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ORIGINAL ARTICLE

Predicting future cognitive decline by olfactory testing: a longitudinal study in the Iwaki Health Promotion Project 2016–2017

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Abstract

Objective: The incidence of dementia is increasing in developed countries, and early detection and treatment are important. Considering that olfactory disorders are correlated with cognitive dysfunction, olfactory testing might be a useful screening tool for dementia. In the present study, we investigated whether a simple olfactory test could predict the short-term progression of cognitive decline using data from a longitudinal study of a community-dwelling population.

Subjects and Methods: Subjects were participants of the Iwaki Health Promotion Project, a community-based program aimed at improving average life expectancy. The subjects were examined using a 4-item modified Pocket Smell Test (mPST) and the Mini-Mental State Examination (MMSE) in 2016 and 2017. The relationship between the change in MMSE scores and olfactory identification ability in 2016 was analyzed in subjects with good MMSE scores in 2016.

Results: Among participants in their 60s and 70s, the olfactory-impaired group showed significantly lower MMSE scores in 2017 than those of the good-olfaction group.

Conclusion: Olfactory testing may be a tool for early detection of the onset of cognitive decline in elderly people.

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Key words: olfactory test; cognitive decline; MMSE.

Introduction

The increasing incidence of dementia in elderly people has become a global and unavoidable social problem. Because there is no effective treatment for progressive dementia, early detection and intervention are important. Olfactory dysfunction has been observed in various neurodegenerative diseases, particularly Alzheimer's disease (AD), Parkinson's disease (PD), and other similar disorders. Previous studies have revealed that olfactory disorders are correlated with dementia, and olfactory tests can be used as a screening tool[1-5]. These results suggest that otolaryngologists may also contribute to the early detection of dementia.

We previously reported that the results of a simple smell test, using three odorants from the Odor Stick Identification Test for the Japanese and from the 4-item modified Pocket Smell Test (mPST), were correlated with Mini-Mental State Examination (MMSE) scores, using data from

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the Iwaki Health Promotion Project in 2016[6,7]. The Iwaki Health Promotion Project is a community-based program aimed at improving the average life expectancy by conducting general health check-ups. Because check-ups are performed every year, longitudinal evaluation is also possible.

Wilson et al. reported that cognitive decline could be predicted using olfactory identification results, based on a 5-year longitudinal cohort study of community-dwelling persons around the age of 80 with normal cognitive function[1]. Although younger subjects are ideal for the early detection of dementia, few longitudinal studies targeting a wider range of ages have been conducted. In the present study, we investigated the relationship between the level of olfactory function based on mPST and cognitive function after one year among participants of the Iwaki Health Promotion Project aged 40 and above with normal cognitive function.

Subjects and Methods

Participants

We mailed an invitation to all residents aged 20 years and above, living in Iwaki, a district of Hirosaki City, to participate in the Iwaki Health Promotion Project in 2016. Out of approximately 9,400 residents, 1,148 participated. The relationship between cognitive function and impaired olfactory function was analyzed in 827 participants who joined the project again in 2017. Of the 827 participants, 34 were excluded due to lack of data, and 345 due to a history of malignant tumors, cardiovascular disease, intracranial disease, diabetes, or rhinosinus disease. Of the remaining 448, only those who were aged 40 and older were selected. Finally, 355 participants (141 men and 214 women) were enrolled for the analyses.

The data collection method was approved by the Ethics Committee of the Hirosaki University School of Medicine (2016–028, 2017–026), and all participants gave written informed consent.

Lifestyles and physical measurements

Lifestyle information regarding age, sex, years of education, present and past medical histories, and smoking and drinking habits was obtained through self-questionnaires and interviews.

Assessment of olfactory identification function

Olfactory identification ability was assessed using the 4-item mPST of the University of Pennsylvania Smell Identification Test series modified for the Japanese market (UPSIT series, Eisai; Tokyo, Japan), which was developed by Sensonics International (Haddon Heights, NJ)[8]. As described in detail by Yanagimachi et al.[6], the mPST consists of four “scratch and sniff” cards prepared with microencapsulated odor components (soap, grape, onion, and rose). When the examiner gently scratches the area where the smell is applied with a cotton swab, the smell evaporates. Participants sniff and select the corresponding odor among the four choices. The results of these tests are represented by the number of correct answers (0–4 points).

Assessment of cognitive impairment

All participants took the MMSE[9] (licensed by Psychological Assessment Resources, Inc), which is one of the most widely used screening instruments for dementia to measure cognitive function. The examination assesses the orientation of time and place, short-term memory, episodic long-term memory, subtraction, ability to construct a sentence, and oral language ability. The maximum MMSE score is 30, and mild cognitive impairment (MCI) is suspected at 27 points or less[10,11]. The MMSE was conducted by a trained examiner, taking sufficient time, both in 2016 and 2017. The change in scores was calculated by subtracting the score in 2016 from that in 2017.

Table 1. Characteristics of participants

	Men (n = 141)	Women (n = 214)	All (n = 355)
Age (years)	58.8 ± 10.9	59.7 ± 10.8	59.3 ± 10.8
40–49	32	45	77
50–59	41	56	97
60–69	46	75	121
70–79	17	32	49
80+	5	6	11
Education (years)	12.1 ± 1.9	12.1 ± 1.8	12.1 ± 1.8
Smoking (%)	56.0	22.0	35.5
Drinking (%)	74.5	29.4	47.3

Values are expressed as mean ± standard deviation
MMSE, Mini-Mental State Examination

Statistical analysis

Receiver operating characteristic (ROC) analysis was performed to calculate mPST scores in order to predict a decrease in MMSE scores in 2017. Based on the ROC analysis, subjects were divided into two groups based on olfactory identification ability: those with good olfaction and those with impaired olfaction. The relationship between the change in MMSE score and olfactory function was analyzed by age group in a population with good MMSE scores of 28 and above in 2016.

MMSE scores and mPST scores were analyzed by age group using Kruskal-Wallis test and Steel-Dwass test, and the change in MMSE scores was analyzed using the Mann-Whitney U test. SPSS 22.0J software (IBM, Armonk, NY) and BellCurve for Excel ver. 3.20 (Social Survey Research Information Co., Ltd., Tokyo) were used for data analysis, and $p < 0.05$ was considered statistically significant.

Results

Characteristics of participants

There were no significant differences in age or educational history between men and women, although smoking and drinking habits were significantly higher in men (Table 1). In addition, since the number of people aged 80 and over was too small, they were excluded from further statistical analysis.

MMSE and mPST scores by age group

As a result of the Kruskal-Warris test, mPST scores were significantly different between the age groups ($p < 0.001$). Identically, MMSE scores were significantly different between the age groups ($p < 0.001$). Furthermore, no significant difference in mPST scores was found between subjects in their 40s and 50s by multiple comparison test. However, the mPST scores of subjects in their 60s and 70s were significantly lower than those in their 40s and 50s (Fig. 1A). Similarly, no significant difference was found in MMSE scores between subjects in their 40s and 50s. However, MMSE scores of subjects in their 60s and 70s were significantly lower than those in their 40s. (Fig. 1B)

A total of 329 participants (128 men and 201 women) who scored 28 or more on the MMSE in 2016 were analyzed (Table 2). The mPST scores were significantly different between men and women ($p = 0.034$), but no significant difference was found between the initial MMSE scores and the change in MMSE scores. Therefore, gender differences were not taken into consideration in further analyses.

ROC curve and mPST cut-off

Figure 2 shows the ROC curve predicting the decrease in MMSE scores after one year. The

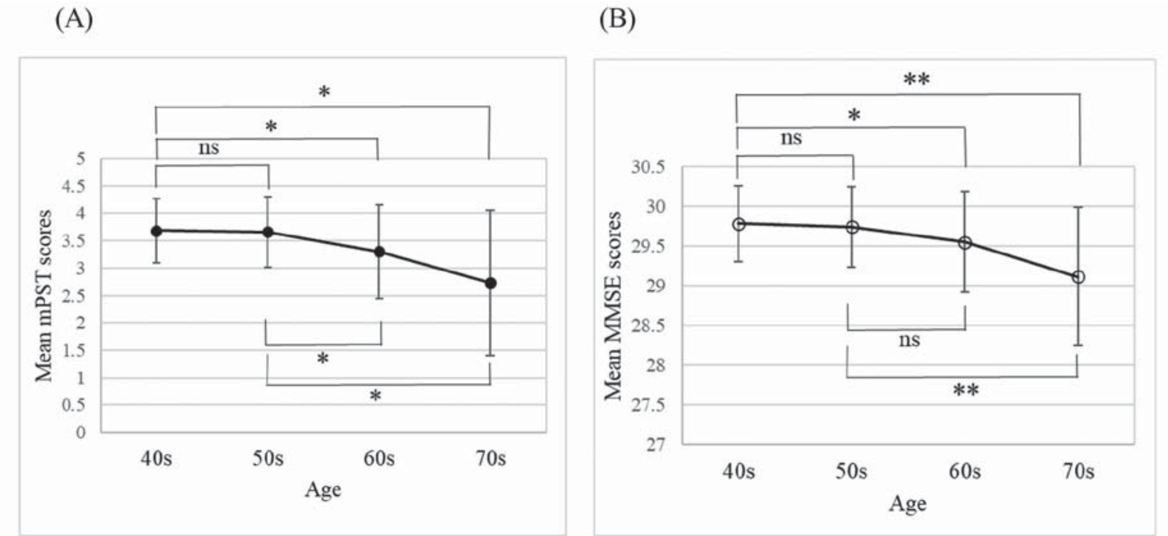

Figure 1 (A) Association between olfaction test scores and age, (B) association between MMSE scores and age. (A) The mean mPST scores of subjects in their 40s, 50s, 60s, and 70s were 3.7 ± 0.6, 3.7 ± 0.6, 3.3 ± 0.9, and 2.7 ± 1.3 (mean ± SD) points, respectively. (B) MMSE scores are 29.8 ± 0.5, 29.7 ± 0.5, 29.5 ± 0.6, and 29.1 ± 0.9 (mean ± SD), respectively. * and ** denote significant ($p < 0.05$ and $p < 0.01$, respectively). MMSE, Mini-Mental State Examination; mPST, modified Pocket Smell Test; SD, standard deviation.

Table 2. Characteristics of subjects

	MMSE ≦ 27	MMSE ≧ 28
Age (years)	64.9 ± 8.5	58.2 ± 10.0
40–49	1	76
50–59	2	95
60–69	8	113
70–79	4	45
Total number (male : female)	15 (7 : 8)	329 (128 : 201)

Values are expressed as mean ± standard deviation

area under the curve (AUC) was 0.578. The mPST score cut-off value that had the best combination of sensitivity (67.6%) and specificity (47.2%) in predicting a decrease in the MMSE scores was set at 3.5 points. Therefore, we assumed that a score of 4 points signified good olfaction, whereas a score of 3 points or less meant impaired olfaction.

Comparison of the change in MMSE scores between subjects with good olfaction and impaired olfaction by age

The change in MMSE scores was analyzed in two age groups: 40–59 years and 60–79 years. No significant change in MMSE scores was found between the good olfaction (mPST =4, n = 127) and impaired olfaction (mPST ≤ 3, n = 44) groups in subjects in their 40s and 50s (Fig. 3A). On the other hand, the change in MMSE scores of elderly subjects in the impaired olfaction group (mPST ≤ 3, n = 80) was significantly larger than that of elderly subjects in the good olfaction group (mPST =4, n = 78) (Fig. 3B).

Discussion

Odor information from the olfactory bulb is transmitted via the olfactory tract to the primary olfactory cortical areas and to secondary olfactory regions, such as the hippocampus and

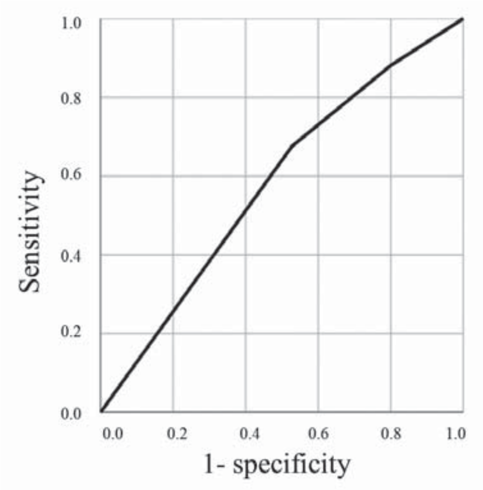

Figure 2 ROC curve predicting a decrease in MMSE scores in the next year. AUC was 0.578. ROC, receiver operating characteristic; MMSE, Mini-Mental State Examination; AUC, area under the curve.

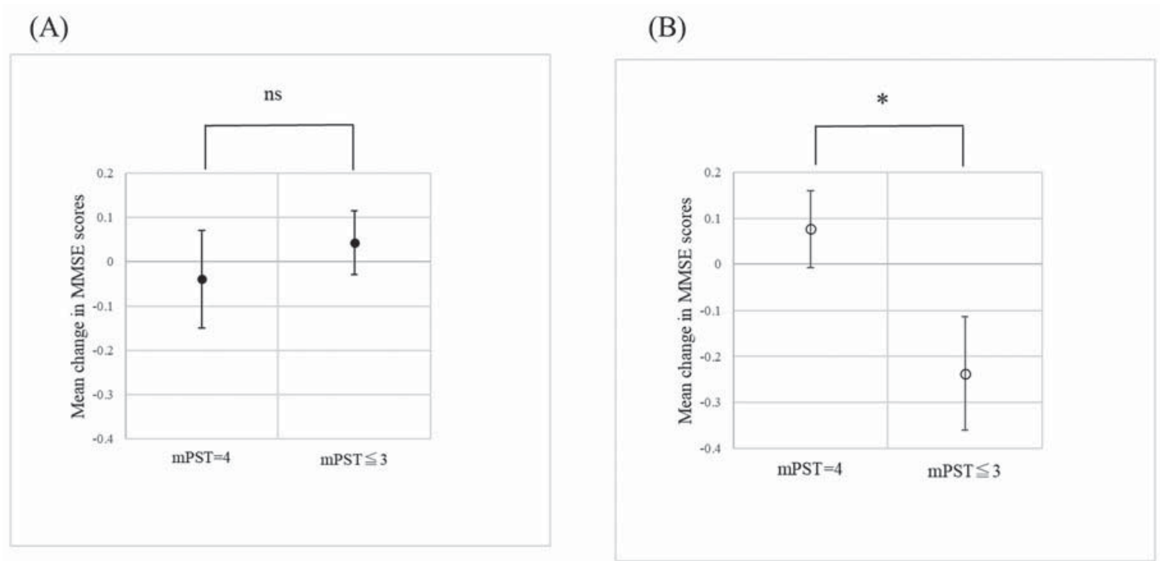

Figure 3 Comparison of the change in MMSE scores between the good olfaction group and impaired olfaction group in subjects aged (A) 40–59 years and (B) 60–79 years.

(A) The mean MMSE scores of in the good and impaired olfaction groups of middle age are −0.04 ± 0.11 and 0.04 ± 0.07 (mean ± SE) respectively. (B) The mean MMSE scores of in the good and impaired olfaction groups of elderly age are 0.08 ± 0.08, −0.24 ± 0.12, respectively. *denote significant ($p < 0.05$). Mann–Whitney U test; MMSE, Mini-Mental State Examination; mPST, modified Pocket Smell Test; SE, standard error.

orbitofrontal cortex[12], which are involved in memory and cognitive functions. Therefore, patients with cognitive decline may develop olfactory and memory impairments simultaneously due to these interrelated anatomical functions[1, 13]. Previous reports have revealed that olfactory tests can be a preclinical diagnostic marker for AD and PD. Olfactory dysfunction progresses earlier in patients with PD than in healthy subjects[2, 3, 14]. In AD, damage to the entorhinal cortex occurs during MCI, before the onset of dementia, which suggests that cognitive decline and olfactory impairment are closely associated[15]. In a prospective study of elderly people without cognitive impairment, Wilson et al. reported that people with low odor identification scores developed MCI after 5 years, a 50% higher risk compared with people with high odor identification scores[1]. These findings imply that olfactory tests may be useful for predicting cognitive decline in the future.

We previously reported the relationship between cognitive function and the results of a simple smell identification test using three odorants from the Odor Stick Identification Test for Japanese (OSIT-J) and found that the 4-item mPST may be useful for rapid screening of cognitive decline[6, 7]. Although both studies showed that a simple smell identification test might be useful for the early detection of dementia, they are cross-sectional studies lacking chronological observation. We expected to derive more conclusive results from the present longitudinal investigation. The results in 2016 from the Iwaki Health Promotion Project showed that mPST and MMSE scores declined significantly with age (Fig. 1), which is consistent with our previous reports.

In the present study, subjects with MMSE scores in 2016 of 27 or less were excluded because it was intended to screen for earlier cognitive decline. Subjects with MMSE scores of 28 and above were included in the statistical analysis as the normal cognitive function group. Participants in their 60s and 70s with olfactory impairment were found to have reduced MMSE scores in the following year compared with those with good olfaction, although no significant correlation was found between olfactory function and the change in MMSE scores among participants in their 40s and 50s. Therefore, olfactory testing may be more beneficial for the early detection of dementia in elderly people. Previous studies have revealed that the estimated number of patients with AD has increased exponentially over time[10]; namely, cognitive decline progresses rapidly in subjects over 60 years of age. It seems reasonable that a significant change in MMSE scores was observed only in subjects in their 60s and 70s in our study.

In conventional MCI screening, questionnaires like the Montreal Cognitive Assessment (MoCA) and MMSE, observation methods, and blood tests are used. However, these evaluation methods have diagnostic value only after the onset of MCI. Moreover, amyloid β deposition and cerebral atrophy have been observed by imaging studies, even in patients with MMSE scores above the cut-off value[8, 9]. Other reports revealed that subjects with severe olfactory disorders showed decreased metabolism in the brain, particularly in the frontal and occipital lobes[16]. Thus, incorporating olfactory tests into dementia screening might be useful for the earlier detection of cognitive decline. Moreover, compared with fluorodeoxyglucose-positron emission tomography (FDG-PET), amyloid PET, cerebrospinal fluid testing, and magnetic resonance imaging, olfactory tests are less invasive, more cost-effective, and less time-consuming, which makes them a simple and practical option as a screening test for cognitive decline.

In the present analysis, we determined that the cut-off point was 3.5 points from the ROC curve created by the mPST score and the degree of change in MMSE scores. Thus, particip ants with an mPST score of 3 or less were classified as having olfactory impairment. Consequently, as many as 80 out of 168 participants aged 60–79 years were assessed as olfactorily impaired. Further investigation is needed to determine whether the number of odorants used for the mPST is appropriate or if other odorants should be included for efficient cognitive function screening.

This study has several limitations. We used only MMSE scores for the cognitive function assessment. In addition, all participants in this study were volunteers who were interested in their health status and may be healthier than other community members who did not participate in the study. These selection biases should be considered when targeting the general population. Finally, since this study surveyed only a short period of one year, it is necessary to set a longer study period for further research.

Conclusion

We conducted a longitudinal study to determine whether a simple olfactory test could predict the progression of cognitive decline. As a result, we found olfactory testing may provide clues for the early detection of cognitive decline in an elderly population.

Disclosure Statement

The authors declare no conflicts of interest associated with this manuscript.

Acknowledgments

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References

1) Wilson RS, Schneider JA, Arnold SE, Tang Y, Boyle PA, Bennett DA. Olfactory identification and incidence of mild cognitive impairment in older age. Arch Gen Psychiatry. 2007;64:802-8.

2) Doty RL, Bromley SM, Stern MB. Olfactory testing as an aid in the diagnosis of Parkinson's disease: development of optimal discrimination criteria. Neurodegeneration. 1995;4:93-7.

3) Baba T, Kikuchi A, Hirayama K, Nishio Y, Hosokai Y, Kanno S, Hasegawa T, et al. Severe olfactory dysfunction is a prodromal symptom of dementia associated with Parkinson's disease: a 3 year longitudinal study. Brain. 2012;135:161-9.

4) Devanand DP, Lee S, Manly J, Andrews H, Schupf N, Doty RL, Stern Y, et al. Olfactory deficits predict cognitive decline and Alzheimer dementia in an urban community. Neurology. 2015;84:182-9.

5) Umeda-Kameyama Y, Ishii S, Kameyama M, Kondo K, Ochi A, Yamasoba T, Ogawa S, et al. Heterogeneity of odorant identification impairment in patients with Alzheimer's disease. Sci Rep. 2017:7:4798.

6) Yanagimachi M, Takahashi I, Bernier F, Takahashi K, Kurauchi S, Mikuniya Y, Sasaki A, et al. Olfactory function evaluation in a 1102 community-dwelling 20-90-year old Japanese population in relation with age, sex and mental decline. Alzheimers Dement Cogn Neurol. 2017; 1(3). (https://www.oatext.com/olfactory-function-evaluation-in-a-1102-community-dwelling-20-90-year-old-japanese-population-in-relation-with-age-sex-and-mental-decline.php DOI: 10.15761/ADCN.1000117)

7) Mikuniya Y, Goto S, Sasaki A, Kudo R, Sawada K, Nakaji S, Matsubara A. Simple smell identification test using three odorants to detect cognitive decline: investigation in community-dwelling volunteers. Hirosaki Med J. 2019;69:172-8.

8) Dalton P, Doty RL, Murphy C, Frank R, Hoffman HJ, Maute C, Kallen MA, et al. Olfactory assessment using the NIH Toolbox. Neurology. 2013;80(Supple. 3): S32-6.

9) Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-98.

10) Saxton J, Morrow L, Eschman A, Archer G, Luther J, Zuccolotto A. Computer assessment of mild cognitive impairment. Postgrad Med. 2009; 121:177-85.

11) Sugishita M, Koshizuka Y, Sudou S, Sugishita K, Hemmi I, Karasawa H, Ihara A, et al. The validity and reliability of the Japanese version of the Mini-Mental State Examination (MMSE-J) with the original procedure of the attention and calculation task (2001). Japanese J Cogn Neurosci. 2018;20:91-110. (in Japanese)

12) Biella G, de Curtis M. Olfactory inputs activate the medial entorhinal cortex via the hippocampus. J Neurophysiol. 2000;83:1924-31.

13) Ottaviano G, Frasson G, Nardello E, Martini A. Olfaction deterioration in cognitive disorders in the elderly. Aging Clin Exp Res. 2016;28:37-45.

14) Iijima M, Kobayakawa T, Saito S, Osawa M, Tsutsumi Y, Hashimoto S, Iwata M. Smell identification in Japanese Parkinson's disease patients: using the odor stick identification test for Japanese subjects. Intern Med. 2008;47:1887-92.

15) Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991;82:239-59.

16) Ikejima C, Hisanaga A, Meguro K, Yamada T, Ouma S, Kawamuro Y, Hyouki K, et al. Multicentre population-based dementia prevalence survey in Japan: a preliminary report. Psychogeriatrics. 2012;12:120-3.