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Olfactory Impairment in Parkinson's Disease: Its Frequency and Correlation to Clinical Severity in Sudanese Patients, Wad-Medani Teaching Hospital, 2022

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Abstract

Background: *The olfactory impairment is the most common non-motor symptom in Parkinson's disease (PD). It may predate the onset of Parkinson's disease by several years and it is one of the supportive criteria for the diagnosis. Its presence is also related to rapid disease progression and more pronounced impairment of Motor symptoms.*

Objective: *The aim of this study is to determine the frequency of olfactory impairment in patients with Idiopathic Parkinson's disease and its correlation to the clinical severity of the disease.*

Methods: *This is a cross sectional hospital-based study, carried out at Wad-Medani Teaching Hospital at the Neurology Department over a period of four months; from March to July 2022. Data was collected using a validated version of olfactory questionnaire and Hoehn and yahr scale, our study covered all PD patients who were fitting the inclusion criteria. Data was processed and analyzed using SPSS version 25.*

Results: *The study included 61 patients, males were 32 (52.46 %) and females were 29(47.54%). The mean age of patients was 63.8 +/- 12.3 SD, about 76% of them had been diagnosed within less than 5 years. Most patients 48 (78. 7 %) were normosmic and only 13 (21.3%) had hyposmia ranging from mild to Severe form. Male patients had higher Frequency of anosmia 9 cases (69.3 %) compared to females (30.7%), the P value was (0.012) statistically significant for sex difference in olfactory dysfunction. The highest number of cases 24 (39.3%) were in stage 3 of Hoehn and yahr (H & Y) scale. There is statistically significant correlation between the scale and the degree of hyposmia (P value <0.013). The study also showed that in near half (45.5%) of hyposmia patients the olfactory impairment had antedated the Parkinsonism by mean of 4.8 +/- 1.6 years.*

Conclusion: *The study concluded that the olfactory impairment presents in about one fifth of Parkinson's disease patients, with male predominance and was associated with more severe impairment in motor performance scales. It also predates PD in about half of the patients by mean of 4.8 years.*

Keywords: Olfactory Impairment, Sudanese Patients, Parkinson's Disease, Wad Medani, Sudan.

Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by loss of dopaminergic neurons in the substantia nigra and other brain stem centers. The pathologic hallmark of this disorder is the presence of eosinophilic cytoplasmic inclusions, called Lewy bodies, within many of the neurons. PD has a prevalence of 160 cases per 100,000 population and an incidence of about 20 cases per 100,000 people per year. Prevalence and incidence

increase with age. The mean age of disease onset is 56 years in both males and females, and PD is twice common in males than females [1]. The clinical features of the Parkinson's disease include: resting tremors about 4 - 6 Hz. Bradykinesia or Akinesia presents as poverty of initiation of movement, expression less face, micrography, sialorrhea, and hypophonia. Postural and gait disturbances, Freezing and non-Motor symptoms (NMS) [2]. The Non-Motor Symptoms (NMS) of Parkinson's disease are found in 88% of the patients [3]. Olfactory Dysfunction is the most common NMS and presents in about 75% to 95% of patients with PD [4]. The Olfactory Dysfunction can predate the diagnosis of PD by many years (at least 4 years), and in normal individuals' olfactory impairment is associated with 10% increased risk of future development of PD. Anosmic patients with PD have poor performance in cognitive scores, that might be an indicator of future PD dementia. Yet, variable degrees of olfaction impairment could be attributed to variable levels of neuro degeneration of the dopaminergic system, reflecting a worse out come in patients with more severe olfactory dysfunction. Worse olfactory performance was recently discovered in patients with higher Hoehn and Yahr stage [4].

Patients and Methods

This is a cross sectional hospital-based study conducted from March to July 2022 at the Neurology Unit (this unit had been established in 2021. it consists of A Neurology specialist one Neurology fellow and ten General medicine Registrars alternate every 4 months as training programme) in Wad-Medani teaching hospital, Gezira state, Sudan.

A total of 61 patients were enrolled in the study. The inclusion criteria were all patients with Parkinson's disease with normal cognitive function according to Mini-mental state examination MMSE, patients with chronic respiratory disease or those who recently recovered from Covid19 infection and those with traumatic injuries to the nose were excluded from the study [5]. Neurological examination for motor system and motor staging was performed by the Neurology Department using modified Hoehn and yahr scale (H&Y), it contains the following stages (table 1) [6]:

Table 1: H&Y scale.

Stage	Criteria
1	Unilateral disease
1.5	Unilateral plus axial.
2	bilateral disease without impairment of balance
2.5	bilateral disease with recovery on pull test
3	mild to moderate bilateral, some postural instability but physically in dependant.
4	Severe disability, still able to walk or stand unassisted.
5	Wheel chair bound or bed ridden.
5	Wheel chair bound or bed ridden.

The olfactory function had been assessed by a validated Korean version of Olfactory Questionnaire, with substitution of question two and three by odorants from Sudanese traditional meals (question two and three were about Smelling of korean foods pizza and korean stew and replaced by Sudanese traditional meals (Takaleya and Kurrasa) respectively. The Korean version of Olfactory questionnaire was created by department of Oto laryngology, Soel national University college of medicine and validated on 2020 by correlation of the questionnaire scores with those of standard olfactory functioning tests using Butanol threshold test BTT and Cross-cultural smell identification test CCSIT [7]. It contains 14 questions in which the subject indicates his odor sense to variable items by one of the following choices: Never (0%), Seldomly (20%), Sometimes (50%), Often (70%), Always (100%). with score points 0, 1, 2, 3, 4 for each choice respectively. (questions 6, 8, 14 where not verified by score).

Please indicate your sense of smell in the 14 situations below: Never 0 () Seldomly 1 () sometimes 2 () often 3 () Always 4().

1. Can you smell while eating or cooking?
2. Can you smell kimchi, ramen, or pizza?
3. Can you smell Korean stew?
4. Can you smell coffee, tea, or wine?
5. Can you smell fruits?
6. Can you smell sesame oil?
7. Can you smell meat grilling?
8. Can you smell cosmetic or perfume?
9. Can you smell soap or shampoo?
10. Can you smell toothpaste
11. Can you smell cigarette?
12. Can you smell restroom odor?
13. Can you smell smoky or burnt scent?
14. Can you relate when people around you say something smells?

By the end of the questionnaire the summation of answers will be interpreted as the following:
normosmia (42 _44). Mild hyposmia (28_41).

Moderate hyposmia (18_27). Severe hyposmia (5_17).
Anosmia (0_4).

The data was coded, processed and analysis using statistical package for social science (SPSS) for window version 25. The data of numerical value were expressed in form of (mean+/- standard division SD). Chi squire test was used for analysis of categorical values and Spearman's test was used for correlation between olfaction score and motor severity of the disease. Any P value <0.05 was considered statistically significant. The results were presented in tables sand graphs. Ethical clearance was obtained from Sudan Medical Specialization Board besides approval from the Wad Madani hospital directory which was tak-

en to conduct the study. Written informed consent was obtained from all patients.

Results

The study included 61 patients with Parkinson's disease who fulfilled the inclusion criteria within the study period. Males were 32(52.46%) and females were 29(47.54%); with a male to female ratio of 1.10 to 0.90. The mean age of patients was 63.8 years +/- 12.3 SD, while the mean age of diagnosis was 61 years and most 47 (76%) of cases had been diagnosed within 5 years of the disease onset table 2.

Regarding the smell disturbances, forty-eight (78.7%) patients were normosmic, while thirteen (21.3 %) patients had hyposmia distributed as the following, 7 (11.48%), patients had mild hyposmia, 5(8.20%) had moderate hyposmia and only one (1.64%) had severe hyposmia. Figure 1.

Questionnaire scores showed that olfactory impairment was more common in males compared to females (P value = 0.012); hyposmic males were nine (69.3 %), while hyposmic females accounted in four (30.7 %) of patients.

Interestingly about half of hyposmic patients 6 (54.5%) had developed impairment of olfaction after being diagnosed with Parkinson's disease, with a mean of 2.6 years post-diagnosis, while in five (45.5%) patients the hyposmia had antedated the disease by mean of (4.8 +/- 1.6 SD) years. Two patients were not sure about the exact time of onset of smell disorder.

Stage of motor symptoms according to the Hoen and Yahr scale showed the stages, in order of frequency, as follows: commonest was stage three in 24 (39.3%) patients, followed by stage 2.5 in 13 cases (21.3%), stage 2 in 10 (16.4%) patients, stage four in 5 (8.2%) patients and stage one 4 (6.6 %) patients Table 3. the mean stage was 2.5. Stage 5 patients were zero cases due to co-existent low mental state score (indicates presence of dementia), which disqualified them from the study.

Regarding the relation between the questionnaire score of olfactory performance and Hoen and Yahr scale; the study revealed that 16 (33.3%) normosmic patients were stage three and 4 (8.3%) were stage one, 8(16.6%) patients in stage 2, 12 (25%) cases in stage 2.5 and 3(6.25%) cases for stage 4. In the seven patients with mild hyposmia, 2 (28.6%) of them were at stage 1.5 and 5 (71.4 %) were stage 3. In the five moderately hyposmic patients 3(60%) were at stage three and the other 2 patients were distributed between stage 2.5 and stage 4; (20%) for each stage. The single patient with severe hyposmia (100%) was at stage four (table 3). The more severe olfactory dysfunction is associated with higher stage of Hoehn and yahr scale by using Spearman 's test the P value was (0.013); which shows statistically significant correlation between the olfactory dysfunction and H & Y scale (table 4) With regard to the relation between the age and impairment of olfaction the (P value= 0.861) which was statistically insignificant.

Table 2: Time since the diagnosis

	Frequency	Percent
Less than one year	13	21.3
1 and less than 5 Years	34	55.7
5 and less than 10 Years	11	18.0
More than 10years	3	4.9
Total	61	100.0

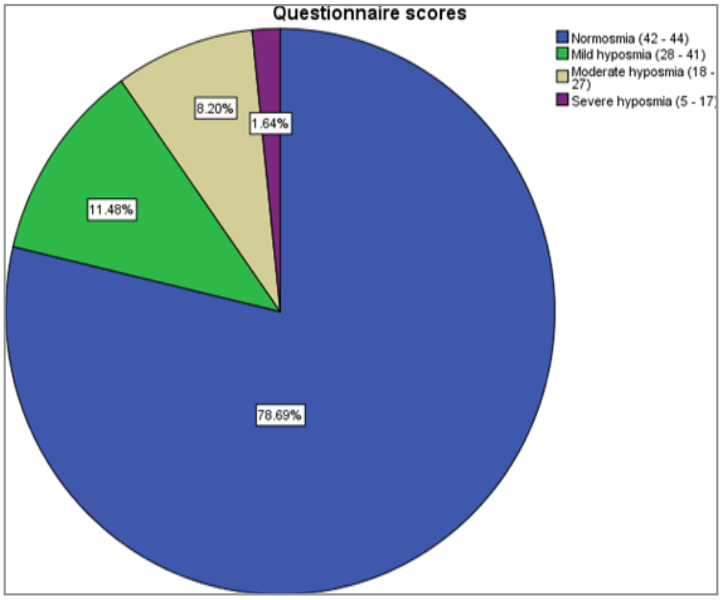

Figure 1: questionnaire score for grading of hyposmia.

Table 3: olfactory questionnaire score VS Hoen and Yahr stage

		Hoen and yahr scale stage						
Questionnaire scores		1.00	1.50	2.00	2.50	3.00	4.00	Total
	Normosmia (42 - 44)	4	5	8	12	16	3	48
	Mild hyposmia (28 - 41)	0	0	2	0	5	0	7
	Moderate hyposmia (18 - 27)	0	0	0	1	3	1	5
	Severe hyposmia (5 -17)	0	0	0	0	0	1	1
Total		4	5	10	13	24	5	61

Table 4: Spearman's test for Correlation between motor disability using H & Y scale iand Degree of olfactory impairment, Correlations

			Hoen and yahr scale stage	Questionnaire scores
Spearman's rho	Hoen and yahr scale stage	Correlation Coefficient	1.000	.315*
		Sig. (2-tailed)	.	.013
		N	61	61
	Questionnaire scores	Correlation Coefficient	.315*	1.000
		Sig. (2-tailed)	.013	.
		N	61	61

Discussion

This is a cross sectional Hospital based study, aimed to study the Frequency of Olfactory impairment in Parkinson's disease and its correlation to clinical severity of the illness and covered 61 participants

The study showed one fifth (21.3%) of the patients involved in this study had smell impairment. A study in Egypt by Khaled Hussein et al , with the mean age of patients was 57.7 +/- 3.5 years (6 years younger than our cohort) , males were 19 (59.4%) and 13 (40.6%) females with disease duration 2.1 +/- 0.6 years, showed that only 10 patients (31.25%) were aware of their impaired olfaction (near to our cohort) , with use of sniffin stick test SST 13 (40.6%) were hyposmic and (59.4 %) had functional anosmia [8] and this may explain the difference between the awareness of the patients to their olfaction and the actual state of Smelling ,because with the use of the standard psychophysical tests in this study almost all the Egyptian PD were found to be hyposmic . Similar results were obtained by Binyam et al on 123 PD patients, their age was also Similar to our cohort (mean age in the Ethiopian study was 62.9 years) showed that olfactory dysfunction was found in about 25.2% of Ethiopian patients with PD, this study had used the NMS questionnaire for data collection [9], the Ethiopian study had estimated the frequency of hyposmia near to our Sudanese Patients and this may be due to similarities in both genetic and environmental factors or due to subjective assessment of hyposmia using the NMS questionnaire in the Ethiopian cohort.

Our study was inconsistent with a study done in Australia by Sara Cavaco and others conducted on 160 non-demented patients with PD using brief smell identification test for assessment of Olfactory dysfunction and H and Y scale for motor symptoms demonstrated a smell impairment in 82% of patients [10], and many large series have estimated the Frequency of olfactory dysfunction between (75 - 95 %) [4].Of our hyposmic patients (69.3%) were males and (30.7%) females (P value 0.012), this is in keeping with the result of large prospective study in USA by Rui Liu et al which revealed that males with PD had significantly more impairment in olfaction (p 0.02) and in certain cognitive measurements (all p, 0.01) than female patients [11].

Another longitudinal study by The et al conducted on 105 hyposmic PD patients and 59 normosmic, using Sniff stick for assessment of olfaction and H&Y scale and Unified parkinson's disease rating scale UPDRS part 2 & 3 for motor function, at base line they showed no difference in motor subtype, Hoehn and yahr scale (P value 0.915) Or levodopa equivalent dose, and after two years follow up the hyposmic patients showed higher rigidity bradykinesia and Hoehn and yahr scale P value 0.027, these results in Same line with our series in term of that ; higher Hoehn and yahr scores were obtained in the participants with more severe olfactory impairment (P value 0.000) [12].

Similarly, a study done in Taiwan by Ting - chun fang and others conducted on 105 PD patients that devided to anosmia and normosmic groups, concluded that anosmic group had higher UPDRS 3 scores compared to control group (95 % confidence interval CI 5.69 - 18.82, P value < 0.001), in contrary to our study the gender (male) was not associated with more severe motor symptoms according to unified parkinson's disease rating scale UPDRS 3, p value 0.572 [13].

Also, the former Egyptian study stated that the olfactory performance was negatively correlated to disease duration and had no relation to the severity of the disease [5] while our study has reported a strong correlation between the Degree of olfaction impairment and severity of the disease according to H and Y scale (P value <0. 013).

Shoichi et al study conducted on 79 patients recently diagnosed with PD, 71 Previously diagnosed with PD and 128 age matched control group, found that patients with previous diagnosis of Parkinson's Disease showed more pronounced olfactory impair-

ment than those who were recently diagnosed PD in term of odor stick identification test (P value <0.0001), and having higher UPDRS 3 scores (mean score 10.9 for previously diagnosed and 6.3 for recently diagnosed patients with Parkinson's disease), these findings consistent with strong association between smell impairment and disease severity and duration in PD [14] the same as the result of our series.

Interestingly 6 (54.5) % of our study patients have appreciated their impaired sense of olfaction after being diagnosed with Parkinson's disease by mean of 2.6 years in contrary to other studies [4], which confirm the presence of Olfactory dysfunction up to 10 years before diagnosis, and in only 5 cases of our patients (45.5 %) the hyposmia had predated the PD by mean of 4.8 years. Concerning the relation between the age and impairment of olfaction our series showed that there was no significant relation between these items (P value. 0.861), while a large study among 117 Moroccan patients (using Argentina hyposmia rating scale for smell assessment and UPDRS 3 for motor assessment) revealed that hyposmia accounted for 28 % of patients, with mean age of hyposmic participants (67.7 +/- 8 years VS 58.63 +/- 1 for those with normal olfaction, p =0.009) indicating that, hyposmia is associated with older age of PD [15].

M. E. Fullard et al stated that about 72% of PD patients were unaware of their hyposmia before testing and in another study 63% of patients over rating their olfactory ability [16,The theory of lack awareness of impairment of olfaction may explain the wide variation in number of hyposmic participants in our cohort compared to the international figures, also the majority of our cases experienced impairment of olfactory function after being diagnosed with PD, probably due to lack of awareness of Mild hyposmia in the pre motor stage of Parkinsonism. Another observation is that the international studies that used the questionnaires to assess the olfaction have obtained results similar to our study and this may imply variations between subjective and objective assessment of smell sense. Ethnic variations may also play a role in the olfactory function (as the African cohorts eg, Sudanese, Ethiopian and Moroccan patients have approximately similar result and less impairment of Olfaction compared to other countries of study that we came across during this discussion). Up to our knowledge, this is the first study that used this validated version of olfactory questionnaire.

Limitations

The first limitation is unavailability of validated psychophysical test according to our Sudanese culture, as the internationally available forms contains unfamiliar odorants to our Sudanese patients. Another Limitation is that subjective assessment of the olfactory function may lead to under estimation of olfactory impairment, as many patients may be unaware of their hyposmia. The small sample size and a relatively short duration of study (4 months) may affect the results so further studies with larger sample size are needed.

Conclusions

The study concluded that olfactory impairment presents in about one fifth of Parkinson's disease patients (21.3٪). The hyposmia is more common in Male gender (69.3%). Most of participants had stage 3 of motor disability (39.3%), and (21.3%) were stage 2.5. More severe olfactory impairment is associated with more pronounced impairment in motor performance scales. It also represents a prodromal Parkinson's disease in about one-half of the participants. Olfactory impairment predates the Parkinsonism by mean of 4.8 years.

Recommendations

The study recommends assessment of olfaction in all PD patients to detect those who are at risk of more severe and progressive disease.

formulation of a locally agreed approach for assessment and diagnosis of Olfactory disorders according to our Sudanese culture. Further future studies with larger sample size for further assessment of olfaction impairment in parkinson's disease.

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