., 2013, Kershaw et al., 2018, Shah M et al., 2009).

Ultra-structural studies have revealed that olfactory and lower brainstem pathways are targets of alpha-synuclein deposition and Lewy body formation long before nigrostriatal pathways are affected; inhibitory dopaminergic neurons are found to be overexpressed within the olfactory bulb's glomerular layer of Parkinson's disease patients. (Doty, 2012).

There are few published studies of olfactory dysfunction in South Indian PD patients. The present hospital-based study aims at investigating olfactory function in a cohort of patients from Central Kerala. It also seeks to compare olfactory functions in classical elderly patients PD and those with Young-onset Parkinson's disease(YOPD), defined as an age of onset below 40 years.

MATERIALS AND METHODS

The study was approved by the Institutional Ethics committee of Little Flower Hospital and Research Centre (EC/25/2018), Angamaly, Kerala, India and performed respecting the guidelines for biomedical studies involving human subjects (Helsinki/Somerset West).

Patients diagnosed with PD and attending the Neurology Outpatient Department at the hospital were selected randomly and enrolled after obtaining informed consent. Those patients with other co-morbid neurological disorders or upper respiratory tract infections were excluded. Healthy controls were used as comparators. Demographic data concerning age, sex, and duration of illness were collected. A general physical examination was carried out, and current neurological status documented.

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For testing olfaction, ginger, cardamom, garlic, coffee and vanilla were selected as five common, locally recognized, culturally appropriate, odoriferous substances and validated in an in-house pilot study. Solutions of these five substances were prepared in deionized water in three different concentrations each. The concentrations selected on the basis of the pilot study were Ginger: 1%, 2%, 3%; Cardamom: 0.4%, 2%, 3%; Garlic: 0.8%, 1.4%, 2%; Coffee:1.6%, 2%, 4% and Vanilla:2%, 3%, 4% .These olfactory stimuli were separately and individually applied to the nostrils of the participants using an olfactometer, constructed and tested in-house by the blast injection method (Elsberg et al.,1936). The olfactometer consists of a bottle with a tight rubber stopper equipped with sterilizable inlet and outlet tubes. The test solution is introduced to the bottom of the bottle. When both tubes are occluded using pinch clamps, the air in the bottles become saturated with vapour from the odorous liquid in the bottle. The outlet tube was introduced by the examiner into the nostrils of the participants through a nose-piece and the pressure within the bottle raised by controlled, manual injection of specific volumes of air through the inlet tube leading to the emission of odorous vapour into the nostrils of the participants through the outlet tube when the pinch-clamp is released. The following olfactory parameters were then recorded:

Olfactory recognition threshold: The minimum pressure of the odorous vapours, which is required by the participants to recognize the presence of odour in the vapours released into their nostrils at a particular concentration, which correlates with the volume of air injected into the inlet tube. It is expressed in unit pounds per square inch (psi).

Olfactory identification score: The participants were blindfolded and tested with the 5 different odours at the highest concentration and maximum pressure; they were asked to select the correct odour from the 5 choices provided. Each correct response was scored 1 and incorrect or no response was scored 0.The maximum score was 5.

Olfactory discrimination score:10 pairs of olfactory stimuli were presented, with 5 pairs of similar odour and 5 pairs of different odours. Each pair was then presented in random order, and the participants asked to state whether the odours were ‘the same’ or ‘different’. Each correct answer scored 1 and incorrect response 0. The maximum score was 10.

The results were tabulated; the olfactory parameters of the patients with PD were compared with those of controls and correlations attempted with the duration and severity of disease. Comparisons were also made between patients with YOPD and those with onset beyond 60 years.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 20.0 software. For testing the statistical significance of the difference in the mean and median of olfactory recognition thresholds between the PD group and control groups, Mann Whitney U test was used. Statistical significance of the difference in the mean and median of olfactory recognition thresholds at different concentrations among the YOPD group and elderly PD groups were tested using the Friedman test. Spearman rank correlation was used for studying the relationship of olfactory scores with age, BMI and duration of PD; its statistical significance

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was tested using the Linear Reg t-test. The Mann Whitney U test was used to test the statistical significance of the difference in the mean and median of olfactory identification score and olfactory discrimination score between YOPD and classical patients.

RESULTS

The studied population consisted of 32 PD patients and 63 healthy controls. Among the 32 PD patients, 2 had drug-induced/aggravated PD and 7 had YOPD. The control group varied in age from 23 to 75 years (Mean 47.9±15.9 years), whereas the PD group ranged between 23 to 75 years of age (mean 57.9±10.8 years). There was a male predominance in the PD group (58.8%) compared to controls (46%). Among the 30 Idiopathic PD patients, 1 was found to be anosmic and 29 had hyposmia. Olfactory recognition thresholds were significantly higher in the PD group compared to age-matched controls (p-value <0.001), indicating impaired olfactory function (Table 1). Olfactory identification scores and discrimination scores were significantly decreased among the PD group, compared to the control group (Mann Whitney U test, ***p<0.001) (Table 2). The positive correlation of olfactory recognition thresholds with the duration of disease was statistically significant. Only ginger at the concentration level of 0.80% shows a significant negative correlation (Table 3). A negative correlation was observed between olfactory identification score and olfactory discrimination score with a duration of PD (p value=0.029 and <0.001)(Table 4). The correlation between olfactory recognition thresholds with Hoehn and Yahr staging of severity of PD was statistically significant (Spearman Rank Correlation, *p<0.05,**p<0.01,***p<0.001)(Table 5).Comparisons of olfactory recognition threshold of Ginger at 2% and 3%, Cardamom at 2% and 3%, Garlic at 2% and that of Coffee and Vanilla at all concentrations showed a statistically significant difference between YOPD and patients with later-onset PD indicating higher olfactory performance in YOPD patients than that of elderly PD group using Friedman Test, *p<0.05, **p<0.01, ***p<0.001(Table 6). Among YOPD, olfactory identification score and olfactory discrimination scores was found to be higher compared to more elderly PD, indicating better olfactory function (Mann Whitney U test,**p<0.01) (Table 7).

Table 1: Comparison of Olfactory Recognition Thresholds between PD and control groups

Olfactory Variables	Concentration	PD group Olfactory Recognition Threshold(psi)	Control Group Olfactory Recognition Threshold(psi)	U-statistics value	p-value
		Mean±SD	Mean±SD		
Ginger	1%	20±0	8.6±7.1	225	<0.001***
	2%	14.3±6.3	3.0±2.8	54.5	<0.001***
	3%	10.8 ±7	2.0±2.5	102	<0.001***
Cardamom	0.40%	19.7±1.8	2.4±1.85	0.50	<0.001***
	2%	12.2±7.7	1.6±1.1	58	<0.001***
	3%	8.9±7.0	1.3±0.5	33	<0.001***

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Garlic	0.80%	17.7±6.0	1.9±1.3	70.5	<0.001***
	1.40%	8.8±6.9	1.4±0.57	69	<0.001***
	2%	6.5±6.5	1.2±0.22	124.5	<0.001***
Coffee	1.6%	19.7±3.2	2.2±1.6	4.5	<0.001***
	2%	10.1±6.9	1.4±0.5	21	<0.001***
	4%	7.8±6.8	1.4±1.1	52	<0.001***
Vanilla	2%	19.7±3.2	2.5±1.9	8	<0.001***
	3%	10.7±7.7	1.4±0.4%	81	<0.001***
	4%	6.9±6.5	1.26±0.27	47.5	<0.001***

Mann Whitney U test, * statistically significant at p<0.001**

Table 2: Comparison of Olfactory Identification and Discrimination scores between PD and control groups

Olfactory Parameters		**Controls**	**PD group**	**Mann Whitney U Value**	**p-value**
		Mean±SD	**Mean±SD**		
Olfactory Scores	**Identification Score**	4.87±0.34	3.27±1.04	205.50	<0.001***
	Discrimination Score	9.86±0.35	6.42±2.44	193.50	<0.001***

Mann Whitney U test, * statistically significant at p<0.001**

Table 3: Correlation of Olfactory Recognition Thresholds with duration of PD

Olfactory Variables		**Duration of PD**	
		Correlation Coefficient	**p-value**
Ginger	1%	0.094	0.598
	2%	0.482	0.004**
	3%	0.458	0.006**
Cardamom	0.40%	0.167	0.344
	2%	0.537	0.001**
	3%	0.644	<0.001***
Garlic	0.80%	-0.364	0.034*
	1.40%	0.798	<0.001***
	2%	0.815	<0.001***
Coffee	1.60%	0.244	0.164
	2%	0.819	<0.001***
	4%	0.753	<0.001***
Vanilla	2%	0.242	0.168
	3%	0.499	0.003**
	4%	0.749	<0.001***

Spearman rank Correlation, statistically significant at*p<0.05, **p<0.01, ***p<0.001

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Table 4: Correlation of Olfactory scores with age and duration of PD

Olfactory Parameters		Age		Duration of Disease	
		Correlation Coefficient	p-value	Correlation Coefficient	p-value
Olfactory Scores	Identification Score	-0.640	<0.001***	-0.399	0.029*
	Discrimination Score	-0.633	<0.001***	-0.784	<0.001***

Spearman rank correlation analysis, statistically significant at *p<0.05, ***p<0.001

Table 5: Correlation of Olfactory Recognition Threshold with Hoehn and Yahr (H&Y) staging of PD

Variables		H&Y stage of PD	
		Correlation Coefficient	p-value
Olfactory threshold			
Ginger	1%	0.291	0.106
	2%	0.554	0.001**
	3%	0.611	<0.001***
Cardamom	0.40%	0.362	0.042*
	2%	0.626	<0.001***
	3%	0.777	<0.001***
Garlic	0.80%	0.538	0.001**
	1.40%	0.857	<0.001***
	2%	0.888	<0.001***
Coffee	1.6%	0.425	0.015*
	2%	0.841	<0.001***
	4%	0.852	<0.001***
Vanilla	2%	0.425	0.015*
	3%	0.524	0.002**
	4%	0.834	<0.001***
Identification score		-0.371	0.044*
Discrimination score		-0.762	<0.001***

Spearman Rank Correlation, statistically significant at*p<0.05, **p<0.01, ***p<0.001

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Table 6: Comparison of Olfactory Recognition Thresholds between YOPD and classical PD groups

Variables		YOPD Olfactory Recognition Threshold(psi) Mean±SD	Classical PD Olfactory Recognition Threshold(psi) Mean±SD	Chisquare value	p-value
Ginger	1%	20±0	20±0	31.3	1.00
	2%	6.8±2.4	16.7±5.2		<0.001***
	3%	2.7±1.0	13.2±6.3		<0.001***
Cardamom	0.40%	18.6±3.8	20±0	37.0	0.070
	2%	3.2±1.2	14.9±6.7		<0.001***
	3%	2.1±0.31	10.9±6.8		0.002**
Garlic	0.80%	15.2±8.2	18.4±5.2	41.4	0.184
	1.40%	4.5±2.1	10.1±7.3		0.124
	2%	2.2±1.4	7.9±6.9		0.015*
Coffee	1.6%	16.4±6.3	20±0	42.6	0.009**
	2%	4.9±3.1	11.7±7.0		0.022*
	4%	2.3±1.0	9.5±6.9		0.001**
Vanilla	2%	16.4±6.3	20±0	45.4	0.009**
	3%	3.11±1.4	13.0±7.3		0.001**
	4%	2.1±0.9	8.4±6.8		0.002**

Friedman Test, statistically significant at*p<0.05, **p<0.01, ***p<0.001

Table 7: Comparison of Olfactory scores between YOPD and Classical PD groups

Olfactory Parameters	PD based on Age of onset	n	Mean (SD)	U-statistics value	p-value
Olfactory Identification Score	YOPD	7	3.8(0.69)	24	0.003**
	Classical PD	23	2.65(0.9)		
Olfactory Discrimination Score	YOPD	7	8.1(1.2)	18	0.002**
	Classical PD	23	5(2.2)		

Mann Whitney U test, statistically significant at **p<0.01

DISCUSSION

The present study aimed at identifying and quantifying the olfactory dysfunctions among PD patients in our region with respect to their age-matched controls by using various odours which are common and locally recognized. Using a comparatively novel approach, three different olfactory parameters - olfactory recognition threshold, olfactory identification and olfactory discrimination - were assessed and quantitated using recognizable odorous substances common to the region and culture in solutions of different concentrations. The

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University Pennsylvania Smell Identification Test (UPSIIT), as well as other olfactory assessment tests developed in various parts of the world, uses many odours which are unfamiliar to the local populace(George et al., 2013).Our methodology has the advantages of being inexpensive while relatively easy to administer, quantify and replicate.

Olfactory dysfunction was confirmed in patients with PD compared to age-matched controls in the local population. The olfactory recognition threshold was raised in patients with PD, similar to studies from India and elsewhere (Muller et al., 2002). Investigators have reported a correlation between the volume of the olfactory bulb and olfactory thresholds (Haehner et al., 2008). Recently diagnosed PD patients also showed an increase in the olfactory recognition thresholds indicating early olfactory dysfunction. However, the olfactory recognition thresholds at various concentrations were significantly lower in the YOPD group compared to classical PD with the age of onset above 60 years, albeit higher than the control group. The olfactory scores were significantly higher among the young-onset group, indicating that higher olfactory functions like identification and discrimination are relatively better preserved among the young-onset group.

Our results are notable in contradicting other studies that found no change in the odour discrimination and odour identification (Doty et al., 1988; Hawkes et al., 1998; Stern et al.,1994). The Odour Identification Score and Odour Discrimination Score were found to be significantly reduced in our population of patients with PD and there was a significant negative correlation with duration of disease and H&Y stage of PD. Pearce et al. reported a significant correlation between cellular loss in the olfactory bulb and the duration of PD (Pearce et al., 1995), which provides a plausible explanation. Boehnen et al. have also found cholinergic denervation of the limbic archicortex to be a more robust determinant of hyposmia than nigrostriatal dopaminergic denervation in subjects with moderately severe PD (Bohnen et al.,2010). Inability to identify and discriminate between odours could have negative prognostic consequences in situations such as cooking-gas leaks.

The olfactory loss was not observed in patients with drug-induced PD and their olfactory identification score and olfactory discrimination score were all similar to that of controls. This could potentially be a distinguishing feature between patients with drug-induced PD and those with IPD whose disease was aggravated or triggered by drugs but needs to be evaluated in larger samples. Olfactory dysfunction is a feature of synucleinopathies like IPD and olfactory parameters were normal in 2 patients with atypical Parkinsonism who were tested. Olfactory dysfunction thus has diagnostic and, potentially, prognostic significance.

CONCLUSION

Our results confirm that olfactory dysfunction is a feature of PD. Olfactory parameters like Olfactory Recognition Threshold, Identification Score and Discrimination Score can be used as cost-effective, quantifiable and replicable biomarkers in PD, which are of diagnostic and potentially prognostic, value.

ACKNOWLEDGEMENTS

The authors are thankful to the management, Little Flower Hospital and research centre for providing support and needed facilities for conducting the research work.

The authors are grateful to Ms Anithadevi T.S, Assistant Professor, Department of Biostatistics, Little Flower Institute of Medical Science, Angamaly, for her assistance in data analysis.

CONFLICT OF INTEREST

The author declares that there was no conflict of interest in the present study.

FUNDING OF SUPPORT

The authors declare that they have no funding support for this study.

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