Comparison of Olfactory Thresholds between Elderly with Parkinson Disease and Controls

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Abstract: *Introduction*: Olfactory dysfunction is an early warning and most common symptom of Parkinson's disease (PD). It is a promising marker mainly at the early stage of the disease for PD. The purpose of the survey was to evaluate the deficits in odor detection in Elderly with PD. We hypothesized that trigeminal sensitivity dysfunction would be less important than olfactory sensitivity impairment in elderly with PD and could improve diagnostic accuracy. *Experimental procedure*: Olfactory detection thresholds to Phenyl ethyl alcohol (PEA) [activating only the olfactory system] and n-Butanol (BUT) [activating both olfactory and trigeminal systems], were determined in twenty four patients with PD aged over 65 years old [mean age: 75 +/-4.5 years, range: 70-86 years] and in twenty-four healthy controls who were matched for age and gender [mean age: 73 +/-7.1 years, range: 65- 84 years]. The study also included neuropsychological evaluations and stage of PD estimations. *Results*: Results show a trend towards an impaired olfactory (CN I) detection sensitivity in relation to PEA thresholds in patients with PD compared to controls independently of age and stage of PD, although no significant difference was observed. Furthermore, no significant difference was observed for BUT thresholds between PD's patients and controls. PEA and BUT thresholds were significantly correlated in both patients with PD and controls. *Conclusion*: These findings suggest that the olfactory senescence and decreased detection threshold in elderly (both patients with PD and controls) may influence our results by reducing detection olfactory threshold differential between the two groups, contrary to previous findings in young adults with PD and controls. Trigeminal sensitivity seems to be preserved in Elderly with PD. Future investigations should focus on odorants with higher properties to highlight a potential difference between the two groups.

Keywords: Elder, idiopathic Parkinson disease, olfactory dysfunction, olfactory (CN I) sensitivity, trigeminal (CN V) sensitivity.

1. INTRODUCTION

Olfactory information processing involves "peripheral" and "central" levels which determine the global olfactory perception. The "peripheral" level corresponding to the olfactory epithelium (located high inside the nostrils) is implied in the olfactory sensibility and it is assessed by olfactory threshold of detection. The integration of olfactory information continuing at a more "central" level refers to a higher degree of treatment (localized on olfactory areas of the brain and brain structures that are involved in producing emotions such limbic system and amygdala) and involves more complex cognitive processes such as the ability to differentiate the quality of odorants (discrimination), to recognize odor targets previously smelt (memory) or to give the name of an odorant in a list of words (identification) [1]

During ageing, degenerative changes occur in receptors in the nasal cavity [2], in sensory neurons of the olfactory bulb [3, 4] and in cortical and subcortical regions such as thalamus, hypothalamus and hippocampus [5]

The neurotransmitter pathways can also be affected. All these physiological changes in both "peripheral" and "central" nervous system olfactory structures are characterized by a decrease of the olfactory sensitivity [6, 7] and a decrease of the discrimination, memory and identification abilities [8-11]. Several studies reported the decrease ability to smell as common in older age and as an early sign of age-related neurodegenerative disorders, including Alzheimer's disease (AD) [12-14], Dementia with Lewy bodies (DLB) [15] and Parkinson's disease [14, 16-18].

Idiopathic Parkinson disease (PD) is mainly attributable to a dysfunctioning of dopaminergic neurons in the basal ganglia (substantial nigra and corpus striatum) with a prevalence of 1.6 ‰ in the general European population and of 1.8 to 2.6% in the elderly [19]. PD was conventionally considered as a motor system disease with a cardinal motoric signs (e.g. rigidity, bradykinesia, tremor and postural reflex disturbance). However, non-dopaminergic and non-motor symptoms including depression, pain,

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E-ISSN: 2309-6128/14

genitourinary problems, sleep disorders [particularly REM (Rapid eye movement) sleep behavior disorder (RBD)], paraesthesia and olfaction dysfunction have been described. Olfactory dysfunction and RBD are often preceding the diagnosis of PD and almost PD's non-motor symptoms emerge with disease progression [20].

Elderly's PD have specific characteristics and concern in theory patients aged of 70 years old or more. Two clinical forms of PD in the elderly were identified: (1) the late-onset form, arising after 70 years old and characterized by a bilateral hypokinetic-hypertonic syndrome which is often atypical and associated with a weak response to L-dopa; (2) the early-onset form in which the first clinical signs of PD appeared before 70 years old; this form is marked by a L-dopa resistance generating a loss of autonomy [21-24].

Prior to the onset of the cardinal motor features of PD, olfactory dysfunction is an earlier and prevalent nonmotor symptom of PD [25]. Therefore, olfactory dysfunction appears as a significant marker for PD due to its high prevalence among PD patients over 90% [26]. Olfactory dysfunction includes deficits in odor detection, discrimination and identification [1]. Examination of the olfactory function is currently considered as a supportive diagnostic tool for PD, but is it also relevant for elderly, i.e. >65 years, with PD?

The capacity to detect and react to volatile odorant molecules is mediated mainly by two independent neural systems, the olfactory (CN I) and the somatosensory or trigeminal (CN V) systems [27]. The trigeminal system is mainly implicated in protective reflexes whereas the olfactory system which is specially implied in identification, recognition, memory and many aspects of human behavior. Very few odorant molecules or chemosensory stimulants produce exclusively olfactory or trigeminal sensations, the vast majority possessing both characteristics [28]. This interaction between the olfactory and the trigeminal systems is an important determinant of the global sensory perception. There is also evidence that olfactory and trigeminal chemoreceptions are markedly impaired as a result of ageing and various diseases. Thus, the interactions between the olfactory and trigeminal systems are not straightforward and may be difficult to predict [28].

The question arises whether the interaction between the trigeminal and olfactory sensitivities would reliably precise the diagnosis of PD in the elderly and discriminate between elderly patients with PD and age-matched healthy controls?

Our hypothesis is that trigeminal sensitivity alteration could be less important than olfactory sensitivity in elderly with idiopathic PD, which could improve diagnostic accuracy.

2. EXPERIMENTAL PROCEDURE

2.1. Participants

2.1.1. Patient's Group

It consisted of twenty-four patients with PD aged over 65 years old and twenty four healthy ambulatory controls matched for age and gender. Because smoking is known to induce smell disorders [29], subjects should not have any history of active smoking during the ten past years.

Patients and controls had not history of nasal/sinus disease, head injury or stroke (cerebrovascular accident) within six months prior to the olfactory tests insofar as traumatic brain injury is responsible for olfactory disorders in 5-30% of cases [30]. Subjects using or misusing drugs or presenting nasal congestion and other conditions which are occasionally associated with hyposmia, were excluded from the study.

Additionally, during the testing period, participants were free from upper respiratory disease, moderate or severe cognitive impairment, nor patent depression.

Neurocognitive tests were performed to exclude moderate and severe dementia. All subjects scored 21/30 or more on the Mini-Mental State Examination (MMSE) [31]. Depression symptoms were also assessed using the Mini-Geriatric Depression Scale (Mini-GDS) to exclude patients with active and severe signs of depression subjects scored ¼ or more on Mini-GDS (strong probability of depression).

A neurological examination of both patients and controls was conducted at least once by a neurologist, an experienced geriatrician or an internist trained to care for elderly PD patients.

Patients with PD [mean age: 75 +/-4.5 years, range: 70-86 years] were diagnosed according to the UK PD Society Brain Bank diagnostic criteria [22]. Neuropsychological evaluations were carried out as well as stage of PD estimations.

The PD patients were outpatients seen in consultation or hospitalized in neurology or geriatric

wards. "Unified Parkinson's disease Rating Scale" (UPDRS) (parts I, II, III, IV) and modified 'Hoehn and Yahr scale' (stages: 0; 1; 1,5; 2; 2,5; 3; 4; 5) evaluations were used to assess global clinical severity and motor impairment and symptoms progression of the patients.

At the time of the testing most of the patients was taking L-Dopa or another dopaminergic agent either alone or in conjunction with other patient's medications.

2.1.2. Control Group

None of the control subjects had a history or signs of Parkinsonism or major neurological disorders. They were aged 65 years old and over [mean age: 73 +/- 7.05 years, range: 65- 84 years] and had a good autonomy.

2.2. Olfactory Testing

2.2.1. Stimuli

The olfactory detection threshold tests used two odorants: Phenyl Ethyl Alcohol (PEA) (C8H10O; molecular weight, 122.2) [activating only olfactory (CN I) system] and n- Butanol (BUT) (C4H10O; molecular weight, 72.12) [activating both the olfactory (CN I) and the trigeminal (CN V) systems] [32]; PEA has a pleasant and sweet rose-like (floral) smell and does not produce intranasal trigeminal sensations [32].

n- Butanol (normal butanol) is a clear, colorless liquid that is flammable. It has a characteristic banana-like odor [33] and has more trigeminal components than do purely olfactory stimuli such as phenyl ethyl alcohol (rose-like odorant) or vanillin [27] but has less trigeminal component than Pyridine for instance.

PEA and n-Butanol (Table **1**) are considered as good odorants for detection threshold testing.

2.2.2. Procedure

Dilutions of each odorant were prepared in a previous experiment carried out with a sample of 15 subjects with a range of dilution scored from 1 to 17 for n-Butanol and from 1 to 20 for PEA. Dilutions series were obtained by successive dilutions by a factor 2 with distilled water as solvent, providing a measure of the lower limits of olfactory detection. The dilutions were prepared in a geometric series starting from solutions of pure n-Butanol or pure PEA.

The odorant stimulus in liquid form was presented in a bottle pipe (7.5 cm high, 1 cm in diameter at the opening) filled with 4 ml of liquid. The bottle was presented to the subject for a period of 3 s at a distance of 1 cm from the nostrils using a holder to avoid any olfactory or thermic interference with the experimenter's hand. The olfactory stimuli were delivered bilaterally. Threshold testing was based on an ascending, binary (stimulus *vs*. blank) forced-choice method.

Each pair of stimuli consisted of a blank and an odor stimulus. The subject sniffed each stimulus and then chose which of the two smelled stronger. In order to minimize the effects of adaptation, testing progressed from weaker to stronger concentrations with approximately 90 seconds between trials. An incorrect choice led to an increased concentration on the next trial.

The dilution step (Table **2**) at which the odorant stimulus was first detected three times was recorded as the detection threshold. Prior to testing, subjects were instructed to say where the smell where more important between the two bottle pipe presented to them.

Local Institutional Review Board approvals were obtained for all the procedures and tests undertook in this study and informed consent of patients and controls were obtained before participation.

2.3. Data Analysis

Statistical analyses were performed using Statview (SAS Institute Inc., Statistical Software). For the analyses at the baseline, the continuous demographic characteristics (age, sex, socio-professional groups...) of the controls and patients were assessed. BUT and PEA odor detection thresholds of elderly patients with PD and control subjects were compared using the two-sample Student's t-test. We also assessed the impact

Table 1: Properties of phenyl ethyl alcohol and n- Butanol

Chemical	Compagny	CAS[a]	Molecular formula	Mol.wt[b]	Density g/cm^3	mol/cm^3
Phenyl ethyl alcohol	Sigma	60-12-8	$C_8H_{10}O$	122.2	1.02	$8.34x10^{-3}$
n - Butanol	Sigma	71-36-3	$C_4H_{10}O$	74.12	0.81	$10.9x10^{-3}$

[a]The American Chemical Society's Chemical Abstracts Service (CAS) registry number
[b]Mol.wt: molecular weight

Table 2: Concentrations of Phenyl Ethyl Alcohol and *n*-Butanol Obtained by Successive Dilutions (Factor 2)

Dilution step	Concentration (% v/v)	Phenyl ethyl alcohol		n-Butanol	
		g/cm^3	mol/cm^3	g/cm^3	mol/cm^3
1 Pur liquid	100	1.02	8.34×10^{-3}	0.81	10.9×10^{-3}
2	50	0.51	4.17×10^{-3}	0.41	5.45×10^{-3}
3	25	0.26	2.08×10^{-3}	0.20	2.72×10^{-3}
...	...	...	...	...	...
8	0.78			6.33×10^{-3}	8.81×10^{-5}
...	...	...	...	...	...
11	9.76×10^{-2}	9.99×10^{-4}	8.14×10^{-6}	7.89×10^{-4}	1.06×10^{-5}
...	...	...	...	...	...
17	1.53×10^{-3}	1.56×10^{-5}	1.27×10^{-7}	1.24×10^{-5}	1.66×10^{-7}
...	...	...	...	...	...
20	1.90×10^{-4}	1.94×10^{-6}	1.58×10^{-8}	1.54×10^{-6}	2.07×10^{-8}
...	...	...	...	...	...
25	5.96×10^{-6}	6.06×10^{-8}	4.95×10^{-10}		

of PD clinical characteristics (global clinical severity and motor impairment) on odor detection thresholds using ANOVA (analysis of variance) test (SAS). Group comparisons were considered significant at $p < 0.05$.

3. RESULTS

Twenty-four PD patients (Hoehn and Yahr: all stages) underwent olfactory testing using the odors detection thresholds. The median Unified Parkinson's Disease Rating Scale score was 17/147 (range: 3–35/147).

The median duration of disease was 12.91 years in general, and 6.7 years [range: 2-13 years] and 15.9 years [range: 7 -26 years] respectively in PD with late-onset and early-onset, respectively.

Patients with PD tend to have impaired olfactory (CN I) sensibility (mean PEA threshold: 16.7) compared with control subjects (mean PEA threshold: 18.28), independently of age and stage of PD; but this difference did not reach statistical significance.

Concerning BUT, results showed mean thresholds of 14.2 for patients with PD and of 13.04 for control subjects. The test scores are represented in Figure **1**.

Analyses were performed to evaluate possible effects of several clinical factors, gender-wise or age. Results showed that the PEA and BUT thresholds were correlated for patients with PD (rho = 2.199; P <0.02) as well as for controls (rho = 2.637; P <0.008).

No significant differences in odor thresholds (BUT and PEA) were identified concerning age of control subjects and of PD patients.

There was also no significant gender effect in odor thresholds (BUT and PEA) within PD's patients and control subjects. Correlation coefficients were non-significant (NS) for men as well as for women.

There was a borderline signification between BUT thresholds and global UPDRS score (clinical severity stage of PD) (ANOVA F= 3.092, P= 0.066) but no significant between PEA thresholds and global UPDRS score (ANOVA F=0.632, NS).

Finally, we did not find any significant correlation between odor thresholds and (1) length of evolution of PD (Spearman's Rho PEA = 0.361, Spearman's Rho BUT = 1.03; NS) and (2) the two clinical forms of PD in elderly (PD with late-onset and with early-onset) (NS).

4. DISCUSSION

Olfactory dysfunction is recognized as an early non-motor sign of PD and olfactory testing may be used as clinical diagnosis aid in youngers patients with PD. But olfactory dysfunction also occurs in about half of the population beyond the age of 65 years [34]; this

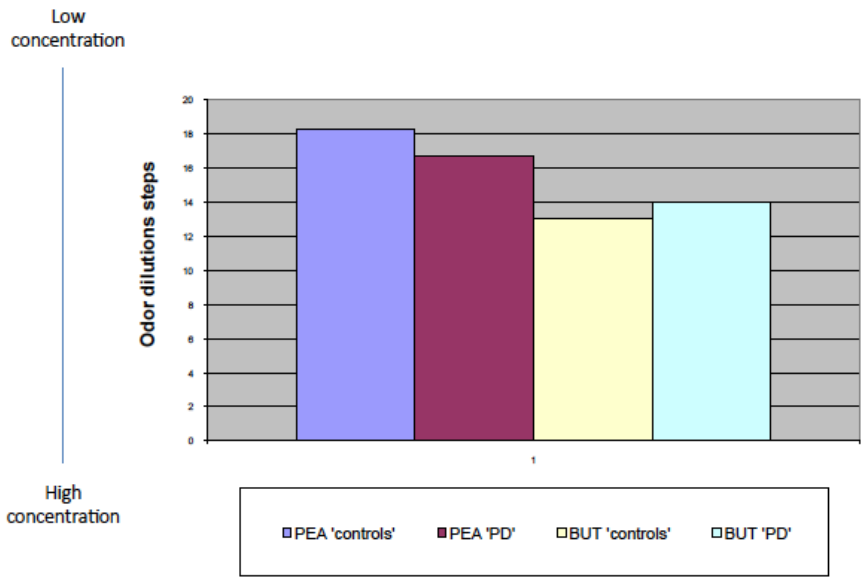

Figure 1: Mean Phenyl Ethyl Alcohol (PEA) and n-Butanol (BUT) thresholds for Parkinson Disease (PD) patients (24 subjects) and matched healthy controls

[t de student PEA 'PD' / PEA 'controls' t=1.545; p< 0.064 BUT 'PD' /BUT 'controls' t =1.408; p<0.082]

raises the issue of the accuracy of some olfactory tests (among them olfactory thresholds) in elderly.

Hyposmia is described as an impairment of both sensitivity and odor quality perception [35]. Each addresses different competencies: whereas sensitivity reflects perceptual processes that do not strongly depend on language abilities, identification relies on language and culture. Cultural variations influence odor identification which is based on learning of odors that have become familiar and "ecologically valid" [36]. Familiarity varies from country to country [37-39], as does stimulus typicality for a given target odor [40]. However, until now identification tests are almost always used in clinical routine [41] contrary to detection olfactory tests.

In our study we found that patients with PD had a lower olfactory (CN I) sensitivity to PEA (mean thresholds: 16.7) compared with control subjects (mean thresholds: 18.28); independently of age and stage of PD; however the difference did not reach statistical significance. On the contrary, results of BUT thresholds showed a mean of 14.2 for patients with PD and at 13.04 for control subjects. This finding tends to support the assumption that the trigeminal function is preserved in PD [42]. Indeed, in a study investigating olfaction in PD patients using olfactory event-related potentials (OERPs) in association with psychophysical testing, Bartz *et al.* suggested that the neuronal degeneration seen in PD as well as the treatment with antiparkinsonian drugs did not alter the intranasal chemosensory trigeminal system [42].

Contrary to Quinn NP *et al.* [43] who suggested that olfactory dysfunction was unrelated to odorant stimulus type, we found a difference between BUT and PEA detection thresholds even though this difference was not statistically significant which is probably due to the small sample size. The interaction between PEA and BUT detection thresholds would also be of diagnosis value with respect to PD symptoms in the elderly insofar as it could help to distinguish idiopathic PD from other forms of parkinsonism or other neurodegenerative diseases with motor symptoms, including disorders which are also often misdiagnosed as PD (e.g., Progressive supranuclear palsy (PSP), methylphenyl-tetrahydropyridine (MPTP)-induced PD, essential tremor, vascular parkinsonism).

The findings of the present study confirm that the combination of BUT [activating both olfactory and trigeminal systems] and PEA [activating only the olfactory system] detection thresholds are more accurate than one of the two odor detection thresholds alone.

Some studies have dealt with the interrelationships between the olfactory and the trigeminal systems; each of these systems is highly specific in terms of localization, transduction pathways, and central projections, emotional and cognitive treatment [27]. Nevertheless, both systems are simultaneously

activated by the same odorant molecule in the nasal cavity (except few molecules which selectively stimulate one or the other), which contributes to the global sensory perception and makes the mechanism of the olfactory and trigeminal difficult to understand. In an attempt to explore the role of each system in the detection processes, specifically in the just noticeable difference (JND), Jacquot *et al*., suggested a better capacity to perceive intensity changes for pungent odorants than for relatively pure odorants [49].

The basis for the olfactory deficit in PD still remains unclear. Since the pioneering study of Anasari and Johnson [45] who first demonstrated a decreased olfactory sensitivity in 10 out of 22 (45%) Parkinsonians, neurologists or neurophysiologists, have tremendously explored olfactory dysfunction mostly at early phase of PD [45]. Although the basis for PD-related olfactory impairment is unknown, it presumably reflects the pathogenicity of PD somewhere within the olfactory system.

In previous studies olfactory dysfunction in patients with PD has been attributed to early pathological deposition of Lewy bodies and Lewy neurites in primary olfactory centers [46, 47]. But the absence of olfactory dysfunction progression with the PD progression suggests the existence of additional pathobiological mechanisms contributing to olfactory dysfunction in PD, such as changes in olfactory neurotransmitter functions. It also may reflect the adverse effects of an environmental toxin or other exogenous agent which enters the brain via the olfactory epithelium [48].

Anyway, olfactory dysfunction is present to some degree in the general population and age-related declines in the ability to smell or to detect low concentrations of odorants are well documented [49, 50]. The chart of PEA detection thresholds disclose a hemi- parabola in the both sexes and the decline in PEA detection sensibility threshold tends to happen at a much earlier age in men than in women [51]. After the age of 80 years, it is estimated that about 70 percent of individuals have a marked impairment of olfactory functions and between 65 and 80 years, around 50 percent have a quantifiable deficit [52].

Olfactory dysfunction relative to other clinical signs of idiopathic PD is unique on several aspects; for instance it, does not evidence longitudinal progression (stable over time) or it is unrelated to disease stage [43, 50]; it is also unrelated to the use of antiparkinsonian medications (e.g., L-dopa, dopamine agonists, anticholinergic compounds) [43, 46]; it does not differ during the 'on' and 'off' states of patients with severe motor fluctuations who are on L-dopa therapy, and is unrelated in magnitude to the degree of motoric dysfunction [43, 46]. In addition, the difference of olfactory sensibility between the patients with idiopathic PD and healthy controls decreases with age.

As reported by Doty *et al.* [46], we also found no correlation between thresholds detection to BUT or PEA and (1) the duration of disease; (2) the motor disability measured by Hoehn and Yahr rating scale; (3) the severity of PD measured by UPDRS.

5. CONCLUSION

Findings of the present study indicated that Elderly PD's patients have a moderate PEA sensitivity deficit compared to healthy controls but this difference did not reach statistical significance. No such difference was observed for BUT activating both the olfactory and the trigeminal systems.

Our data suggest that the olfactory detection threshold test using PEA and BUT would not easily discriminate Elderly PD's patients from healthy controls, mainly due to the olfactory senescence.

However the combination of PEA and BUT detection thresholds or the use of an odor activating mainly the trigeminal system, such as Pyridine (which also more irritant) would help discriminating Elderly PD's patients from healthy controls and it may constitute a screening tool for idiopathic PD diagnostic in Elderly as in younger adults.

Further research using olfactory detection threshold tests (a non-invasive test that would be less expensive than other PD biomarkers) in larger cohorts of Elderly patients with PD will be needed to assess the combination of two or more odorants detection thresholds to validate olfactory dysfunction as a nonmotor feature diagnostic of PD in Elderly as in youngest.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest with regard to this research.

ACKNOWLEDGEMENTS

We thanks Drs A Doe de Mandroville, M Kack, JC Nwatchok, E Beck and D Kholer for providing some of the Patients evaluated in this study. The authors are also grateful to Mrs. Laurence Jacquot.

FUNDING

For this research Dr. Clovis Foguem was laureate of the Health Research Advancement Award of the Corporate foundation 'Groupe Pasteur Mutualité' (a French mutual's group of leading insurance administered by healthcare professionals) in 2011.

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Received on 14-03-2014 Accepted on 17-03-2014 Published on 04-09-2014

DOI: http://dx.doi.org/10.12974/2309-6128.2014.02.01.2