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Olfactory dysfunction in incidental Lewy body disease and Parkinson's disease

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Abstract

Background—Olfactory dysfunction in Parkinson's disease (PD) is well-established and may represent one of the earliest signs of the disease.

Objective & methods—The objective of this study was to evaluate the relationship of olfactory dysfunction, using the University of Pennsylvania Smell Identification Test (UPSIT), to clinical and pathological parameters of clinicopathologically diagnosed PD ($n = 10$), incidental Lewy body disease (ILBD) ($n = 13$), and identically assessed controls who lacked a neurodegenerative disease ($n = 69$).

Results—Mean UPSIT scores were significantly lower in PD (16.3, $p < 0.001$) and ILBD (22.2, $p = 0.004$) compared to controls (27.7). Using an UPSIT cutoff score of <22 (the 15th percentile) the sensitivity for detecting PD was 9/10 (90%) and ILBD 6/13 (46%), while the specificity was 86% (Controls with score of <22 = 10/69).

Conclusions—= These results add to the growing body of evidence suggesting that olfactory testing could be useful as a screening tool for identifying early, pre-motor PD.

Keywords

Parkinson's disease; Hyposmia; Incidental Lewy body disease

1. Introduction

While olfactory dysfunction occurs during normal aging, there are strong data supporting olfactory dysfunction preceding the clinical symptoms of Parkinson's disease (PD), perhaps representing one of the earliest signs of the disease [1,2]. Some data suggest olfactory dysfunction precedes motor findings in PD by up to seven years and recent data also shows

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olfactory dysfunction is a biomarker in two other synucleinopathies, rapid eye movement (REM) sleep behavior disorder (RBD) [3] and incidental Lewy body disease (ILBD) [2]. Patients with idiopathic RBD clearly are at high risk for developing either PD or dementia with Lewy bodies (DLB) and studies have shown RBD subjects have impaired olfaction and dopamine transporter uptake [3]. Hyposmia predating motor PD is also suggested by studies that have shown asymptomatic relatives of PD patients may have hyposmia as well as decreased dopamine transporter uptake on SPECT imaging and higher conversion rates to clinical parkinsonism versus normosmic relatives [1].

The main pathologic hallmark of PD is intraneuronal aggregates of the protein α-synuclein, termed Lewy type α-synucleinopathy (LTS). Upon autopsy, the olfactory bulb in PD is degenerated and contains LTS suggesting a link to olfactory dysfunction [4]. Olfactory bulb and tract LTS has been found in autopsied subjects who do not have clinical signs of PD or dementia, and these subjects are neuropathologically classified as incidental Lewy body disease (ILBD) [5,6]. Given the presence of LTS without PD or dementia, it is hypothesized that ILBD may have hyposmia and be a precursor state to PD. Therefore, finding an association between hyposmia and ILBD would further establish olfactory testing as a premotor biomarker for PD.

The objective of this study was to evaluate the relationship of olfactory dysfunction to pathological findings in autopsy confirmed PD, ILBD, and control subjects.

2. Patients and methods

This study was conducted as part of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) by the Arizona Parkinson Disease Consortium/Banner Sun Health Research Institute Brain and Body Donation Program (BBDP). All subjects in the BBDP had signed informed consent approved by Banner Sun Health Research Institute IRB and were followed antemortem with annual standardized medical, movement, and cognitive assessments [7]. The database was queried for autopsied subjects with olfactory testing who had a clinicopathologic diagnosis of either PD, ILBD, or control (no neurodegenerative disease). Subjects with coexistent dementia were excluded. In addition, the following were excluded: Alzheimer's disease, vascular dementia, dementia NOS, dementia with Lewy bodies, Parkinson's disease with dementia, parkinsonism, progressive supranuclear palsy, multiple systems atrophy, cerebellar degeneration, amyotrophic lateral sclerosis, meningioma, multiple sclerosis, glioblastoma, radiation necrosis, and brain cancer. Patients with MCI were not excluded.

All subjects completed the University of Pennsylvania Smell Identification Test (UPSIT) [8] a widely used olfactory test that requires subjects to identify, in a multiple-choice format, 40 odorants microencapsulated on “scratch and sniff” labels. The UPSIT was administered by a trained technician and scored using standard procedures (scores 0–40). Raw scores are calculated as the number of correct identifications and divided into age and gender standardized cut-offs for the number of correctly identified odorants [8]. The battery of UPSIT testing was added to the BBDP in June 2002.

Subjects were autopsied and received a final diagnosis based on clinicopathologic correlation as previously described [7]. Densities of LTS in the olfactory bulb and tract (OBT), as well as other nuclei in the olfactory circuitry (the amygdala, and entorhinal cortex) were graded on a five-point semi-quantitative scale using formalin-fixed, paraffin embedded 5 μm sections immunohistochemically stained using an antibody against phosphorylated α-synuclein peptide (1:10,000; rabbit polyclonal anti-human phosphoserine 129) [9] (See Acknowledgments).

3. Statistical analysis

Groups were compared using the pairwise contrasts with a oneway analysis of variance model. Confounding variables were assessed by using a general linear model with terms for group, sex, smoking history, and age.

4. Results

There were 532 subjects with cognitive and motor examinations and a final clinicopathologic diagnosis. From these autopsied cases, 205 had completed smell testing. Following exclusion criteria 92 subjects were identified for this study. Of the 92 identified there were 10 PD cases, 13 ILBD and 69 controls (Table 1). Gender ratio, age of death and mean interval between UPSIT and death did not differ amongst groups (Table 1). Both the PD (UPSIT = 16.3 ± 5.3, $p < 0.001$) and ILBD (UPSIT = 22.2 ± 9.1, $p = 0.004$) groups had lower mean UPSIT scores compared to the control group (UPSIT = 27.7 ± 5.7) (Fig. 1). Adjustment for age ($p = 0.008$) did not significantly change the results. UPSIT scores were lower in PD compared to ILBD ($p = 0.03$) (Table 1). Using an UPSIT cutoff score of <22 (the 15th percentile) the sensitivity for detecting PD was 9/10 (90%) and ILBD 6/13 (46%), while the specificity was 86% (Controls with score of <22 = 10/69). There were no other significant correlations between LTS and UPSIT scores. MCI was identified in 6 (60%) PD cases, 2 (15%) ILBD cases and 11 (16%) of the controls.

5. Discussion

Confirmed ILBD and PD cases when compared to a similarly assessed control group, had significantly lower UPSIT scores even after adjusting for age and time from UPSIT till death. This corroborates prior data showing early pathological changes in the anterior olfactory region in PD [10], hyposmia in ILBD [2], and olfactory bulb synucleinopathy as predictive of Lewy body disorders [6]. If ILBD is indeed a precursor to PD then these early pathological changes could explain the milder hyposmia seen in ILBD vs. PD and provide evidence of hyposmia as a premotor symptom of PD or other Lewy body disorders.

Olfactory testing could be a useful screening tool for identifying individuals at higher risk for developing PD or possibly other Lewy body disorders. These high risk groups include those with RBD, hyposmic relatives of PD patients, or individuals with genetic predisposition or mutations. Additionally, hyposmic individuals in the general population may also be at increased risk of developing

PD. These patients when seen by nonspecialists could be referred to neurologists for further evaluation and participation in studies, such as the Parkinson's Progression Markers Initiative (PPMI) and the Parkinson At-Risk Syndrome (PARS) Study [11], both are using hyposmia as a screening test to identify early PD. These hyposmic at risk groups are then undergoing other biomarker testing, such as dopamine transporter neuroimaging, transcranial ultrasound, or cardiac scintigraphy. Combining clinical biomarkers may increase the sensitivity for diagnosing early, pre-motor PD versus DLB. As olfactory testing is inexpensive compared to the imaging modalities mentioned, an initial screen for hyposmia would appear to make fiscal sense. Identifying at-risk individuals is crucial for improving future symptomatic and disease-modifying treatment studies of PD [12] as well as leading to a better understanding of the neurodegenerative process of PD [1].

In conclusion, this clinicopathological study revealed hyposmia in neuropathologically proven ILBD and PD compared to controls. Although the sample size of the PD and ILBD groups were not large, the evidence for hyposmia was significant, providing further evidence that ILBD is a pre-clinical state for PD and that olfactory dysfunction occurs before the onset of motor symptoms.

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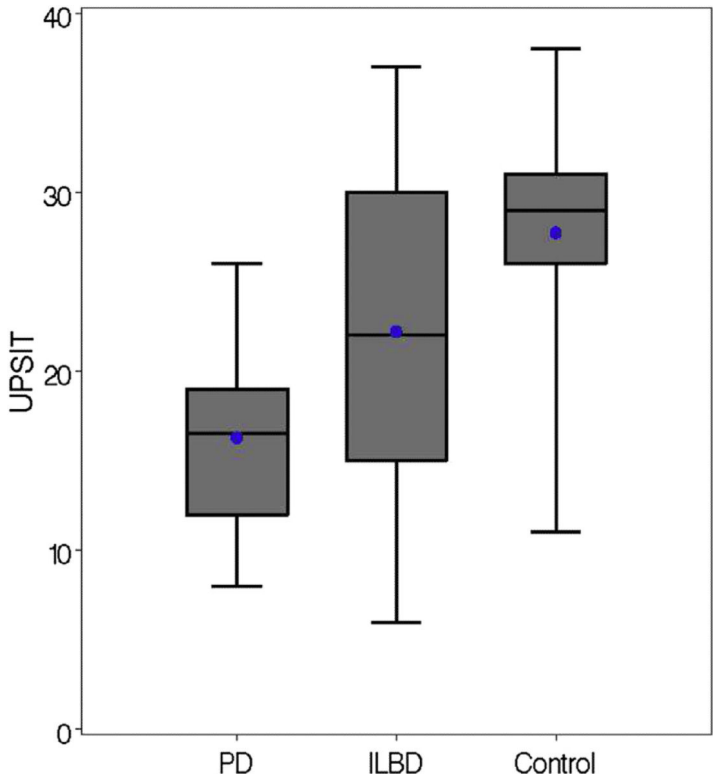

Fig. 1.

UPSIT score for 10 subjects with PD, 13 subjects with ILBD, and 69 control subjects. Dots indicate means, boxes indicate quartiles, and whiskers indicate ranges.

Table 1

Demographics, UPSIT scores and pathology.

	PD	ILBD	Control
N	10	13	69
Characteristics			
Female	5 (50%)	6 (46%)	35 (51%)
Ever smoked	5 (50%)	7 (54%)	33 (48%)
UPSIT interval (y); mean (SD) [min–max]	1.6 (1.5) [0.3–5.1]	3.0 (1.5) [0.4–5.9]	2.9 (2.2) [0.1–10.1]
Age at UPSIT (y); mean (SD)	79.7 (8.0)	86.2 (6.2)	84.2 (5.9)
Age at death (y); mean (SD)	81.3 (7.9)	89.2 (6.3)	87.2 (6.0)
LB density OBT (0–4); mean (SD)	2.9 (1.1)[a]	2.1 (1.1)	0.0 (0.0)
LB density amygdala (0–4); mean (SD)	3.00 (0.82)	1.1 (1.4)	0.0 (0.0)
LB density entorhinal (0–4); mean (SD)	2.1 (1.1)[a]	0.31 (0.85)	0.0 (0.0)
Braak score (0–6); median [min–max]	3 [2–4]	3 [1–5]	3 [3–4]
Braak score > 3	4 (40%)	6 (46%)	33 (48%)
UPSIT			
Score (points); mean (SD)[b]	**16.3 (53)**	**22.2 (9.1)**	**27.7 (5.7)**
p	<0.001	0.004	Reference
p	0.03	Reference	0.004
Adjusted score (points); mean[b,c]	15	23	28
p	<0.001	0.008	Reference
p	0.004	Reference	0.008
Adjusted score (points); mean[c]	NA	23	28
p	NA	0.01	Reference
<22 points[b] [<15th percentile]	9 (90%)	6 (46%)	10 (14%)
<23 points[d]		7 (54%)	11 (16%)

[a] *N* 9.

[b] $p < .001$.

[c] Adjusted for age. Adjustment for age reduced the difference between ILBD and control by less than 12%.

[d] Maximized Youden index.