Olfactory dysfunction and cognitive impairment in patients with Parkinson’s disease

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ABSTRACT

Olfactory deficit has been described in some neurodegenerative diseases as well as in normal aging. There is pathological and biochemical evidence suggesting that hyposmia might be more severe in subjects with cognitive dysfunction. **Objective:** the association between olfactory dysfunction and cognitive impairment in Mexican Parkinson’s disease (PD) patients is analyzed. **Material and methods:** a cross-sectional and analytic study with consecutive patients was carried out. The “sniffin’ sticks” (SS-16) testing and Montreal Cognitive Assessment (MoCA) were applied to all patients. **Results:** a total of 104 patients were included (64.4% male). An olfactory deficit was found in 82.9% of the sample. Additionally, 47.1% of the patients scored less than 26 points in Montreal Cognitive Assessment. No correlations was found between the total SS-16 score and the total MoCA score. When analyzing individual domains a weak correlation was found between lower scores in both tests (r=0.24, p=0.04). **Conclusions:** we did not find a relation between the presence of olfactory dysfunction and global cognitive function. A significant relation between olfactory deficit and visuospatial/executive dysfunction was noted.

Key words: cognition, Parkinson’s disease, SS-16; MoCA.

Disfunción olfatoria y deterioro cognitivo en pacientes con enfermedad de Parkinson

RESUMEN

La disfunción olfatoria ha sido descrita en algunas enfermedades neurodegenerativas; así como, en el envejecimiento normal. Existe evidencia patológica y bioquímica que sugiere que la hiposmia pudiera presentarse de forma más severa en sujetos con disfunción cognitiva. **Objetivo:** analizar asociación entre disfunción olfativa y deterioro cognitivo en pacientes mexicanos con enfermedad de Parkinson. **Material y métodos:** se llevó a cabo un estudio transversal, analítico consecutivo en pacientes con enfermedad de Parkinson. Las pruebas de “sniffin’ sticks” (SS-16) y evaluación cognitiva de Montreal (MoCA) fueron aplicadas a todos los pacientes. **Resultados:** se incluyeron un total de 104 pacientes (64.4 % hombres). Se encontró disfunción olfatoria en el 82.9% de la muestra. Adicionalmente, el 47.1 % de los pacientes presentó puntuación inferior a los 26 puntos en la evaluación cognitiva de Montreal. No se encontró correlación significativa entre la puntuación de SS-16 y la total del MoCA. Al analizar distintos dominios de forma independiente, se encontró una correlación entre las puntuaciones bajas en ambas pruebas (r=0.24, p = 0.04). **Conclusion:** no se encontró relación entre la presencia de disfunción olfativa y la función cognitiva global. Se observó relación significativa entre el déficit olfativo y disfunción visuoespacial/executoria.

Palabras clave: cognición, enfermedad de Parkinson, SS-16, MoCA.
Olfactory deficit has been described in several neurodegenerative diseases, such as Alzheimer disease and Parkinson’s disease (PD), as well as in normal aging. Disturbances in smell can be found in three different areas: odor identification, recognition, and detection threshold. A multicentric study including 400 patients with PD reported a significant loss of olfaction in up to 96% of the cases. Moreover, hyposmia may be present early in the disease course and has been recognized as a premotor symptom.

Neuronal degeneration with deposition of alpha-synuclein within the olfactory bulb, anterior nucleus and limbic rhinencephalon has been reported in PD. Hippocampal dopaminergic denervation and dysfunction and the limbic cholinergic denervation has been suggested to play a role in the development of hyposmia. Additionally, odor identification performance has been associated with cortical hypometabolism in PD patients without dementia suggesting that severe olfactory dysfunction may predict future.

Studies have reported a relation between olfactory deficit and cognitive impairment in PD patients. One study reported a correlation between verbal and nonverbal memory with olfactory loss in PD. Another study reported impairment in visual and verbal memory, processing speed, and in language scores in anosmic PD patients. Parrao et al. showed significant deficits in olfactory function and working memory, executive function, speed of information processing, visuospatial skills and phonological verbal fluency tests in PD patients in comparison with the control group.

In the present study, we analyzed the association between olfactory function assessed by a smell identification (sniffin’ sticks) test and cognitive functioning addressed by a screening tool (Montreal Cognitive Assessment).

MATERIAL AND METHODS

A sample of 104 consecutive patients fulfilling the criteria for PD according to the United Kingdom Parkinson’s Disease Society Brain Bank was assessed. Patients currently receiving biperiden or any other anticholinergic, patients with secondary causes of cognitive impairment, and patients with any known cause of anosmia/hyposmia were excluded. All patients were in the “on” state at the time of the assessment. Clinical evaluation was performed by a neurologist with expertise in movement disorders. Disease severity was assessed using the Hoehn and Yahr staging (HY) and motor evaluation was performed using the Scales for Outcomes in Parkinson’s disease (SPES/SCOPA).

All patients underwent smell testing and were screened for cognitive decline. Smell identification was evaluated using the “Sniffin’ sticks” (SS-16). This test evaluates olfactory identification of 16 common odors. Odorants were presented in felt-tip pens. For odor presentation the cap was removed by the experimenter for three seconds and the pen’s tip was placed two centimeters in front of both nostrils. Identification of odorants was performed as a multiple forced choice from a list of four descriptors. A cutoff score of d”10 was used to indicate olfactory dysfunction.

The Spanish version of Montreal Cognitive Assessment (MoCA) was administered to all patients by an independent rater blinded to the smell test result. This tool evaluates eight cognitive domains: visuospatial and executive function, short-term memory, attention, concentration, working memory, language, and orientation. A score of less than 26 was used as a cutoff value. One error in any domain was interpreted as failure of the domain. The Institutional Review Board and local ethics committee approved the study, and all subjects provided informed consent before participating.

Statistical analysis

Demographic data were reported as frequencies, means and standard deviation. Total scores on the MoCA and Sniffin’ Sticks were compared using unpaired t tests. Nominal variables were compared using Chi-square test. Correlation coefficients were used. A p value <0.05 was considered significant.

RESULTS

A total of one hundred four patients (67 male and 37 female) were included. The mean age of the sample was 61.3 ± 10.8 years. Mean age at PD onset was 54.2 ± 13.4 years. In regards to education, 60% of the sample had 12 years of education or more. The mean of years of schooling was 9.1 ± 4.9. Antiparkinsonic treatment was as follows: 73 (70.1%) patients were on levodopa and 61 (58.7%) patients were treated with a dopamine agonist.

In terms of PD subtype, 46% were tremor dominant, 52% were rigid-akinetic and only 2% were
postural instability-gait disturbance type. Regarding HY stage, 95% of the sample had a mild to moderate disease (HY 1-3). The total mean score of the SPES/SCOPA was 18.5 ± 8.6 points.

The mean SS-16 score was 7.6 ± 2.8 (median 7, range 1 to 14). Using a cutoff score of d”10, a total of 87 (82.9%) patients had an olfactory deficit. The mean MoCA score was 24 ± 5.4 (median 26, range 8 to 30). A total of 49 (47.1%) patients scored below the 26 cut-off value in the MoCA.

No correlation was found between the SS-16 score and the MoCA score (r = 0.16, p = 0.11). Mean SS-16 score did not differ between patients with or without cognitive decline (7.2 ± 3 vs 8 ± 2.7, p = 17). No association was found between the presence of olfactory deficit and the presence of cognitive decline (table 1). No correlation was found between the SS-16 total score and the MoCA total score (figure 1). When analyzing each of the cognitive domains only the visuospatial/executive domain showed a statistically, although weak, correlation with the total SS-16 score (r=0.24, p=0.04).

### Table 1. Number of patients with scores above and below the cutoff on Sniffin’ sticks’ and Montreal Cognitive Assessment.

<table>
<thead>
<tr>
<th></th>
<th>MoCA = 26</th>
<th>MoCA &lt; 26</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS-16 &gt; 10</td>
<td>12</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>SS-16 = 10</td>
<td>43</td>
<td>43</td>
<td>86</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>49</td>
<td>104</td>
</tr>
</tbody>
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SS-16: Sniffin’ sticks’; MoCA: Montreal Cognitive Assessment. p = 0.29.

**DISCUSSION**

In the present study, almost 83% of the patients had an olfactory deficit using the recommended cut-off value for the SS-16. No association between olfactory dysfunction and cognitive functioning was found.

When analyzing results per domain, we did not find any relationship between olfactory dysfunction and the following cognitive domains: short-term memory, attention, concentration, working memory, and orientation. Nevertheless, the group with olfactory dysfunction had a significantly lower score in the visuospatial/executive function domain.

Our results and interpretations concur with previously published work regarding visuospatial and executive functioning decline in hyposmic PD patients. Damholdt et al compared anosmic nondemented PD patients with nonanosmic nondemented healthy controls; they found that the anosmic group showed impairment in several cognitive domains, including visual and verbal memory, and processing speed. In contrast, the groups did not differ on executive functioning. The only domain affected, reduced language score, concur with our results. Parrao et al also reported a significant association between olfactory deficits and impairments of executive function in PD patients. Baba et al, in a three-year longitudinal study, found that PD patients with severe hyposmia exhibited mild impairments in general cognition, as well as in memory and visuoperceptual functioning at baseline. These findings may suggest an impaired cognitive processing of olfactory information in anosmic PD patients. The specific deficit of executive functioning found in almost all studies could be explained by the widespread notion of limbic and neocortical Lewy bodies; being the main determinant of cognitive decline. Although the presence of amyloid plaques and neurofibrillary tangles has been well described in PD, their role in cognitive decline is controversial. Indeed, Bohnen et al suggested that the relation of hyposmia and episodic verbal learning could be better explained by cholinergic denervation of the limbic archicortex rather than nigrostriatal dopaminergic denervation.

In our study we used two screening tools for both, smell identification and cognitive decline. Olfactory dysfunction could detect PD patients using a more practical and rapid method for testing olfactory identification such as Sniffin’ sticks. The lower education level may have accounted for the frequency of cognitive decline in our patients. However, as stressed in previous studies, it is unlikely that the olfactory deficit is exclusively the result of lexical difficulties. Also MoCA correction for years of schooling was used in all patients.
On the other hand, the fact that only screening tools were used, instead of a more extensive smell identification testing and a more comprehensive neuropsychological evaluation, may result in and over or underestimation of the actual prevalence of smell and cognitive impairments. Nevertheless, in the clinical setting, the diagnostic approach used in the present study is more convenient and less time-consuming; and probably resembles more to a real-life scenario in an outpatient clinic. A study with a more thoroughly evaluation might be warranted to confirm our findings.

In conclusion, our study showed a relation between olfactory dysfunction and visuospatial/executive dysfunction in Mexican patients with PD. The relevance of this olfactory dysfunction is not in the sensitive disorder itself (since lack of olfaction does not impose an important handicap for activities of daily living), but in its potential as an adjuvant screening tool for cognitive impairment. Since hyposmia is a well recognized premotor symptom of PD, the question arises to whether olfactory tests could be useful in following otherwise asymptomatic patients in prospective studies evaluating progression to overt disease. Further research needs to focus on standardizing cut-off scores for olfactory tests examining healthy controls, as well as their test-retest validity and predicting values. Moreover, the temporal and epidemiological relation between hyposmia and other premotor symptoms, with the possible occurrence of different phenotypes, needs yet to be established.

**REFERENCES**