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Evaluation of olfactory impairment using a simple test kit “The Odor Stick Identification test for the Japanese ”(OSIT-J) in neurodegenerative diseases

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Purpose: Olfactory deficit has been studied in aging, amnestic mild cognitive impairment (aMCI), Alzheimer’s disease (AD). Parkinson's disease (PD), dementia with Lewy bodies (DLB) and idiopathic REM-sleep behavior disorder (iRBD). Our aim was to investigate the usefulness of a simple test kit “The Odor Stick Identification test for the Japanese ”(OSIT-J) in clinical practice.
Methods: A total of 240 patients were enrolled in this study, including 44 cognitively normal subjects (NS), 31 patients with aMCI, 70 patients with mild AD (AD-mild), 28 patients with DLB, 31 patients with PD and 36 patients with iRBD. The OSIT-J consists of 12 types of odor sticks. The subjects were asked to select an odor from a list of 4 odors that were rubbed on the medicine wraping paper for each odor stick. The maximum score was 12.
Results: The mean odor identification (OI) score decreased in the order of aMCI, iRBD, AD-mild, PD and DLB (NS: aMCI, $P<0.05$, NS: AD-mild, DLB, PD and iRBD, $P<0.001$, aMCI: DLB, $P<0.001$, aMCI: PD, $P<0.01$ (Kruskal-Wallis, Dunn’s test). The sensitivity and specificity in differentiating each disease from NS at a cutoff value of 8 was 96.8% and 79.5%, respectively, in PD, and 96.4% and 79.5% in DLB. An ageing effect was observed in NSs ($r=-0.453$ ($p<0.01$)).
Conclusions: Olfactory deficit is a non-specific phenomenon. However, it is important to be aware of the underlying diseases or future development of diseases. The OSIT-J, which is a simple test, is useful for detecting OI abnormalities in daily clinical practice.

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Key words: Odor identification, OSIT-J, Alzheimer’s disease, Dementia with Lewy bodies, amnestic mild cognitive impairment, REM sleep behavior disorder, Parkinson’s disease

Introduction

Neural responses to olfactory stimuli are transmitted from the nasal epithelium to the olfactory bulb and, thereafter, to the olfactory cortex and its main projections in the brain [1,2)]. The olfactory cortex includes the anterior olfactory nucleus, the olfactory tubercle, the piriform cortex, the amygdala and the entorhinal cortex, all of which receive direct, monosynaptic input from the olfactory bulb output neurons.

Olfactory deficit has been studied in aging, aMCI, AD. PD, DLB and iRBD [3-7)] . Odor identification (OI) appears to be the most sensitive method to measure olfactory dysfunction. OI deficit is a useful screening tool for AD-related amnestic disorder, with sensitivity and specificity comparable to other established biomarkers; its benefits include ease of administration and low cost. OI deficit can be utilized to stratify the risk of conversion from aMCI to AD [4)].

In this study, we assessed whether olfactory deficit can differentiate normal aging from an amnestic disorder (mild Alzheimer’s disease (AD-mild) and aMCI), DLB, PD and

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iRBD using a simple test kit "The Odor Stick Identification test for the Japanese "(OSIT-J) and investigated its utility in clinical practice.

Materials and methods

Materials

A total of 240 patients were enrolled in this study, including 44 cognitively normal subjects (NSs), 31 patients with aMCI, 70 patients with AD-mild, 28 patients with DLB, 31 patients with PD and 36 patients with iRBD. The demographic data are shown in Table 1. The age of the subjects in the AD-mild, DLB and PD groups was significantly older in comparison to the NSs ($p<0.001$, $p<0.01$, $p<0.05$, respectively (Kruskal-Wallis, Dunn's test)).

The clinical diagnosis of probable AD was made according to the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [8]. aMCI was diagnosed according to the criteria of Petersen et al. [9]. Probable DLB was diagnosed according to the criteria of McKeith et al.[10]. The clinical diagnosis of iRBD was made according to the criteria of Schenck CH, et al.[11]. The following subjects were excluded from the study: patients with AD who were associated with widespread leucoaraiosis, cerebral infarction, cerebral hemorrhage or subarachnoid hemorrhage; patients with non-amnestic MCI; patients with DLB who were associated with cerebral vascular diseases; patients with neurodegenerative diseases, such as multiple system atrophy, progressive supranuclear palsy and corticobasal syndrome; and patients with normal pressure hydrocephalus, severe diabetes mellitus and heart diseases. Patients with an MMSE scores of ≦19 were excluded because of inaccuracy in the OI.

Methods

The OSIT-J, developed in Daiichi Yakuhin Sangyo Co. Tokyo, Japan, was used in testing the olfactory function. The OSIT-J consists of 12 types of odor sticks. The subjects are asked to select an odor from a list of 4 odors that are rubbed on the medicine wraping paper for each odor stick. The maximum score is 12.

NSs were volunteers from the staff, healthy partners of the patients and subjects who visited the outpatients clinic and were judged to be cognitively normal based on various examinations that were performed for the diagnosis of dementia at the first visit to the outpatients clinic. All patients, with the exception of patients with PD, underwent a clinical evaluation that included a mini-mental state evaluation (MMSE) test [12], Hasegawa's Dementia Scale-Revised (HDS-R) [13], Japanese version of Montreal Cognitive Assessment (MoCA-J) [14], Wechsler memory scale-revised (WMS-R)[15], Clinical dementia rating (CDR) [16], brain MRI analysis using the voxel-based specific regional analysis system for Alzheimer's Disease (VSRAD) [17] and a quantitative assessment of brain SPECT images using the easy Z-score Imaging System (eZIS) [18] , and voxel-based stereotactic extraction estimation (vbSEE) [19]. In addition to the above examinations, ^{123}I-MIBG cardiac scintigraphy (cMIBG) was performed in DLB patients, and cMIBG and polysomnography were performed in iRBD patients. Patients with PD were recruited from the Parkinson's disease study group and half of them did not undergo neurol-opsycological examinations.

Table 1. Demographic data of enrolled subjects

Disease	Number of cases	Age mean ± SD	Sex M/F	MMSE score mean ± SD
NS	44	69.8 ± 8.2	13/31	29.5 ± 0.7
aMCI	31	75.2 ± 5.5	6/25	28.3 ± 1.2
AD-mild	70	76.2 ± 6.1	17/53	24.1 ± 2.3
DLB	28	77.3 ± 5.6	18/10	25.3 ± 2.8
PD	31	76.0 ± 6.5	20/11	27.1 ± 3.0*
iRBD	36	69.2 ± 8.4	21/15	28.7 ± 1.2

* N=15 (number of patients who MMSE was performed)

Statistical analyse

The IBM-SPSS v.24, (U.S.A) , SAS v9.3 (SAS Institute Inc, Japan) and StatMate v.5. (Atms, Tokyo, Japan) software programs were used for the data analyses. Descriptive data are reported as the mean and standard deviation (SD) or as the number and percentage. Differences between each disease were assessed with a one-way ANOVA, followed by the Tukey's test for pairwise comparison when an ANOVA showed a significant difference. In the ANOVA analysis, if the sample data was not normally distributed, the Kruskal-Wallis test followed by Dunn's test was used to compare multiple groups.

To estimate the predicative ability, the sensitivity and specificity of the different items were calculated.

Results

The number of correct answers for the OSIT-J test (OI) in each disease and 99% confidence intervals were listed in table 2. The mean OI score decreased in the order of aMCI, iRBD, AD-mild, PD and DLB (NS: aMCI, P<0.05, NS: AD-mild, DLB, PD and iRBD, P<0.001, aMCI: DLB, P<0.001, aMCI: PD, P<0.01 (Kruskal-Wallis, Dunn's test) (Fig.1). The MMSE scores decreased in the order of iRBD, aMCI, PD, DLB and AD-mild (Ns: aMCI and PD, P<0.05, Ns: AD-mild and DLB, P<0.001 (Kruskal-Wallis, Dunn's test). No correlation was found between the OI score and MMSE scores in aMCI, AD-mild and DLB patients (Pearson's correlation coefficients).

Determination of the cut-off value in OI using OSIT-J test

In the ROC analysis, the AUC value was highest in PD and decreased in the order of DLB, AD-mild, iRBD, and aMCI (Fig.2). The cut-off value of the OI was set at 8 based on the lower limit of the 99% confidence interval of NSs. The sensitivity, specificity, and efficacy at a cutoff value of 8, as well as the sensitivity and specificity at a cutoff values of 7 and 9, for differentiating each disease from NSs are listed in Table 3. At a cutoff value of 7, the sensitivity was extremely high in DLB and PD, and low in aMCI and AD-mild, while at a cutoff value of 9, the specificity was low in these diseases. Finally, we decided to use 8 as a cut-off value.

Table 2. Results of OSIT-J test and 99% confidence interval

Disease	No of correct answer (Mean)	Lower limit	Upper limit
NS	9.25	8.13	10.37
aMCI	6.42	5.09	7.75
AD-mild	5.10	4.22	5.98
DLB	2.89	1.49	4.29
PD	3.13	1.80	4.46
iRBD	5.31	4.07	6.54

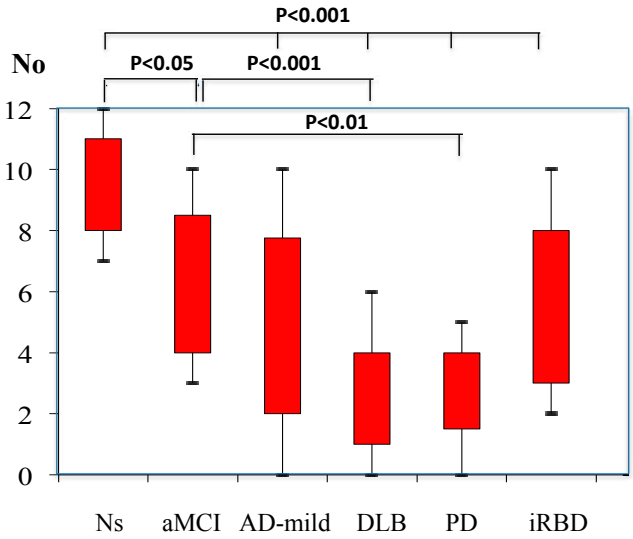

Fig.1. Odor identification scores in each disease.
The values in the box show 90%, 75%, 25%, and 10% from the top. The OI scores of patients with each disease were significantly lower than those of the NSs.

Aging effect of odor identification

The correlation between the OI score and the age in each disease was examined; the OI score in NS, PD and iRBD showed a significant decrease, r=-0.453 (p<0.01), r=-.0.452 (p<0.01), r=-0.565 (p<0.001), respectively (Pearson's correlation coefficient). Such a correlations were not observed in aMCA, AD-mild and DLB (Fig. 3). Considering the existence of aging effect, multiple regression analysis was performed for NSs and each disease, taking into account the effects of age, sex and MMSE score (Table 4). The OI scores in NSs were significantly higher in comparison to those with each disease. There were also significant differences between aMCI and DLB, between PD and iRBD, between AD-mild and DLB, and between AD-mild and PD. The results of regression analysis were similar to those of the Kruskal-Wallis analysis comparing the NS of the OI score and each disease, with the exception of the significant difference between aMCI and iRBD.

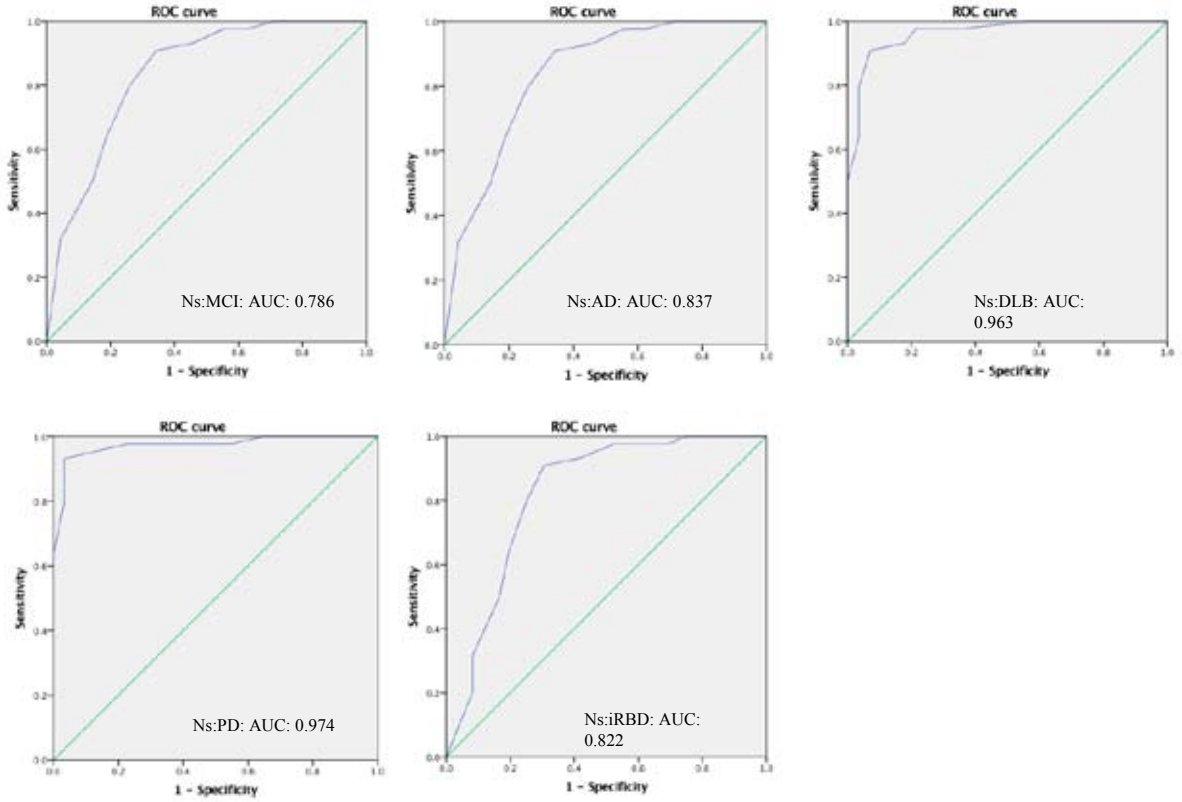

Fig.2. The ROC curve and AUC values in each disease in comparison to NSs.
The AUC value was highest in PD and decreased in the order of DLB, AD-mild, iRBD, and aMCI.

Table 3 Sensitivity, specificity and efficay for differentiating patients with each disease from NSs

Cut-off value		7	8	9
aMCI	sensitivity	51.6	64.5	74.2
	specificity	90.9	79.5	63.6
	efficacy	74.7	73.3	68.0
AD-mild	sensitivity	65.7	74.3	81.4
	specificity	90.9	79.5	63.6
	efficacy	75.4	76.3	74.6
DLB	sensitivity	92.9	96.4	96.4
	specificity	90.9	79.5	63.6
	efficacy	91.7	86.1	76.4
PD	sensitivity	96.8	96.8	100.0
	specificity	90.9	79.5	63.6
	efficacy	93.3	86.7	80.6
iRBD	sensitivity	69.4	75	80.6
	specificity	90.9	79.5	63.6
	efficacy	81.3	77.5	71.3

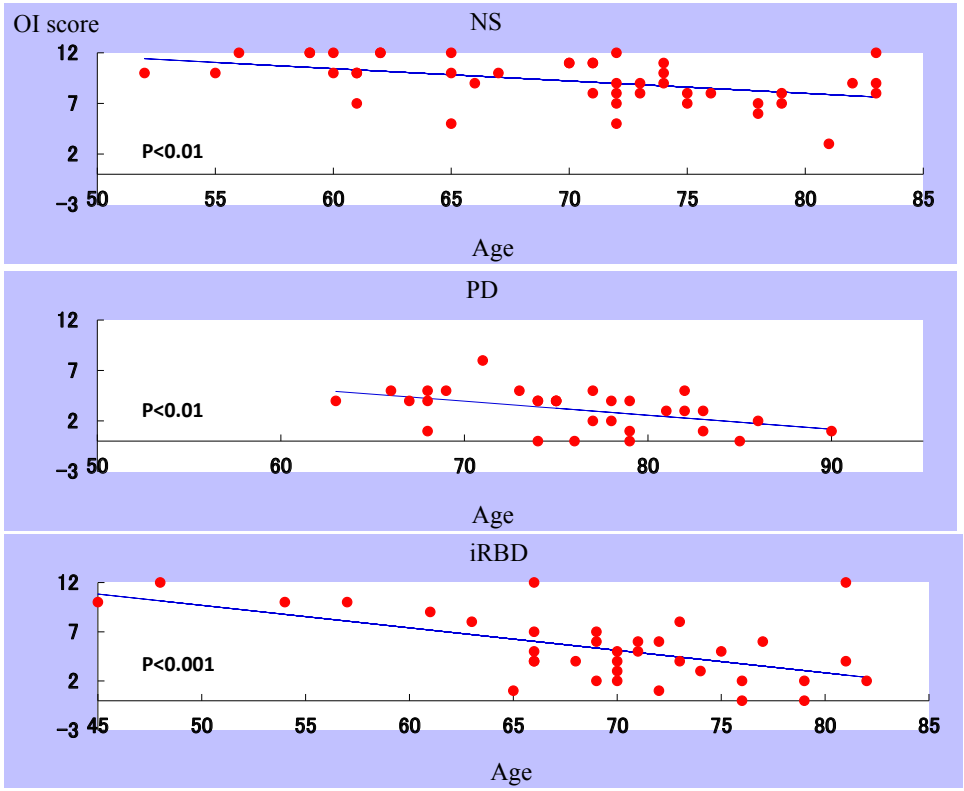

Fig.3. The correlation of the OI scores and age in NSs, patients with PD and patients with iRBD. The OI scores showed a decrease with age.

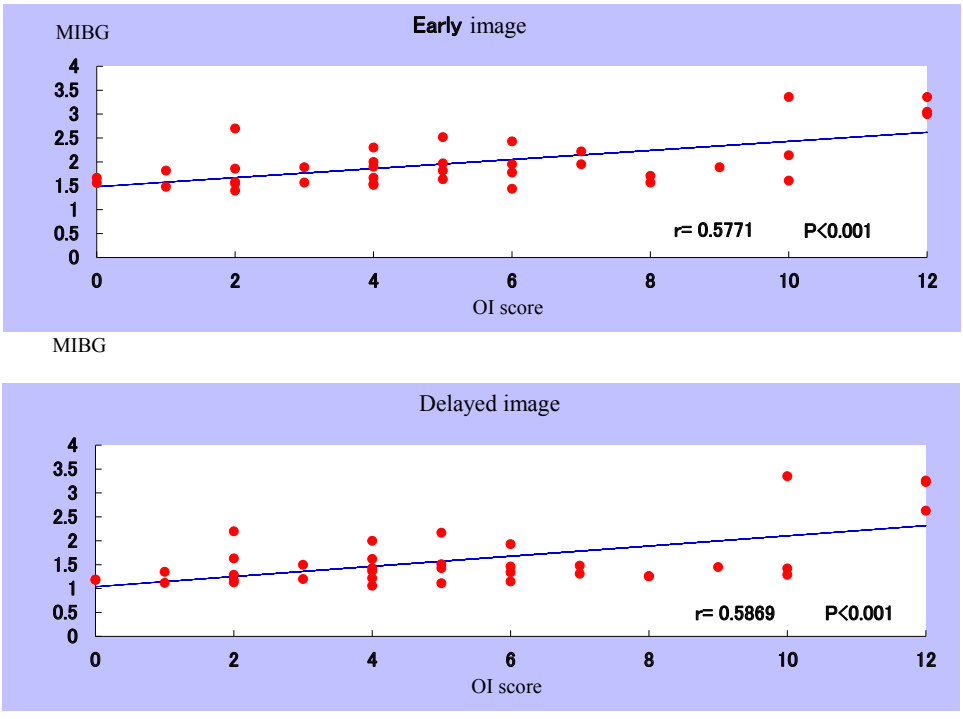

Fig.4. The correlation of OI scores and MIBG values (H/M ratios) in iRBD patients. Decreased OI scores in iRBD patients were significantly correlated with decreased MIBG values.

Table 4 Multiple regression analysis of OSIT-J score after adjustment for age, sex and MMSE scores

	NS	aMCI	AD-mild	DLB	PD	iRBD
NS		0	0	<0.0001	<0.0001	<0.0001
aMCI	0		0.66	0.01	0.02	0.04
AD-mild	0	0.66		0.01	0.04	0.14
DLB	<0.0001	0.01	0.01		0.9	0.5
PD	<0.0001	0.02	0.04	0.9		0.45
iRBD	<0.0001	0.04	0.14	0.5	0.45	

Correlation between the OI and cMIBG in iRBD and DLB patients

The OI score and cMIBG values of both the early image and delayed image in iRBD patients showed highly significant correlations (P<0.001, Pearson's correlation coefficient) (Fig. 4). In DLB patients, a significant correlation was only observed on the delayed image (P<0.05, Pearson's correlation coefficient) .

Risk of conversion from aMCI to AD

Twenty-one of 31 aMCI patients were followed for 2 to 4 years. Two out of eight aMCI patients with a cut-off value of ≧8 showed a ≧3 point decrease in MMSE score, while 6 out of 13 cases with a cut-off value of ≦7 showed a ≧3 point decrease in MMSE score. However, there was no statistically significant difference between them.

Risk of conversion from iRBD to DLB or PD

Three iRBD patients (female; age, 73 years; OI score, 8; MIBG value, decreased; female; age, 66 years; OI score, 12; MIBG values, normal; male; age 79 years; OI score, 0; MIBG values decreased in 3 years), non- with parkinsonism, were transferred to DLB. However, no iRBD patients were transferred to PD. Because of the small number of cases that converted from iRBD to DLB, further investigation is necessary to clarify the significance of OI in this matter.

Discussion

Olfactory disorders increase with age and often affect aged persons with predementia or dementia. Despite the frequent occurrence of olfactory changes at the early stages of neurodegenerative disorders, such as AD or PD, olfactory disorders are rarely assessed in daily clinical practice, mainly due to a lack of standardized assessment tools. To assess olfactory disorders objectively, clinicians should have access to sensitive, easy-to-use olfactory tests in their daily practice. Several tests have been developed for investigating different aspects of olfaction, ranging from odor sensitivity to odor identification. However, no 'gold standard' has been established and published studies have used assessment tools targeting different aspects of olfactory disorders and employing different odors (because odors are often culture- and country-specific), resulting in incomparable findings across studies and cultures. Different types of olfactory disorders have been reported, including quantitative disorders, which affect odor detection thresholds; and qualitative disorders, which affect odor identification.

The main objective of this study was to determine whether a simple odor test kit, OSIT-J, which targets an odor identification, is useful for the diagnosis of neurodegenerative diseases. The number of correct answer for the OSIT-J test (OI score) in each disease decreased in order of aMCI, iRBD, AD-mild, PD and DLB. The olfactory decline rate in NSs and in subjects with each disease when the cut-off value of the OSIT-J test was 8 was as follows: NS 20.5%, aMCI 64.5%, AD-mild 72.2%, DLB 96.4%, PD 96.8% and iRBD 75.0%.

The causes of olfactory decline are varied: the predominant cause in the general population is aging, with prevalence rates of around 24.5% in individual of 53 – 97 years of age, 5% in individual of 45 – 65 years of age, and 50 – 62.5% in individual of > 80 years of age [20-25]. The frequency of hyposmia in NSs in this study was 20.5% which is similar to previous reports and the aging effect was also consistent with the results of previous reports.

Olfactory deficit for AD and aMCI

Numerous papers on olfactory deficit in AD and aMCI have been reported [26-31] .

Woodward et al. reported that they studied the OI using the University of Pennsylvania Smell Identification Test [UPSIT], based on the 10-item subset with a cutoff of 7 (>7, smeller) and that this showed 88% sensitivity and 71% spec-

ificity in differentiating AD patients from normal subjects and 74% sensitivity and 71% specificity in differentiating patients with an amnestic disorder from normal subjects [26]. In this study, the sensitivity was lower for both AD and aMCI in comparison to their results, whereas the specificity was higher in comparison to their results. OI deficit has been reported to be a useful screening tool for AD-related amnestic disorder, and can be utilized to stratify the risk of conversion from aMCI to AD. A total of 36.4% of participants with impaired olfaction and 17.3% of participants with intact olfaction converted to AD [4]. In this study, 25% of aMCI patients who showed OI scores of ≧8 showed a ≧3 decrease in their MMSE score, while 46% of patients who showed an OI score of ≦ 7 showed a decreased ≧3 scores in their MMSE score. However, there was no significant difference between them.

Olfactory deficit for PD and DLB

Impairment of olfaction is a characteristic and early feature of Parkinson's disease. More than 95% of patients with Parkinson's disease present with significant olfactory loss. Deficits in the sense of smell may precede clinical motor symptoms by years and can be used to assess the risk of developing Parkinson's disease in otherwise asymptomatic individuals [32, 33]. DLB is an another harmful disease that is typically associated with an olfactor disorder [34-36].

The incidence of olfactory abnormalities in PD and DLB in this study was similar to that reported in previous studies.

Olfactory deficit in iRBD

In recent years, iRBD has been reported to be an extremely powerful predictor or prodromal marker of neurodegenerative synucleinopathies, including PD, DLB, and MSA, and the conversion rates from iRBD to full clinical synucleinopathies were reported to range from 17.7% to 90% , depending on the follow-up period [12,28-31, 33-38].

Olfactory dysfunction could also predict the conversion of patients with iRBD to mild Parkinsonism and Lewy body disease. Nevertheless, the exact causal relationship between olfactory dysfunction and iRBD needs to be assessed.

In the previous paper, we reported that a cardic MIBG scintigraphy study in iRBD patients showed a marked reduction in the uptake in many patients at the time of the examination, and that these iRBD patients may be a predictor of DLB, but not PD or other neurodegenerative diseases [39]. In the present study, the OI score and cMIBG of both early image and delayed imaging in iRBD patients showed highly significant correlations. These results indicate that the OI scores also serve as a predictor of DLB or PD, particularly of DLB.

Conclusion

The causes of olfactory decline are varied: the predominant cause in the general population is aging, followed by upper respiratory tract infections, head trauma, sinonasal diseases, neurodegenerative diseases, and it has recently attracted attention, as a symptom of COVID-19 infection [40]. In the present study, the regression analysis revealed that patients with PD and DLB showed significantly lower OI scores in comparison to those with aMCI, AD or iRBD. However, an abnormal OI score does not enable the diagnosis of these diseases.

When encountering a patient with an abnormal OI score, it is important to be aware of the possibility that a latent disease underlies the condition and that such diseases may develop in the future. The OSIT-J, a simple test, can be performed within 10 minutes and is useful for evaluating the presence or absence of OI abnormalities in daily clinical practice.

Ethics Statement

This study was carried out in accordance with the recommendations of the Ethics Committee of the Nagasaki Kita hospital.

Conflict of Interest Statement

All authors declare that this study was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

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