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ORIGINAL COMMUNICATION

Olfactory anosognosia is a predictor of cognitive decline and dementia conversion in Parkinson's disease

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Abstract

Objective Parkinson's disease (PD) patients are often unaware of olfactory deficits despite having hyposmia from the early stages. We aimed to evaluate whether olfactory anosognosia is a predictor of cognitive decline in PD.

Methods In this retrospective cohort study, we recruited 77 PD patients who underwent both olfactory and neuropsychological tests and were followed-up for over 5 years. Based on the degree of olfactory dysfunction and awareness of its presence, patients were classified as normosmic patients (Normosmia group, $n=15$), hyposmic patients without olfactory anosognosia (Hyposmia-OA−, $n=40$), or hyposmic patients with olfactory anosognosia (Hyposmia-OA+, $n=22$). We compared the rates of cognitive decline using linear mixed model and dementia conversion using a survival analysis among the groups.

Results A higher proportion of patients in the Hyposmia-OA+ group had mild cognitive impairment at baseline (77.3%) and dementia converter at follow-up (50.0%). The Hyposmia-OA+ group exhibited a faster decline in frontal executive and global cognitive function than did the Normosmia and Hyposmia-OA− groups. A Kaplan–Meier analysis demonstrated that the conversion rate to dementia was significantly higher in the Hyposmia-OA+ group than in the Normosmia ($P=0.007$) and Hyposmia-OA− ($P=0.038$) groups. A Cox regression analysis showed that olfactory anosognosia remained a significant predictor of time to develop dementia in the Hyposmia-OA+ group compared to the Normosmia group (adjusted hazard ratio 3.30; 95% confidence interval 1.10–8.21).

Conclusion This study suggests that olfactory anosognosia is a predictor of cognitive decline and dementia conversion in PD.

Keywords Olfactory dysfunction · Anosognosia · Cognitive decline · Dementia · Parkinson's disease

Introduction

Impaired olfactory function is one of the earliest prodromal symptoms of Parkinson's disease (PD) and is present in up to 90% of patients with early-stage PD [1, 2]. Intracellular aggregates of α-synuclein, the pathologic hallmark of PD, involve the olfactory bulb and anterior olfactory nucleus at Braak stage I [3]. Olfactory deficits can precede clinically overt parkinsonian motor symptoms by at least 4 years [4]. Thus, olfactory dysfunction appears to be an important clinical biomarker to predict the future development of PD [5]. Olfactory dysfunction has been reported to be associated with the progression of cognitive decline [6]. While olfactory dysfunction is independent of cognitive impairment at baseline [2], patients with PD who exhibit decreased olfactory ability have a significant increase in their risk of progression to dementia [7]. PD patients with severe hyposmia also exhibit a characteristic distribution of cerebral metabolic decline that is identical to that of dementia associated with PD [8]. On the other hand, normal olfaction in PD predicts a benign motor and cognitive course after diagnosis [7, 9].

With respect to hyposmic patients with PD, some patients deny their olfactory dysfunction, referred to as olfactory anosognosia [10]. Anosognosia refers to a deficit of self awareness or impaired insight for behavioral and cognitive problems [11]. It is a complex mental function dependent mainly on memory and executive function, and has frequently been reported in patients with dementia, including Alzheimer's disease (AD) and frontotemporal dementia

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(FTD) [12]. Anosognosia is prevalent not only in patients with AD but also in those with mild cognitive impairment (MCI) [13], and independently predicts conversion from MCI to AD [14]. However, the clinical relevance of olfactory anosognosia in the cognitive prognosis has not been studied in patients with PD.

In this study, we hypothesized that olfactory anosognosia at baseline would implicate faster progression of cognitive decline. To clarify this, we identified hyposmic patients with PD who were unaware of their olfactory deficits and then, performed comparative analysis of the cognitive deterioration over more than 5 years between hyposmic patients with and without olfactory anosognosia.

Methods

Study design

In this retrospective cohort study, patients were recruited from the Movement Disorders outpatient clinic in the Yonsei University Health System. We enrolled 136 drug-naïve patients with PD in the PD cognition cohort from September 2008 to August 2013. The patients were followed longitudinally, during which time they underwent neuropsychological tests every 2–3 years or when they or their caregivers complained of a cognitive decline in their activities of daily living. At baseline neuropsychological evaluation, we excluded patients with PD who were illiterate and could not complete the neuropsychological tests ($n=7$), already met the criteria for dementia ($n=6$), had severe white matter hyperintensities (WMHs) ($n=5$) [15], developed PD before age of 40 ($n=3$), or had conditions affecting olfactory function ($n=6$). Among the 109 eligible patients, we further excluded patients with PD who were followed-up for less than 5 years ($n=18$); had other neurologic, psychiatric, or metabolic illnesses ($n=8$); or were diagnosed with a disease other than PD ($n=6$) during follow-up. Finally, 77 patients with PD who had been followed-up for over 5 years were included in this study. The details of the enrollment of the study participants are illustrated in Fig. 1.

Patients

All patients underwent baseline assessments that included neurologic examination, olfactory function tests, detailed neuropsychological tests, brain magnetic resonance imaging (MRI), and *N*-(3-[^{18}F]fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane (^{18}F-FP-CIT) positron emission tomography (PET) scanning. The diagnosis of PD was based on the clinical diagnostic criteria of the United Kingdom PD Society Brain Bank [16], and only patients diagnosed with PD who responded to dopaminergic medication during the follow-up period (≥ 6 months) were included in this study. All patients with PD had undergone ^{18}F-FP-CIT PET imaging at the time of their PD diagnosis, which revealed decreased uptake in the posterior putamen.

This study was approved by the Institutional Review Board of the Yonsei University Severance Hospital. Written

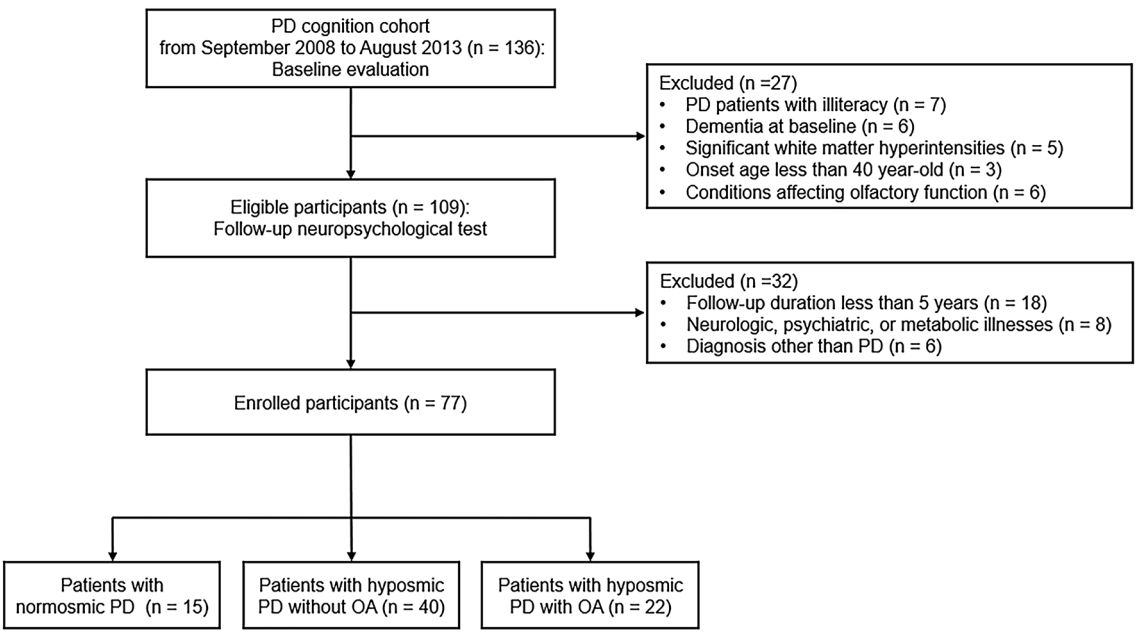

Fig. 1 Flowchart of enrollment of the study participants. *NP* neuropsychological test, *OA* olfactory anosognosia, *PD* Parkinson's disease

informed consent was obtained from all patients who participated in this study.

Assessment of olfactory function and olfactory anosognosia

Olfactory function was assessed using the Cross-Cultural Smell Identification Test (CCSIT), which consists of 12 smells [17]. The CCSIT score was calculated as the sum of the correct responses. Based on the original study by Doty et al. [17], we classified our patients into normosmic PD if the CCSIT score was ≥ 9 and hyposmic PD if the score was ≤ 8. All participants responded to a question about their self-rated olfactory ability that asked them to characterize their own sense of smell [2]. There were three response options: normal sense of smell; decreased, but not absent; and no sense of smell. Olfactory anosognosia was defined as when the patients with PD had an objective olfactory deficit (CCSIT ≤ 8) but selected the "normal sense of smell" response when asked about their olfactory ability. According to the presence of hyposmia and olfactory anosognosia, we divided participants into three groups; normosmic patients with PD (Normosmia), hyposmic patients with PD without olfactory anosognosia (Hyposmia-OA−), and hyposmic patients with PD with olfactory anosognosia (Hyposmia-OA+).

Clinical assessment and parameters

Parkinsonian motor symptoms were assessed during the drug-naïve state at the time of ^{18}F-FP-CIT PET acquisition using the Unified PD Rating Scale motor (UPDRS-III) subscales. Baseline height and weight were measured at the initial visit, and body mass index (BMI) was calculated by dividing weight expressed in kilograms by the square of the height expressed in meters (kg body weight/m^2 height). The presence of rapid eye movement sleep behavior disorder (RBD) was assessed using an RBD Screening Questionnaire, as described in our previous work [18]. The self-rated Beck Depression Inventory (BDI) was used to assess depressive symptoms. The levodopa dose and levodopa-equivalent dose (LED) were calculated according to a previously described method [19]. Increments in levodopa or LED per year were calculated by dividing the total levodopa dose or LED at the final visit by the total duration of levodopa treatment. Apolipoprotein E (*APOE*) genotyping was performed in a subset of study participants.

Neuroimaging acquisition and parameters

All MRI scans were acquired using a Philips 3T scanner (Philips Intera; Philips Medical System, Best, The Netherlands) with a SENSE head coil (SENSE factor = 2). A high-resolution T1-weighted MRI volume data set was obtained from all participants using a three-dimensional T1-TFE sequence configured with the following acquisition parameters: axial acquisition with a 224 × 256 matrix; 256 × 256 reconstructed matrix with 182 slices; 220 mm field of view; 0.98 × 0.98 × 1.2 mm3 voxels; TE (echo time), 4.6 ms; TR (repetition time), 9.6 ms; flip angle, 8°; and no slice gap. Based on MR images, visual rating scales of medial temporal atrophy (MTA) and white matter hyperintensities (WMHs) were assessed. MTA was rated visually using a five-grade rating scale that ranged from 0 (no atrophy) to 4 (severe atrophy) [20]. The visual rating scale of the WMHs was modified from the Fazekas scale [15]. Periventricular WMHs were classified as P1 (cap and band < 5 mm), P2 (5 mm ≤ cap or band < 10 mm), or P3 (10 mm ≤ cap or band), and deep WMHs were classified as D1 (maximum diameter of a deep white matter lesion < 10 mm), D2 (10 mm ≤ lesion < 25 mm), or D3 (≥ 25 mm).

Neuropsychological evaluations and diagnosis of cognitive status

All patients underwent a standardized and comprehensive neuropsychological battery of tests called the Seoul Neuropsychological Screening Battery [21], which contained the following tests: digit span (forward and backward), repetition, Korean version of the Boston Naming Test (K-BNT), six-point pentagon drawing test, Rey–Osterrieth Complex Figure Test (RCFT: copying, immediate recall, 20-min delayed recall, and recognition), Seoul Verbal Learning Test (SVLT: immediate recall, 20-min delayed recall, and recognition), contrasting programming and go/no-go test, clock drawing test, phonemic and semantic Controlled Oral Word Association Test (COWAT), and Stroop Test (word and color reading). Standardized z scores are available for all scorable tests based on age-, sex-, and education-specific norms [21]. A composite score was calculated for each cognitive domain by dividing the sum of the *z* scores by the number of tests. The following two scorable tests were designated to represent each of the four cognitive domains except language: digit span task and Stroop test (attention domain), K-BNT (language domain), RCFT copy and pentagon drawing test (visuospatial domain), SVLT and RCFT (memory domain), and clock drawing test and COWAT (frontal executive domain). We calculated the following three summary scores to assess global cognitive performance: global z-score composite derived by averaging all z-scores, the Korean version of the Mini-Mental State Examination (K-MMSE), and Clinical Dementia Rating-Sum of Boxes (CDR-SOB). Patients were diagnosed with PD with intact cognition when impairments were observed in less than two items in the detailed neuropsychological

test. A diagnosis of PD with MCI by level II criteria was made in accordance with the Movement Disorder Society Task Force guideline [22]. Patients with PD were diagnosed with MCI if they expressed a subjective cognitive complaint, had impairments on at least two tests in neuropsychological evaluation, and showed no evidence of abnormal activities of daily living (ADL). Patients were diagnosed with Parkinson's disease dementia (PDD) if they fulfilled the clinical criteria of probable PDD [23].

Statistical analyses

The baseline clinical and neuropsychological characteristics of the patients with PD were analyzed. For continuous variables, Kruskal–Wallis test was used, and data are expressed as median (interquartile range). We performed Pearson's χ^2 test for nominal variables and Mantel–Haenszel χ^2 test for ordinal variables, and the data are expressed as number (percentage). A linear mixed model was used to examine the differences in the rates of cognitive decline among the groups. We performed a Kaplan–Meier analysis of the probability of progression to PDD and used a log-rank test to compare the Kaplan–Meier plots of the groups. The hazard ratio (HR) of converting to PDD was calculated using a Cox proportional hazards model. In linear mixed model and Cox proportional hazards model analyses, age, sex, years of education, initial UPDRS-III score, and LED increment per year were used as covariates, all of which have been reported to affect cognition or reflect the disease progression in PD. Variables which were comparable among the groups were not considered as covariates. The data were analyzed using SPSS software 23 (IBM Corporation, Armonk, NY, USA). For the survival analyses, the R (v3.3.2) package packHV (https://www.r-project.org/) was used. *P* values less than 0.05 were considered significant.

Results

Demographic and clinical characteristics

The baseline demographic characteristics of the patients are summarized in Table 1. Among the 77 patients with PD, 62 patients (80.5%) had decreased olfactory function, of whom 22 (28.6%) had olfactory anosognosia at baseline. The Normosmia group had slower LED increment per year than did the hyposmic PD groups. Clinically, the age at disease onset, sex, years of education, PD and follow-up duration, BMI, RBD, CCSIT, BDI, proportion of *APOE4* carrier, and vascular risk factors did not differ among the groups. Radiologically, there were no differences in the degree of MTA or WMHs among the groups.

Baseline neuropsychological profiles in the Normosmia, Hyposmia-OA−, and Hyposmia-OA+ groups

Age at initial neuropsychological evaluation and number of follow-up tests were comparable among the groups (Table 2). All cognitive items (attention, language, visuospatial, memory, and frontal executive function composite scores) and global cognitive performance assessments (global composite scores, total MMSE scores, and CDR-SOB scores) did not differ significantly among the groups. A higher proportion of the Hyposmia-OA+ group had MCI at baseline (77.3% vs. 55.0%, $p=0.048$) and PDD converter (50.0% vs 27.5%, $P=0.046$) than the Hyposmia-OA− group.

Comparison of the progression of cognitive decline among the Normosmia, Hyposmia-OA−, and Hyposmia-OA+ groups

A linear mixed model analysis showed that the visuospatial and global composite decreased significantly over time in the Normosmic group (Table 3). The patients in the Hyposmia-OA− group showed a significant decrease in cognitive performance on the visuospatial, global composite, and total MMSE scores and increase in CDR-SOB scores over time. All cognitive functions worsened progressively in the Hyposmia-OA+ group. In post hoc analysis, the Hyposmia-OA− group showed a faster decline of the total MMSE score than the Normosmia group. The Hyposmia-OA+ group had more rapid change of visuospatial, frontal executive, and global composites, total MMSE score, and CDR-SOB than the Normosmia group. In a between-hyposmic group comparison, the Hyposmia-OA+ group had a more rapid change in frontal executive composite ($P=0.008$), total MMSE score ($P=0.015$), and CDR-SOB ($P<0.001$) than the Hyposmia-OA− group.

Conversion to PDD in the study participants

A Kaplan–Meier analysis of time-to-conversion showed difference in the conversion rate to dementia between PD patients with normosmia and hyposmia ($P=0.032$ by log-rank test; Fig. 2a). The Normosmia, Hyposmia-OA−, and Hyposmia-OA+ groups showed different conversion rate to dementia ($P=0.012$ by log-rank test; Fig. 2b). In post hoc analyses, the Hyposmia-OA+ group had a higher rate of conversion to dementia than the Normosmia ($P=0.007$) and the Hyposmia-OA− ($P=0.038$) groups. In the Cox regression model, after adjustment for age, sex, years of education, baseline UPDRS-III score, and LED increment per year, the

Table 1 Demographic and clinical characteristics of the patients with PD

	Normosmia group ($n=15$)	Hyposmia-OA− group ($n=40$)	Hyposmia-OA+ group ($n=22$)	P value
Age at PD onset (year)	60.5 (54.5–67.0)	65.5 (60.5–69.8)	66.0 (60.0–70.3)	0.202
Sex, female, *n* (%)	9 (60.0)	17 (42.5)	11 (50.0)	0.613
Education (year)	9.0 (5.3–16.0)	9.0 (6.0–12.0)	8.0 (3.0–12.0)	0.430
PD duration (year)	9.4 (8.5–10.5)	8.5 (7.0–9.2)	8.0 (7.0–8.9)	0.086
Follow-up duration (year)	8.5 (7.3–9.2)	7.4 (6.3–8.1)	7.3 (6.5–7.90)	0.010
UPDRS-III	14.5 (8.0–20.3)	15.5 (10.0–22.8)	18.5 (14.5–22.0)	0.187
Body mass index (kg/m^2)	24.1 (22.3–25.7)	23.9 (21.7–25.9)	25.6 (23.2–27.2)	0.156
RBD, *n* (%)	10 (66.7)	22 (55.0)	14 (63.6)	0.523
CCSIT	10.0 (9.0–10.3)	6.0 (4.0–7.0)	6.0 (4.8–7.0)	< 0.001
BDI	13.0 (8.5–20.0)	10.0 (7.0–15.0)	16.0 (8.8–20.0)	0.241
APOE4 carrier, *n* (%)	1/5 (20.0)	4/14 (28.6)	2/8 (25.0)	0.930
LED increment per year till the last follow-up	94.1 (74.4–121.0)	117.8 (96.5–133.7)	127.4 (102.5–153.9)	0.029
Risk factors, *n* (%)				
Hypertension	7 (46.7)	17 (42.5)	13 (59.1)	0.455
Diabetes mellitus	5 (33.3)	6 (15.0)	7 (31.8)	0.166
Dyslipidemia	6 (40.0)	8 (20.0)	6 (27.3)	0.246
Ischemic heart disease	2 (13.3)	4 (10.0)	4 (18.2)	0.654
Ischemic stroke	1 (6.7)	4 (10.0)	4 (18.2)	0.529
Brain MRI				
Deep WMH, *n* (%)				0.443
Mild	13 (86.7)	33 (82.5)	19 (86.4)	
Moderate	1 (6.7)	6 (15.0)	2 (9.1)	
Severe	1 (6.7)	1 (2.5)	1 (4.5)	
Periventricular WMH, *n* (%)				0.793
Mild	13 (86.7)	29 (72.5)	18 (81.8)	
Moderate	1 (6.7)	9 (22.5)	3 (13.6)	
Severe	1 (6.7)	2 (5.0)	1 (4.5)	
MTA grade, right	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.775
MTA grade, left	1.5 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.915

Values are expressed median (interquartile range) or number (percentage) if appropriate. Kruskal–Wallis test was used for continuous variables and χ^2 test was used for categorical variables

BDI Beck Depression Inventory, *CCSIT* cross-cultural smell identification test, *LED* levodopa-equivalent dose, *MRI* magnetic resonance imaging, *MTA* medial temporal atrophy, *PD* Parkinson's disease, *RBD* rapid eye movement sleep behavior disorder, *UPDRS-III* Unified Parkinson's disease Rating Scale-part III, *WMH* white matter hyperintensities

hazard ratio was 3.30 for the Hyposmia-OA+ group [95% confidence interval (CI), 1.10–8.21; $P=0.047$] relative to the Normosmia group. The difference of conversion rate to dementia between the hyposmic groups did not reach statistical significance ($P=0.120$) in the Cox regression analysis.

Discussion

The present study assessed the association between the presence of olfactory anosognosia and longitudinal changes in cognition in PD. The major findings were as follows. First, the presence of olfactory anosognosia combined with olfactory dysfunction is related to an increased proportion of patients with MCI at baseline and PDD converter at follow-up. Second, the PD patients with olfactory anosognosia showed faster cognitive declines than those with normosmia or with hyposmia without olfactory anosognosia. Third, we demonstrated the ability of olfactory anosognosia to predict the progression to dementia in patients with PD. Thus, these findings suggest that the presence of olfactory anosognosia is closely associated with faster cognitive decline in patients with PD.

Anosognosia was initially used to describe the unawareness of impairments due to focal lesions of the brain [24]. The usage of anosognosia has been extended to imply a general unawareness of one's disease or impairments. It is typically observed in patients with primary dementia, such

Table 2 Comparison of the neuropsychological characteristics of patients with PD

	Normosmia group ($n=15$)	Hyposmia-OA− group ($n=40$)	Hyposmia-OA+ group ($n=22$)	*P* value
Age at initial NP (year)	62.0 (57.8–71.0)	67.0 (63.0–70.8)	67.5 (61.8–71.3)	0.348
PD onset to initial NP (year)	1.3 (0.5–2.7)	1.1 (0.7–2.0)	1.1 (0.7–1.8)	0.911
Number of NP during follow-up	3.0 (3.0–4.0)	3.0 (3.0–3.0)	3.0 (3.0–3.3)	0.586
PDD converter, *n* (%)	2 (13.3)	11 (27.5)	11 (50.0)	0.038
PD onset to PDD (year)	9.3 (7.9–10.5)	8.4 (6.8–9.0)	7.7 (6.2–8.9)	0.055
Cognitive status of initial NP				
IC/MCI	10 (66.7)/5 (33.3)	18 (45.0)/22 (55.0)	5 (22.7)/17 (77.3)	0.032
Non-amnestic/amnestic	1 (20.0)/4 (80.0)	6 (27.3)/16 (72.7)	4 (23.5)/13 (76.5)	0.368
Baseline neuropsychological profiles				
Attention composite	0.04 (− 0.26 to 0.67)	0.05 (− 0.59 to 0.64)	− 0.19 (− 0.95 to 0.23)	0.156
Language composite	0.25 (− 0.53 to 0.65)	0.50 (− 0.36 to 0.93)	− 0.20 (− 0.89 to 1.27)	0.281
Visuospatial composite	1.18 (− 0.28 to 1.49)	1.07 (0.20–1.38)	0.44 (− 0.60 to 1.29)	0.399
Memory composite	− 0.12 (− 0.39 to 0.61)	0.01 (− 0.51 to 0.48)	− 0.32 (− 0.83 to 0.64)	0.156
Frontal executive function	0.18 (− 0.52 to 0.97)	0.13 (− 0.49 to 0.59)	− 0.23 (− 0.82 to 0.36)	0.263
Global composite	0.12 (− 0.63 to 0.47)	0.15 (− 0.40 to 0.50)	− 0.33 (− 0.71 to 0.07)	0.152
Total MMSE score	28.00 (25.00–30.00)	28.00 (27.00–29.00)	28.00 (25.75–29.00)	0.450
CDR-SOB	1.00 (0.50–1.50)	0.75 (0.50–1.50)	1.00 (0.50–2.00)	0.542

Values expressed are median (interquartile range) or number (percentage) if appropriate. Kruskal–Wallis test was used for continuous variables and χ^2 test was used for categorical variables

CDR-SOB clinical dementia rating-sum of boxes, *IC* intact cognition, *MCI* mild cognitive impairment, *MMSE* mini-mental state examination, *NP* neuropsychological test, *PD* Parkinson's disease, *PDD* Parkinson's disease dementia

Table 3 Longitudinal changes of cognition in patients with PD over 5 years

	Estimated slope (standard error)								
	Normosmic group	*P* value	Hyposmia-OA− group	*P* value	Hyposmia-OA+ group	*P* value	*P* value[a]	*P* value[b]	*P* value[c]
Cognitive domain									
Attention	− 0.04 (0.03)	0.101	− 0.03 (0.02)	0.199	− 0.09 (0.03)	0.002	0.933	0.127	0.073
Language	− 0.05 (0.04)	0.252	− 0.02 (0.03)	0.603	− 0.10 (0.04)	0.011	0.463	0.347	0.109
Visuospatial	− 0.17 (0.05)	0.002	− 0.27 (0.07)	< 0.001	− 0.37 (0.08)	< 0.001	0.255	0.030	0.302
Memory	− 0.03 (0.04)	0.492	− 0.03 (0.02)	0.221	− 0.08 (0.03)	0.010	0.898	0.215	0.163
Frontal executive	− 0.02 (0.01)	0.078	− 0.02 (0.04)	0.521	− 0.14 (0.03)	< 0.001	0.644	0.005	0.008
Global cognition									
Global composite	− 0.04 (0.02)	0.022	− 0.07 (0.03)	0.015	− 1.11 (0.02)	< 0.001	0.428	0.012	0.187
Total MMSE score	0.01 (0.12)	0.957	− 0.27 (0.08)	< 0.001	− 0.57 (0.10)	< 0.001	0.037	< 0.001	0.015
CDR-SOB	0.03 (0.05)	0.597	0.10 (0.04)	0.004	0.32 (0.05)	< 0.001	0.229	< 0.001	< 0.001

The estimate (β) is the change in the composite scores in each cognitive domain and general cognition (i.e., a negative value indicates the decline of cognitive function). The linear mixed model included seven fixed effects (six between-subject effects: PD subgroup, age at PD onset, sex, years of education, baseline UPDRS-III score, and levodopa-equivalent increment per year; and one within-subject effect: time). The effects of PD subgroup on the change in cognitive composite score over time was tested using the time by PD subgroup interaction term

CDR-SOB clinical dementia rating-sum of boxes, *MMSE* mini-mental state examination, *OA* olfactory anosognosia, *PD* Parkinson's disease

[a]Significantly different in the comparison between the Normosmic and Hyposmic-OA− groups

[b]Significantly different in the comparison between the Normosmic and Hyposmic-OA+ groups

[c]Significantly different in the comparison between the Hyposmic-OA− and Hyposmic-OA+ groups

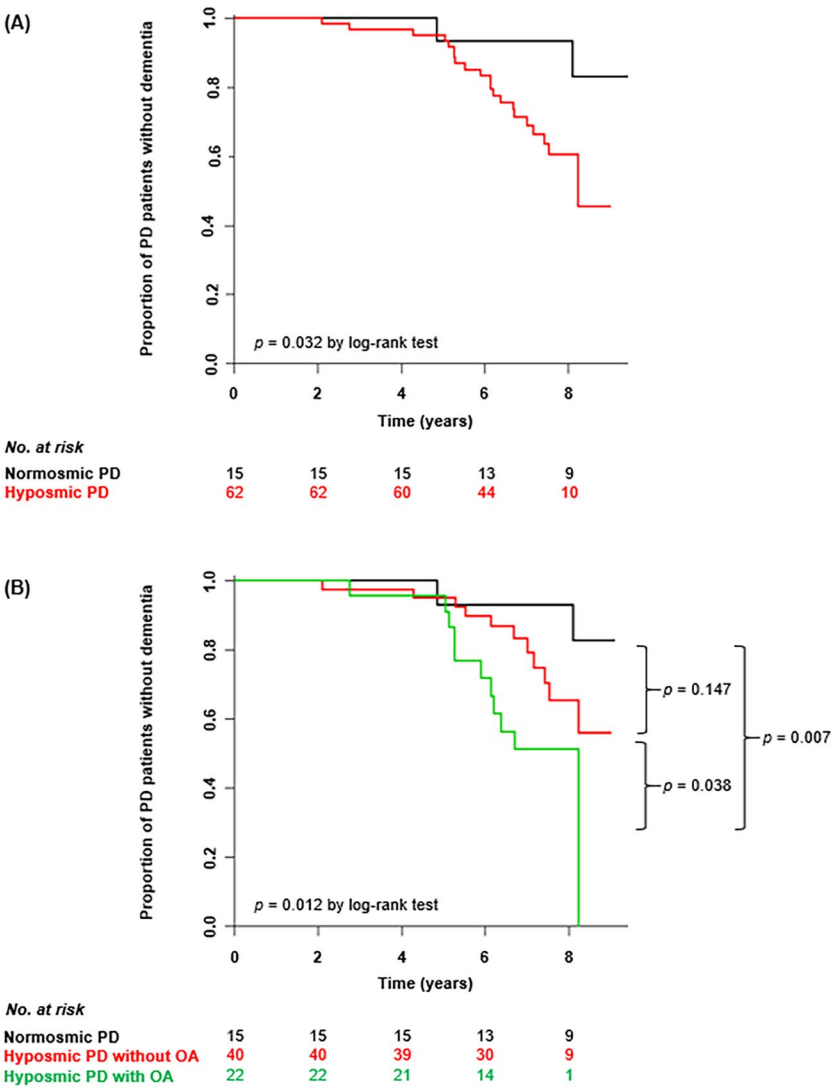

Fig. 2 Kaplan–Meier curves showing the cumulative probability of not developing dementia according to the duration of Parkinson's disease. **a** Comparison of the probability of being dementia-free between the normosmic and hyposmic PD groups. **b** Comparison of the probability of being dementia-free among the Normosmia, Hyposmia-OA−, and Hyposmia-OA+ groups

as AD or FTD [12], and most studies on anosognosia in dementia have focused on awareness of memory impairment [25]. In PD, impaired subjective awareness has been studied primarily in terms of parkinsonian motor symptoms. A substantial portion of non-demented patients with PD (30–50%) has impaired subjective awareness of their motor impairments [26, 27]. The presence of unawareness in non-motor symptoms including cognitive and psychiatric problems has been demonstrated in previous studies [28–30]. Olfactory dysfunction, one of the major non-motor symptoms that develops during the early stages, is not often recognized in patients with PD. The percentage of olfactory anosognosia ranged from 63 to 80% in non-demented PD, significantly higher than that in healthy individuals [2, 10]. Despite the significant frequency of olfactory anosognosia, its clinical significance has been considerably less well explored. One study reported the relationship between the loss of awareness of hyposmia and cognitive impairment in patients with PD by showing a higher proportion of olfactory anosognosia in PD patients with MCI than those with intact cognition [31]. In this study, we demonstrated that the Hyposmia-OA+ group had faster progression of cognitive decline and higher rate of conversion to dementia than did the Normosmia and Hyposmia-OA− groups, suggesting that olfactory anosognosia accompanied by olfactory deficits in the de novo state can be a predictor of cognitive decline and conversion to dementia in PD.

In terms of the neuroanatomical substrate, structural and functional imaging studies showed that multiple cortical substrates, especially cortical midline structures, spanning prefrontal, temporal, and parietal regions with lateralization to the right hemisphere, may be responsible for anosognosia [32, 33]. In patients with AD, anosognosia for cognitive impairment was related to reduced glucose metabolism in the posterior cingulate cortex, orbitofrontal cortex, and hippocampus, as well as a reduction in their

intrinsic connectivity [34–36]. Based on these neural correlates, Salmon et al. suggested a possible mechanism for anosognosia; the medial temporal region is required for the comparison between current information on cognition and personal knowledge, the orbitofrontal region for updating the qualitative judgement associated with cognitive abilities, and the temporoparietal region for self-referential process and perspective taking [36]. Meanwhile, there is a lack of studies investigating neural correlates of anosognosia in PD, particularly with respect to cognitive impairment or other non-motor symptoms. Previously, a significant association with left-side onset of PD and right frontal hypometabolism on fluorodeoxyglucose PET was found in patients with PD who were unaware of their motor impairments [27]. In the present study, we found that the hyposmic PD patients with olfactory anosognosia showed a faster deterioration of cognition, particularly frontal executive and visuospatial functions. However, progressive worsening of memory performance was not evident in PD patients with olfactory anosognosia, suggesting that frontal and right hemispheric dysfunction is closely linked to olfactory anosognosia, while memory deficits mainly due to dysfunction in medial temporal regions are crucial for memory anosognosia. Neuroimaging studies investigating the neural substrates underpinning olfactory or cognitive anosognosia are necessary to uncover this issue.

Considering anosognosia is linked to hypometabolism and cortical atrophy in extensive areas, it can be inferred that anosognosia would affect poor cognitive function and prognosis. Patients with AD with impaired awareness of cognitive decline had a nearly threefold increase in likelihood of conversion to dementia compared to those with intact awareness [14, 37]. Notably, we demonstrated that anosognosia for olfactory deficits affects baseline cognitive status as well as the longitudinal progression of cognition or development of dementia when comparing hyposmic PD patients with and without anosognosia. Along with hyposmia being related to cognitive decline in PD, the present data suggest that unawareness of hyposmia would have a greater influence on cognitive decline and dementia conversion than having awareness. As dementia in PD greatly affects quality of life, health-related costs, mortality, and the burden of caregivers [38, 39], it is important to detect patients with PD who have the potential to experience a faster decline in cognitive function earlier. The presence of both low scores on olfactory identification tests and impaired insight of olfactory dysfunction at baseline would alert clinicians to monitor the patients carefully and possibly warrant early intervention to modify cognitive worsening.

Anosognosia is a metacognitive knowledge which can encompass the denial of the presence of any symptoms [12]. In AD, studies have investigated the awareness of memory or global cognitive function, which revealed similar neural correlates [34, 36]. Anosognosia in PD could be accompanied by motor impairments as well as non-motor symptoms [26]. No studies have so far evaluated various kinds of anosognosia and their neural correlates in the same study participants simultaneously in PD. We could not determine from the current research whether the differences of cognitive changes were simply due to olfactory anosognosia or general anosognosia for PD. Further studies are necessary to investigate whether motor, olfactory, and cognitive anosognosia have different neural correlates or all kinds of anosognosia are associated with similar cognitive dysfunction.

This study had several limitations. First, this study was based on a relatively small sample, which limits the generalization of our result. However, we applied strict inclusion and exclusion criteria and have followed in detail the cognition of patients with PD for more than 5 years. Second, the CCSIT can only measure odor identification ability, although patients with PD show deficits in other olfactory tasks including olfactory detection threshold or discrimination [40]. Third, the cutoff value of nine for determining normosmia and hyposmia could be arbitrary and borderline, although it was defined according to the recommendation of the original study published by Doty et al. [17]. Future studies using larger samples are needed to define absolute cutoff values for CCSIT. Fourth, investigating imaging-based neural correlates for olfactory anosognosia is necessary to understand the pathophysiologic mechanism of olfactory anosognosia in PD. Lastly, various risk factors which can affect cognition may confound the independent relationship between olfactory anosognosia and cognitive decline. Although we confirmed that there were no differences of potential confounding parameters in baseline evaluation (Table 1) and adjusted important variables, considering covariance of other risk factors for cognitive dysfunction with larger ample size must be considered in future studies.

We demonstrated that olfactory anosognosia combined with olfactory dysfunction at baseline was associated with the progression of cognitive impairments, especially frontal lobe dysfunction, and it has implications for PDD development. Olfactory anosognosia can be a useful marker when assessing patients with PD at risk of the early development of dementia.

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Compliance with ethical standards

Conflicts of interest The authors declare no financial or other conflicts of interest.

Ethical standard This study was approved by the Institutional Review Board of the Yonsei University Severance Hospital. Written informed consent was obtained from all patients who participated in this study.

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