OLFACTORY DYSFUNCTION IN PARKINSON'S DISEASE DIAGNOSIS

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ABSTRACT

Parkinson's disease is a common neurodegenerative disorder of unknown cause and with inevitably progressive character. The disease has a long preclinical period-premotor phase when the nonmotor symptoms are in the first plan and when is the time which neuroprotective therapy should start.

One important biomarker for the premotor phase of idiopathic Parkinson's disease is olfactory dysfunction. This deficit is frequent, significant, small-changes once motor features are evident and it is independent of motor and cognitive status and medication use. Smell loss affects all areas of olfaction and is easily measured by standard quantitative tools.

The objective of this study is to evaluate the frequency and character of olfactory dysfunction among 40 patients, recently diagnosed with Parkinson's disease, as well as to assess correlations between olfactory function and the stage, duration or type of Parkinson's disease. Olfactory function was assessed using a 12-marker Smell Test: Sniffin' Sticks-Screening 12. This is a validated method of identification of sense of smell that can be used easily and quickly.

The percentage summed of patients with hypoosmia and anosmia at this testing was important and the study finds no correlation between olfactory function and duration or stage of Parkinson disease.

Hyposmia is one of the cardinal early symptoms of Parkinson's disease and can be evaluated as marker of the premotor state.

Key words: Parkinson's disease, olfactory dysfunction, odor identification, premotor phase, Sniffin Sticks smell test

INTRODUCTION

Olfactory dysfunction was first described by Ansari and Johnson (1,2) in 1975, in idiopathic Parkinson's disease (PD) and from then, it has been an area of active research. The prevalence varies in studies between 70 and 90%, and is at least as common among PD patients as one of the cardinal motor features, resting tremor (1,3-5).

Hyposomia in PD affect all areas of olfaction: 1) the perception of odors at low concentrations (odor threshold), 2) the nonverbal distinction of different smells (odor discrimination) and 3) the ability to name or associate an odor (odor identification) (1).

The smell loss can be severe, Haehner et al. more than 80% of PD patients functionally anosmic or severely hyposmic regardless of the olfactory test being used for diagnosis (6). In addition hipoosmia is bilateral, even when motor signs are unilateral or asymmetric (3,5,7-9). Hipoosmia was observed also at untreated patient (7), could not be improved after therapy with dopaminergic agents (3,6,9), and it has not been shown to have variation between 'off' and 'on' stage (7).

Olfactory loss in PD is pronounced while in other types of parkinsonism is minor or not observed (7, 10) and so, olfactory dysfunction may help in the differentiation of PD from other causes of parkinsonism. It is considered that in assessing a patient with parkinsonian signs but preserved olfaction, the diagnosis of early PD should be reconsidered (1). Olfaction is less impaired in multiple system atrophy compared to idiopathic PD (11), while patients with progressive supranuclear palsy and cor-

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ticobasal degeneration appear to have preserved olfaction (1,11-12). Hyposmia has not been found in vascular parkinsonism. Almost universal in idiopathic PD, hyposmia does not appear in young onset parkinsonian patients with mutations in PARKIN gene, which raises the issue of the specificity of hypoosmia to Lewy body disorders (13).

Hypoosmia may represent a potential biomarker of PD due to increased prevalence, the appearance from an early stage, the fact that is easily tested and may be used in differentiating from others parkinsonian syndromes (1).

OBJECTIVES

The present work has proposed in order to evaluate the frequency and character of olfactory dysfunction among patients recently diagnosed with PD, as well as establish correlations between olfactory function and the stage, duration or type of PD.

MATERIAL AND METHOD

The studied group was represented by 40 patients, aged between 43 and 78 years, diagnosed with PD, in the period January to December 2010 in Clinic of Neurology I Cluj- Napoca,.

Patient's inclusion criteria were:

- patients with diagnosis of idiopathic PD based on the Criteria of the United Kingdom Brain Bank and a negative family history of PDş
- written informed consent signed by patient.

Exclusion criteria were:

- definite diagnosis of symptomatic parkinsonism, secondary parkinsonism or parkinson- plus;
- moderate or severe cognitive impairment associated with the impossibility of interpreting test results (patients with MMSE below 20 were excluded);
- presence of diseases in the field of Otolaryngology, associated with hypoosmie.

The study was retrospective, descriptive. In all patients it was made anamnesis concerning pathological personal antecedents, concomitant medications, risk factors (dietary factors, environmental toxins or occupation, family history of PD) and also a psychological evaluation from which hold MMSE score.

At each patient it was assessed olfactory function using a **12-marker Smell Test: Sniffin' Sticks-Screening 12.**

As the olfactory loss in PD has a general character, all three olfactory qualities (threshold, discrimination, identification) are involved. In the study carried out we used Sniffin' Sticks-Screening 12, as method of identification of sense of smell. The test is

FIGURE 1. *"Sniffin' Sticks-Screening": 12-marker Smell Test Kit*

Sniffin' Sticks

Date, Time _____ , _____

Name _____ Age _____ Sex m w

Identification - Screening 12 **SMELL TEST**

SCORE (Sum of correct identifikations) ☐ left ☐ right

bilateral testing

1	Orange	Blackberry	Strawberry	Pineapple	7	Liquorice	Gum	Spearmint	Cookies
2	Smoke	Glue	Leather	Grass	8	Cigarette	Coffee	Wine	Smoke
3	Honey	Vanilla	Chocolate	Cinnamon	9	Cloves	Pepper	Cinnamon	Mustard
4	Chive	Peppermint	Fir	Onion	10	Pear	Plum	Peach	Pineapple
5	Coconut	Banana	Walnut	Cherry	11	Camomile	Raspberry	Rose	Cherry
6	Peach	Apple	Lemon	Grapefruit	12	Bread	Fish	Cheese	Ham

SCORE (Sum of correct identifikations) ☐ bilateral

FIGURE 2. *Sniffin Sticks smell test.The multiple choice card presented to patient with four possible answers*

Data were processed with Microsoft Excel.

a validated smell test for the practice who allows identifying patients with olfactory dysfunction, serving as the first diagnostic orientation and can be used easily and quickly (14).

Olfactory function was assessed birhinally and the validated test odors are presented in felt-tip pens. For odor presentation, one pen at a time – cap removed – is placed in front of the nostrils at a distance of approximately 1-2 cm. The test contain 12 odor pens with different scents that must be identified by the patient, using a 4-alternative forced-choice task with presentation of a list of 4 descriptors for each. The correct answers are summed up pen (normal value: more or equal 10 correct identifications) and the result is a score that is compared to the age depending normative data from a normogram (14).

RESULTS

TABLE 1. *Demographic dates of the studied group*

Demographic dates	**Patients**			
Sex	Woman		men	
	25 (62.5%)		15 (37.5%)	
Age	40-49	50-59	60-69	> 70
	2	21	15	2
PD stage(H&Y staging scale)	1	1,5	2	
	9	11	20	

Regarding the history, the disease duration ranged from 6 to 42 (mean ± SD, 21±21,21) months.

Patients mental functions were evaluated using the Mini-Mental State Examination (MMSE), and their mean MMSE score was 25.3 (range, 20-30) points. At the time of testing, 36 of the patients were taking anti-parkinsonian medication, 4 patients were newly-diagnosed who were not on medications.

PD onset symptom was represented at majority of patients -24 (60%) by tremor, followed by hypo-akinesia-type symptoms associated with hypertonia-10 (25%), a smaller percentage of patients being included in the mixed form of the disease -6 (15%) (Fig. 3).

Association of olfactory dysfunction in the studied group.

Patients from the study were evaluated also for nonmotor symptoms, using the questionnaire NMS-PDQ (Parkinson disease- non-motor symptoms). For the present study we retained from this questionnaire the change or not of sense of smell at the simple question: "Have you experienced loss or change in your ability to smell?". A percent by 37,5% of patients responded negatively, 45% affirmatively and 17,5% are not sure (Fig. 4).

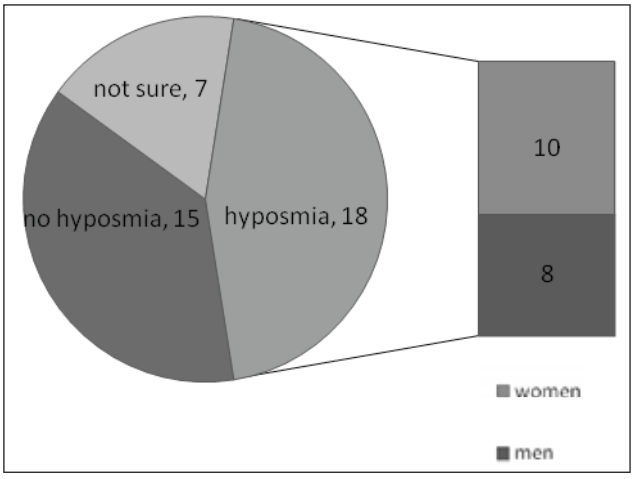

FIGURE 4. *Self-reporting smelling capacity based on answering single screening question*

All patients were tested for olfactory sense using the olfactometer „Sniffin sticks-odor pens-12 smell test" and the results obtained total amount of correct answers on a scale (from one to 12), permitted subsequently to place the patient having normal sense of smell, or presenting anosmia or hypoosmia. At this objective testing, a score between 6 and 10 allowed classification of patients as presenting hypoosmia and at a score under 6, he was assigned as anosmia

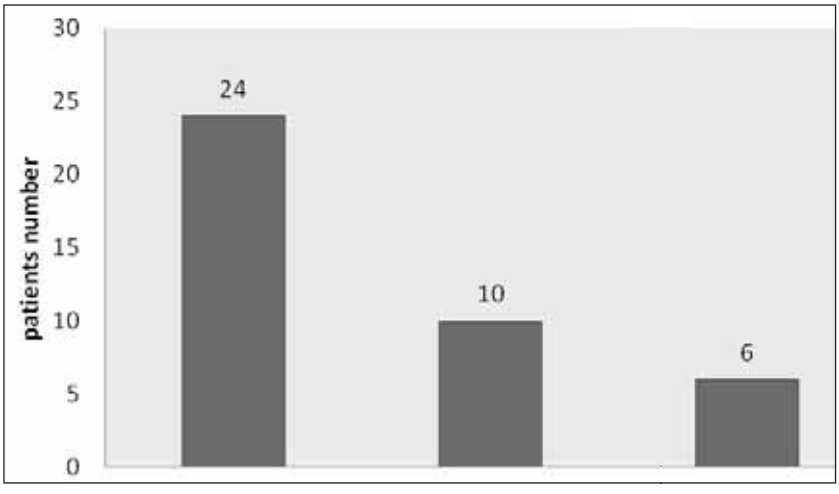

FIGURE 3. *Subtypes of PD (disease onset symptom)*

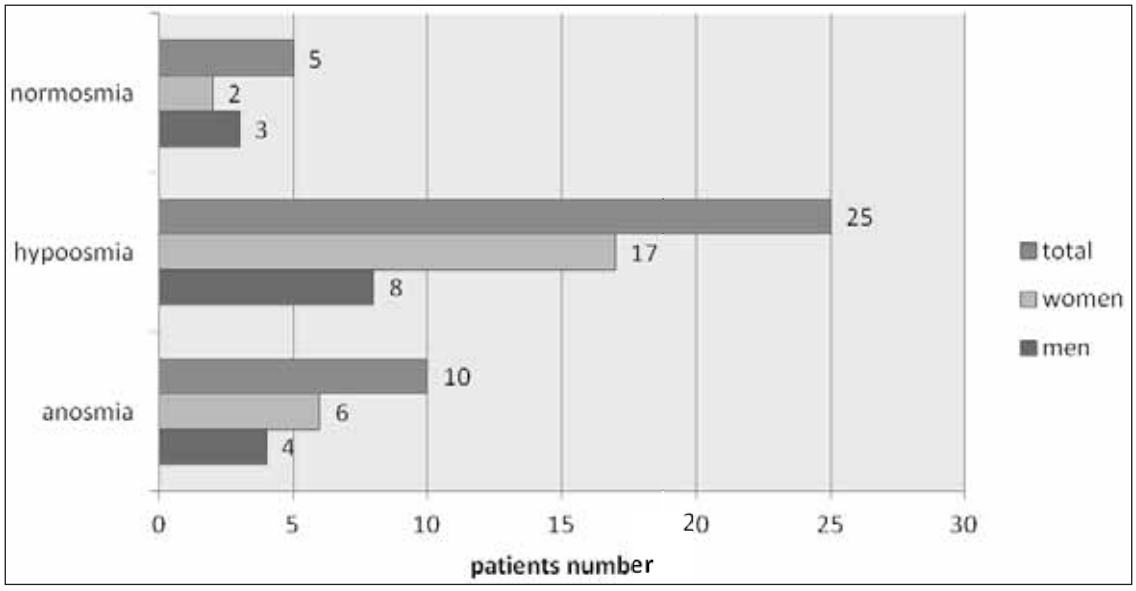

FIGURE 5. *Distribution of olfactory sense at the studied group with the Sniffin sticks smell test*

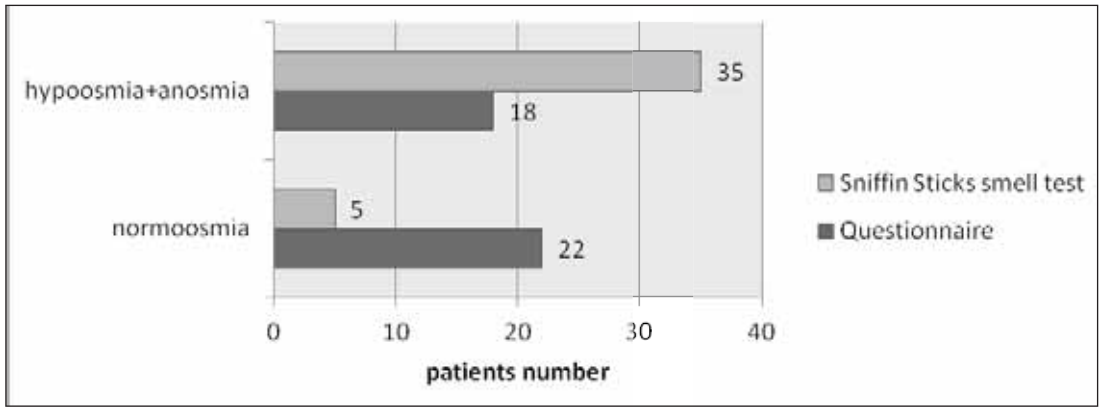

FIGURE 6. *The comparative results obtained by the two tests of smell*

but the results were also analyzed on an evaluation normograme according to age and sex and framed to the corresponding percentile.

It was made a comparison to see the differences between how the patient perceives the sense of smell at questionnaires and the result obtained at Sniffin sticks smell test.

As seen in the Fig. 6, the percentage summed of patients with hypoosmia and anosmia was greater when testing was performed with the Sniffin sticks smell test (87,5%) compared to the percentage obtained by simply asking the patient (45%).

With regard to olfactory function, the study did not find major differences between subtypes of PD, namely tremor-dominant PD, akinetic-rigid PD and mixed-type PD (Fig. 7) at Sniffin Smell test.

Correlation index Pearson - r = 0.174762

Fig. 8 shows that there may be a linear relationship between the two variables, duration of PD in months and the score obtained at smell testing, but the relationship type and degree of correlation can not be determined accurately. Thus, we have calculate Pearson correlation coefficient r = 0.174762 and the value under 0,25 suggests that there is no or a week correlation between this features.

Correlation index Pearson- r = 0.117264

Regarding the relationship between the smell test score and H&Y stage PD we find the same aspect. As shown in Fig.9 there may be a linear relationship between these variables, but the value of correlation coefficient indicate no or a poor correlation.

DISCUSSION

The present study has a relatively uniform distribution of cases by stage, age and sex. The study provides data on the frequency and nature of olfactory dysfunction in patients recently diagnosed with PD. To evaluate the sense of smell we used olfactory identification (12-marker Smell Test) which has

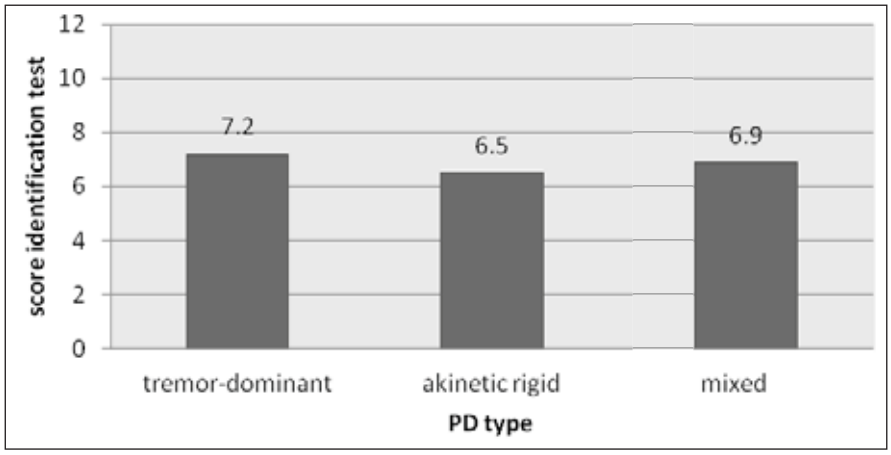

FIGURE 7. *Olfactory function for the subtypes of PD: results from Sniffin Sticks Test*

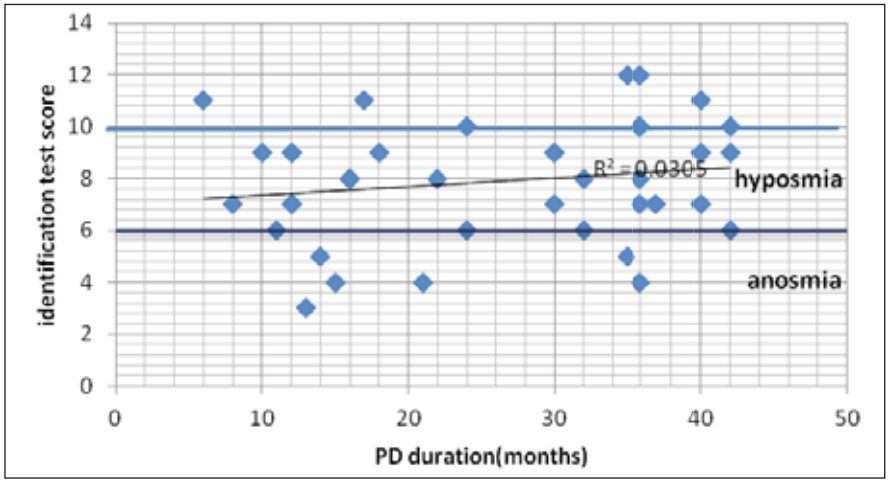

FIGURE 8. *Relationship between olfactory function and duration of the disease*

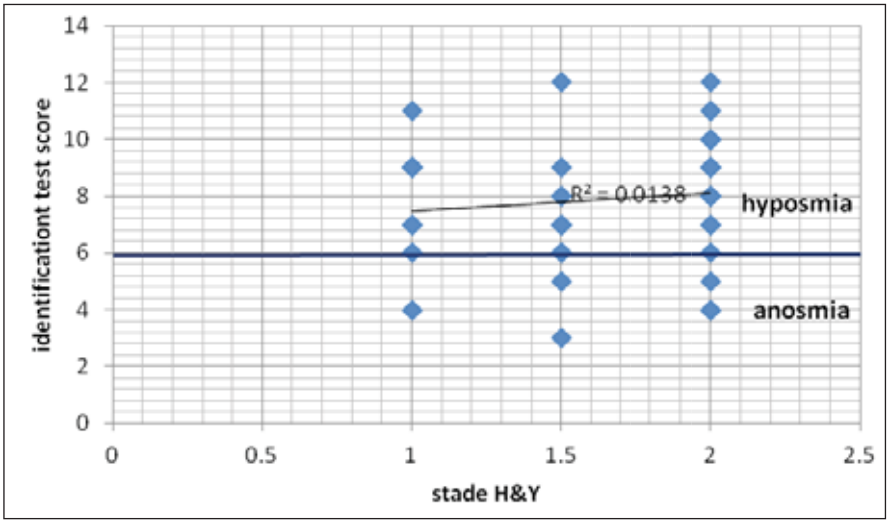

FIGURE 8. *Relationship between olfactory function and severity of the disease, as measured by means of Hoehn and Yahr stage*

been the most widely used method for the assessment of olfactory function in the majority of studies(1).

The frequency of hyposmia on the evaluated lot is comparable with those reported in the literature. Using Sniffin sticks smell test we identified a percentage of 87, 5% of patients with hyposmia or anosmia. In a recent study by Politis et al. (6, 15), olfactory loss belongs to the top-five most prevalent motor and nonmotor symptoms in early stage PD patients that have affected their quality of life and only pain is referred to as a more prevalent nonmotor problem in this patient group.

The studies indicate an awareness of a decrease of olfactory function which preceded the diagnosis of PD (6). PD patients with olfactory loss rarely mentioned spontaneously, when they are asked target- 22-70% may declare subjective loss or decrease of ol-

factory sense(7-9,16) but when tested objectively hyposmia is found in 70-100% of patients (3,5,7-8,10). Similar with the literature, in our study, objective test of smell (the percentage of olfactory dysfunction obtained is 87,5%) is superior to the simple questionnaire of patient (a rate of 45%).

The present findings show profound impairment of olfactory function in almost all patients with idiopathic PD in stages 1; 1,5 and 2 Hoehn & Yahr. Our results suggest that olfactory dysfunction is an early frequent symptom and may represent an important aid in the diagnosis of disease. Olfactory dysfunction has been shown to appear early in the neurodegenerative process, prior to the onset of motor symptoms, which is congruent with the early involvement of the olfactory system in the evolution of Lewy pathology demonstrated by Braak et al.(1,17).

Early appearance and the fact that does not seem to get worse with disease progression led to the hypothesis that hipoosmia could be a possible premotor symptom of PD which may antedate the classic motor signs (7). A significant number of epidemiological studies or studies on patients with idiopathic hipoosmia or asymptomatic relatives of parkinsonian patients have provided evidence which support the hipoosmia as a premotor sign of PD (7, 18-21). Although it is unclear exactly when hipoosmia start, the available data from several studies suggest that it begin with 2-7 years before diagnosis of PD (7, 19-22).

Using multiple olfactory tests together or in combination with imaging studies increases the ability to detect early PD. Montgomery et al. (1, 23) found that specificity for early PD could be increased to 92%, with 68% sensitivity, when combining tests of motor function, mood and olfaction. In a case-control study on 90 PD patients and healthy controls, Bohnen et al. (6,24) found that the accuracy of smell testing in PD diagnosis outweighs the accuracy of motor test batteries, and also other nonmotor tests (depression, anxiety).

As in previous studies (3,5,6,25), we found no correlation between olfactory loss and both duration and severity of disease.

Stern et al. (25) reported significantly better odor identification scores in patients with tremor-predominant PD than in cases with postural instability-gait disorder PD but anothers studies did not find major differences between subtypes of PD-tremor-dominant PD, akinetic-rigid PD and mixed-type PD(6). Also, our study find similar values at Sniffin Smell test in different subtypes of PD.

These observations are similar with the results of many published studies with regard to the missing correlation between olfactory loss and duration of the disease, clinical severity of PD and the type of PD.

CONCLUSIONS

Olfactory dysfunction belongs to the variety of non-motor symptoms that appear before classic motor symptoms of PD and can alert on an early diagnosis of disease. It represents a common feature of PD with a very high prevalence from the early stages of the disease.

Recent data show that olfactory probes improve the diagnosis process in patients with PD and in contrast with imaging tests, olfactory dysfunction testing are inexpensive, quick and easy to perform. Validated test of olfactory function should be a mandatory part of the early and differential diagnosis of PD.

Also olfactory dysfunction can predate PD by years and may be a useful screening tool for identifying population at-risk of developing PD in a stage of the disease when neuroprotective therapies are most useful, so hyposmia may represent a important nonmotor prodromal marker of the disease.

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