Nasal chemosensory tests: biomarker between dementia with Lewy bodies and Parkinson disease dementia*

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Abstract

Background: Dementia with Lewy bodies (DLB) and Parkinson disease dementia (PDD) are progressive and disabling neurodegenerative disorders, which are often misdiagnosed due to their overlapping clinical and paraclinical features. Nevertheless, their adequate management requires an accurate differential diagnosis. The main aim of this study was to investigate the usefulness of olfactory and trigeminal nasal testing for the differential diagnosis between DLB and PDD.

Methods: Odor thresholds to three odorants differentially activating the olfactory and trigeminal systems were assessed in patients with DLB, PDD and healthy controls (n = 20 per group).

Results: Odor thresholds were significantly different between the three groups of subjects. More precisely, we found that DLB patients had significantly lower detection threshold performances compared to PDD patients. Moreover, using a standard canonical discriminant analysis, we confirmed a plain differentiation between the three groups.

Conclusions: The current study highlights that DLB patients have very poor olfactory and trigeminal detection threshold performances, which are significantly lower, compared to PDD patients. These results suggest that olfactory testing, using odorants that stimulate both the olfactory and trigeminal systems, could constitute an interesting biomarker and contribute to the differential diagnosis of PDD and DLB patients. Further researches, notably on olfacto-trigeminal interactions, are warranted in these populations to support our findings.

Key words: biomarker, dementia with Lewy bodies, differential diagnosis, odor detection thresholds, Parkinson disease dementia

Introduction

Dementia with Lewy bodies (DLB), Parkinson disease (PD) and Parkinson disease dementia (PDD) are part of synucleinopathies (1,2). Clinically, DLB and PDD have overlapping clinical appearance, with similar symptoms (including mainly parkinsonism, fluctuating cognition, and visual hallucinations) (3,4). Consequently, their differential diagnosis is often challenging and DLB is often misdiagnosed (1,3), despite the revised 2017 DLB’s diagnostic criteria (5).

Currently, the temporal course of the emergence of the symptoms is used to differentiate between these two diseases. DLB is suspected when dementia precedes or coincides with the occurrence of parkinsonism or appears within the year following the development of parkinsonism. On contrast, PDD is suspected when dementia appears in the context of a previously known PD. However, this “temporal rule” is controversial, since some DLB patients may present with motor symptoms first. Early diagnosis is crucial to ensure adequate follow-up, counseling and treatment. Since patients’ management is not the same for these diseases, it is therefore crucial to develop reliable and accurate biomarkers for their differential diagnosis. Some ongoing researches aim to establish blood, cerebrospinal fluid or imaging biomarkers of PDD and DLB (6); however, their availability is limited and results are not yet formally conclusive.

*Received for publication: February 29, 2020
Accepted: May 26, 2020

Rhinology 58: 0, 0 - 0, 2020
https://doi.org/10.4193/Rhn20.072
It is widely acknowledged that olfactory dysfunction is present in various neurological diseases (7), among which PD, PDD, Alzheimer's disease (AD) (8) and DLB. However, the trigeminal function, although being involved in odors perception (9) is sparsely explored in these diseases. In the present study, we aimed to investigate whether global odors perception (olfactory or trigeminal functions) test could be a useful for the differential diagnosis between DLB and PDD. For this purpose, we assessed nasal detection thresholds for three odorants which differentially activate the olfactory and/or trigeminal systems. In addition, we aimed to determine whether the trigeminal function is also affected in DLB or PDD.

Materials and methods

Ethical standards
Sixty participants distributed into three groups (20 DLB (10), 20 PDD (11) and 20 matched healthy Controls) underwent odors detection thresholds testing using Phenylethyl alcohol (PEA), n-Butanol and Pyridine thresholds. The study was conducted according to the Helsinki’s declaration and was approved by the local Institutional Ethics Review Board. Written informed consent was obtained from all the participants.

Participants
60 elderly participants (83.17 ± 7.48 [65; 97] years old) were included in the present study: 20 DLB patients (12 female), 20 gender-matched moderate PDD patients and 20 healthy controls (Table 1). Overall, these 3 groups differed significantly according to age (p< 0.05), although DLB patients and healthy controls group did not differ (p= 0.984).

The participants had no history of sinonasal diseases, head injury or stroke prior to the olfactory tests and were all non-smokers. Additionally, participants were free from patent depression symptoms (assessed by Mini-Geriatric Depression Scale (Mini-GDS)) (12). Moreover, control participants were free from neurological disease and had no signs of Parkinsonism. The main demographic and clinical variables of the 3 groups of participants are described in Table 1.

Neurocognitive tests were performed to detect cognitive impairment using Mini-mental state examination (MMSE) (13-15) and the clock-drawing test (16). Exclusion criteria were 1) incorrect clock-drawing test (0 or 1 out to 2); and/or 2) MMSE < 15/30 in patients and MMSE < 24/30 in controls.

Odors detection testing
Odors detection thresholds were determined for three odorants known to differentially activate the olfactory and trigeminal systems based on the previous data (17). Phenyl-ethyl alcohol (PEA) was chosen to activate almost exclusively the olfactory system; n-Butanol was considered to activate both the olfactory and trigeminal systems (18). Finally, Pyridine was used to be specifically activating trigeminal afferents (19). Patients were assessed following methods described in our previous publications (18, 20).

In summary, odor thresholds were assessed using an ascending staircase, binary (stimulus vs. blank) forced-choice procedure, with inter-trial intervals of 90 seconds. The dilution step at which the odorant stimulus was first detected correctly three times in a row was recorded as the detection threshold (20). The possible threshold detection scores ranged from 0 to 20 for n-Butanol, 0 to 23 for PEA and 0 to 26 for Pyridine; with higher scores indicating better olfactory function.

Data analysis
Statistical analyses were performed using Statview (SAS Institute Inc., Statistical Software vendor _Version 9.2) and SPSS version 19.0 (IBM, Chicago, IL, USA). As variables were not normally distributed, according to the Shapiro-Wilk test, nonparametric Mann-Whitney-Wilcoxon test (two-tailed) or if needed, Kruskal-Wallis test (with post-hoc tests) were used to compare odor thresholds. Spearman correlation analyses between odor thres-
A factorial discriminant analysis was performed to classify participants based on a linear combination of the odors thresholds (PEA, n-Butanol and Pyridine). The results allowed for building two discriminating and distinct linear functions (functions scores). For a given participant, theses score functions are calculated using the following equations:

- Score1 = 0.760*PEA + 0.430*n-Butanol + 0.159*Pyridine - 3.966;  
- Score2 = 0.029*PEA + 0.203*n-Butanol - 0.175*Pyridine + 0.208.

The group centroids, linear combination of the means for each odor threshold (PEA, n-Butanol and Pyridine), revealed a clear split between the three groups (DLB patients, PDD patients, healthy controls participants). Centroid plots, the resultant of the group centroids plotting are represented in Figure 2.

### Discussion

In the present study, we found that DLB and PDD patients have significantly lower odor detection threshold performances compared to healthy controls; and that DLB patients perform significantly worse than PDD patients, independently of MMSE and age. We found that olfactory performances were not influenced by sex. This is congruent with the results of a recent study and a meta-analysis that found no gender-related differences when performing olfactory tests in people aged > 50 years (21,22).

Discriminant analysis

A factorial discriminant analysis was performed to classify participants based on a linear combination of the odors thresholds (PEA, n-Butanol and Pyridine). The results allowed for building two discriminating and distinct linear functions (functions scores). For a given participant, these score functions are calculated using the following equations:

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Notably, since odor thresholds are thought to reflect peripheral olfactory processing, our results suggest that abnormal protein deposition (mainly alpha-synucleinopathy in these cases) occur at least partly at the level of the olfactory neuroepithelium and olfactory bulb; and that these structures are more severely involved in DLB. Several biomarkers are currently used for the diagnosis of synucleinopathies (i.e. MRI, PET, 123I-metaiodobenzylguanidine cardiac scintigraphy, REM sleep behavior disorder, serum or CSF biomarkers, genetics...). However, correct differential diagnosis remains challenging. Our results suggest that assessment of odor detection thresholds should be considered as a potential biomarker of DLB. Notably, its ability to discriminate between DLB and PDD patients as compared to healthy controls. Patients that would be considered as suspect after olfactory screening would be referred for deeper investigation, using the other biomarkers previously mentioned, therefore minimizing the use of invasive and expensive tests.

The odor test used in this study encompasses three different odorants, know to differentially activate the olfactory and trigeminal chemosensory system. We found that both olfactory and trigeminal sensitivities (most specifically assessed with respectively PEA and Pyridine) were more impaired in DLB patients than as compared to PDD patients; and in PPD patients as compared to healthy controls. In the present study, we chose Pyridine to stimulate trigeminal system. Since it is known that, for a given odorant, odor thresholds are lower than their trigeminal threshold, it can not be excluded that Pyridine threshold reflect at least partly olfactory threshold. However, pyridine have stronger trigeminal (intranasal) components than do more purely olfactory stimuli such as PEA.

Incidentally, n-Butanol thresholds did not significantly differ between PDD and DLB; the results were close to significance level. This might be explained by n-Butanol's characteristics (mediated both by trigeminal and olfactory sensitivities), generating many intermediate (non-extreme) thresholds results in both of the groups, allowing this above-mentioned p-value close to significance level. However, discriminant analyses showed that it was possible to differentiate the three groups of participants (Figure 2), based on two distinct linear functions having as variables the three odor detection thresholds. This finding reinforces the hypothesis that detection thresholds for odorant stimulating both the olfactory and trigeminal systems could be considered as a biomarker of DLB. Finally, previous studies reported a correlation between smell loss and cognitive function. However, this was mainly found for odor identification performances (preferably used to assess olfactory disorders in AD). In the present study, we found no impact of MMSE score on odor detection threshold results. This might be explained by the fact that odor detection threshold tasks require less cognitive functions that identification tasks. We must also mention as potential...
bias the non-inclusion of subjects with cognitive impairments in the healthy controls group.

Conclusion
Assessment of odor detection thresholds, using odorants that activate both olfactory and trigeminal systems, seems to be useful for the differential diagnosis between DLB from PDD. These results suggest that olfactory and trigeminal detection testing could be considered to increase the diagnostic accuracy of DLB, in combination with the classical clinical work-up evaluation. Researches evaluating olfacto-trigeminal interactions in these populations of patients would be of interest to further support our findings.

Acknowledgements
We would like to thank Dr Gerard Brand with whom this work and the olfactory tests have begun; and Dr Bernard Kamsu-Foguem, Dr Donatien Chedom Fotos and Dr Henry Abanda for their contribution and analyses of the data.

Authorship contribution
CF: design of project, collection of the data, drafting of the manuscript and revised it; CF, ML, CH: analysis and interpretation of the data; ML, CH: critical revision of the manuscript; CF, ML, CH: Approval of the final version of the manuscript.

Conflict of interest
The authors declare that they have no conflict of interest with regard to this research.

Abbreviations
SPSS: Statistical Package for the Social Sciences; MRI: magnetic resonance imaging; PET: positron emission tomography; REM: Rapid eye movement; CSF: cerebrospinal fluid.

References

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