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Olfactory Dysfunction and High Blood Pressure Serve as Early Markers of Cognitive Decline in Older Adults

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Abstract

Introduction: Olfactory dysfunction is recognized as an early sign of dementia. Hypertension is a risk factor for dementia in midlife, but it is less clear in old age.

Materials and methods: Fifty-two consecutive volunteers aged ≥ 60 years (mean age, 71.0 ± 4.8 years) were enrolled in this study. We performed the Odor Stick Identification Test for the Japan (OSIT-J) as the olfactory test. Cognitive function was evaluated with the Revised Hasegawa's Dementia Scale (HDS-R), Mini-Mental State Examination (MMSE), Trail Making Test B (TMT-B), and Touch Panel-type Dementia Assessment Scale (TDAS). The systolic blood pressure (SBP), diastolic BP (DBP), and heart rate (HR) were measured using plethysmography.

Results: The TMT-B score was significantly correlated with the HR and OSIT-J score (HR: $r = 0.306$, $p = 0.028$; OSIT-J score: $r = 0.279$, $p = 0.045$), and HR and OSIT-J score were the significant factors of TMT-B score (HR: $\beta = 0.295$, $p = 0.033$; OSIT-J score: $\beta = 0.281$, $p = 0.039$). The TDAS score was significantly correlated with SBP and DBP (SBP: $r = 0.293$, $p = 0.035$; DBP: $r = 0.302$, $p = 0.029$). The SBP and DBP were higher in participants with TDAS scores ≥ 7 than those with TDAS scores < 7 (SBP: 155.6 ± 23.1 mmHg vs. 140.3 ± 16.1 mmHg, $p = 0.017$; DBP: 90.8 ± 10.3 mmHg vs. 80.9 ± 9.9 mmHg, $p = 0.006$).

Conclusions: Decreased olfactory function, high BP, and increased HR were all associated with cognitive decline in older adults.

Keywords: Olfactory function; Heart rate; Blood pressure; Hypertension; Cognitive decline

1. Introduction

Decreased olfactory function is very common among the older individuals [1]. Olfactory impairment, which is recognized as an early sign of dementia [2], is one of the initial symptoms of several neurodegenerative diseases and often occurs many years before the onset of motor symptoms and cognitive decline [3]. Symptoms of Alzheimer's disease (AD) are preceded by memory deficits secondary to hippocampal atrophy; however, it has been shown that olfactory nerve cells are also affected in these patients [4, 5]. A meta-analysis performed to assess olfactory perception and AD symptoms reported that odor identification, recognition, and detection thresholds can predict AD symptoms [6]. Olfactory impairment appears before the onset of motor symptoms and early in the onset of symptoms in Parkinson's disease, [7-9]. Therefore, olfactory dysfunction would prove useful in the early detection of various neurodegenerative disease, and it is essential to develop tests for accurate evaluation of olfactory function.

The Revised Hasegawa's Dementia Scale (HDS-R) [10] or Mini-Mental State Examination (MMSE) [11] is a common screening test for dementia. The Trail Making Test B (TMT-B) [12] is used to evaluate executive function. Executive function comprises high-level cognitive processes that facilitate an individual's behavior to optimize the approach to unfamiliar circumstances [13]. The Touch Panel-type Dementia Assessment Scale (TDAS) is a modified version of the Alzheimer's Disease Assessment Scale (ADAS)-Cognitive Subscale; subjects administered this test are provided instructions to enter their answers directly into a touch panel-type computer [14]. The association between olfactory function and these cognitive tests in the general population remains unclear.

Hypertension and dementia are common conditions observed in the general population [15]. Visit-to-visit in systolic blood pressure (SBP) variability and the maximum SBP are strong predictors of stroke, independent of the mean SBP [16]. Measurement of the heart rate (HR) is a noninvasive method to evaluate autonomic dysfunction and is shown to be associated with the risk of cardiovascular events and all-cause mortality [17]. A growing body of evidence from clinical trials and epidemiological studies has identified elevated resting HR as a predictor of clinical events [18]. Therefore, measurement of the SBP and HR may provide useful information to prevent cognitive decline.

In this study, we investigated the association between cognitive abilities and olfactory function, SBP, diastolic BP (DBP), and HR in older adults.

2. Materials and Methods

2.1 Participants

Fifty-two consecutive volunteers aged ≥ 60 years (28 males, 24 females; mean age, 71.0 ± 4.8 years) were enrolled in this study. We used a questionnaire to collect data on age, body mass index, smoking status, alcohol intake; history of hypertension, diabetes mellitus, and hyperlipidemia; and current medications; Epworth Sleepiness Scale (ESS) [19]; Pittsburgh Sleep Quality Index (PSQI) [20]; and Beck Depression Inventory Second edition (BDI-II) [21]. An active smoker was defined as any participant who was either currently smoking or had quit it within the last

4 years [22]. Alcohol intake referred to regular intake of alcoholic drinks [23]. SBP, DBP, and HR were measured using plethysmography (BP-203RPEIII, OMRON COLIN Co., Ltd., Tokyo, Japan). Those with ≥ 140 mmHg SBP or ≥ 90 mmHg DBP, or those receiving antihypertensive therapy were considered to have hypertension [24]. Diabetes mellitus and hyperlipidemia were defined by the use of oral hypoglycemic and lipid-lowering agents, respectively. The participants had no history of myocardial infarction; angina pectoris; heart failure; cerebral infarction; cerebral hemorrhage; chronic obstructive pulmonary disease; sinusitis; or use of antidepressants, benzodiazepines, and sleep medications. This study was approved by the ethics committee of Chubu University (Number 270098). After explaining the nature of the study and procedures involved, we obtained written informed consent from all participants.

2.2 Odor Stick Identification Test for the Japan (OSIT-J)

We performed the OSIT-J (Daiichi Yakuhin Sangyo Co., Ltd., Tokyo, Japan) as the olfactory test [25]. The experimenter applied an odorous semisolid cream from an odor stick to a 2 cm circle on a thin paraffin paper, folded the paper in half, rubbed it to grind the microcapsules and passed it to the participant. The participant then opened and sniffed the paper and chose one of the six possible answers: four odors, detectable but not recognized' and 'no smell detected'. This test included 12 odors that were familiar to Japanese people (Indian ink, wood, perfume, menthol, Japanese orange, curry, cooking gas, rose, Japanese cypress, sweaty smelling clothes/fermented soybeans, condensed milk, and roasted garlic). A score of 12 and 0 points indicated that the participant's answers were all correct, and incorrect respectively.

2.3 Cognitive function tests

2.3.1 HDS-R: The HDS-R is commonly used as a screening test for dementia. It consists of nine simple questions, with the maximum score of 30 points. The participants were asked to state the age, date, and location; repeat three words, and perform a serial subtraction of seven starting at 100. Then they were asked to recall digits backwards, three words, and five objects, and state the names of vegetables [10].

2.3.2 MMSE: The MMSE was a widely used brief screening test for dementia and a measure of global cognitive function. It is a measure of general cognitive function that measures orientation to time and place, attention and calculation, language and memory [11]. It comprises 11 questions, and the score ranges from 0 to 30, with lower scores indicating worse global cognitive ability.

2.3.3 TMT-B: The TMT provides information on visual search, scanning, speed of processing, mental flexibility, and executive function [12]. In the TMT-B, participants drew lines to connect numbers and letters in alternating patterns by connecting the first number with the first letter, continuing to connect the number-letter pairs until the last number of 13 was reached. Participants were required to perform these procedures sequentially as quickly as possible. Time to completion (score, in seconds) was recorded.

2.3.4 TDAS: The TDAS (NIHON KODEN, Co., Ltd., Tokyo, Japan) was developed by modifying the ADAS-Cognitive Subscale [14]. The following nine test items were included: word recognition, following a command,

visual-spatial perception, accuracy of the order of a process, naming fingers, orientation, money calculation, object recognition, and clock time recognition (non-digital). A total score of zero was defined as perfect. Incorrect answers were scored higher and when all answers were incorrect, the score was 101.

2.4 Statistical analyses

All data are expressed as mean ± standard deviation. Pearson's correlation analyses were performed to evaluate the relationships between cognitive function and OSIT-J score, SBP, DBP, and HR. Additionally, multiple regression analyses were performed to determine the independent parameters that correlated with cognitive function (as assessed by the HDS-R, MMSE, TMT-B, and TDAS), in relation to age, SBP, DBP, HR, and OSIT-J score. We compared the data on SBP, DBP, HR, smoking status, alcohol intake, hypertension, diabetes mellitus, hyperlipidemia, ESS, PSQI, BDI-II, and cognitive performance parameters between the groups (participants with TDAS score < 7 (normal group) vs. those with TDAS score ≥ 7 [mild cognitive impairment (MCI) group]) [26] using the chi-square test or non-paired *t*-test. A probability value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics Version 25.0 (IBM Corporation, Armonk, New York, USA).

3. Results

3.1 Subject characteristics, olfactory function, and cognitive function

Table 1 summarizes participants' characteristics, OSIT-J score and cognitive function from the HDS-R, MMSE, TMT-B and TDAS. Ten participants (19.2%) had a TDAS score of seven points or more. There were seven participants (13.5%) with a BDI-II score of 14 points or more.

Subject characteristics	
Age (years)	71.0 ± 4.8
Height (cm)	160.0 ± 7.9
Weight (kg)	57.0 ± 9.3
BMI (kg/m^2)	22.2 ± 2.7
SBP (mmHg)	143.2 ± 18.5
DBP (mmHg)	82.8 ± 10.6
HR (bpm)	70.2 ± 11.2
Smoking (%)	17.3
Alcohol intake (%)	40.4
Hypertension (%)	67.3
Diabetes mellitus (%)	5.8
Hyperlipidemia (%)	26.9
ESS	5.1 ± 2.9
PSQI	5.6 ± 3.0
BDI-II Score	6.2 ± 5.4

Olfactory function	
OSIT-J score	8.5 ± 2.5
Cognitive function tests	
HDS-R	28.4 ± 1.6
MMSE Score	29.0 ± 1.4
TMT-B Score (s)	111.8 ± 40.8
TDAS	3.3 ± 3.1

Data are expressed as mean ± standard deviation.

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, ESS = Epworth Sleepiness Scale, PSQI = Pittsburgh Sleep Quality Index, BDI-II = Beck Depression Inventory Second edition, OSIT-J = Odor Stick Identification Test for the Japan, HDS-R = Revised Hasegawa's Dementia Scale, MMSE = Mini-Mental State Examination, TMT-B = Trail Making Test B, TDAS = Touch Panel-type Dementia Assessment Scale.

Table 1: Subject characteristics, olfactory function, and cognitive function.

3.2 Relationships among cognitive function, SBP, DBP, HR, and OSIT-J score

The TMT-B score was significantly correlated with the HR and OSIT-J score (HR: $r = 0.306$, $p = 0.028$; OSIT-J score: $r = 0.279$, $p = 0.045$), and HR and OSIT-J score were the significant factors of TMT-B score (HR: $\beta = 0.295$, $p = 0.033$; OSIT-J score: $\beta = 0.281$, $p = 0.039$). The TDAS score was significantly correlated with SBP and DBP (SBP: $r = 0.293$, $p = 0.035$; DBP: $r = 0.302$, $p = 0.029$) (Table 2).

	Simple correlation analysis		**Multiple regression analysis**		**Simple correlation analysis**		**Multiple regression analysis**	
Factor	***r***	***p***	***β***	***p***	***r***	***p***	***β***	***p***
	HDS-R				**MMSE**			
Age	-0.088	0.533	-0.058	0.708	-0.014	0.919	0.094	0.520
SBP	-0.079	0.577	-0.145	0.477	-0.130	0.358	-0.373	0.058
DBP	0.043	0.763	0.127	0.536	0.084	0.556	0.393	0.048
HR	0.079	0.575	0.052	0.734	-0.109	0.443	-0.210	0.153
OSIT-J score	0.045	0.751	0.028	0.854	0.131	0.355	0.154	0.288
	TMT-B				**TDAS**			
Age	0.261	0.061	0.224	0.102	0.220	0.117	0.232	0.106
SBP	0.078	0.584	0.213	0.237	0.293	0.035	0.126	0.501
DBP	-0.030	0.834	-0.135	0.454	0.302	0.029	0.251	0.188
HR	0.306	0.028	0.295	0.033	0.124	0.379	0.071	0.614
OSIT-J score	0.279	0.045	0.281	0.039	0.011	0.939	0.092	0.511

HDS-R = Revised Hasegawa's Dementia Scale, MMSE = Mini-Mental State Examination, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, OSIT-J = Odor Stick Identification Test for the Japan, TMT-B = Trail Making Test B, TDAS = Touch Panel-type Dementia Assessment Scale.

Table 2: Relationships among cognitive function and SBP, DBP, HR, and olfactory function.

3.3 Subject characteristics and cognitive function based on TDAS score

The SBP and DBP were higher in MCI group than normal group (SBP: 155.6 ± 23.1 mmHg vs. 140.3 ± 16.1 mmHg, $p = 0.017$; DBP: 90.8 ± 10.3 mmHg vs. 80.9 ± 9.9 mmHg, $p = 0.006$). The prevalence of hypertension was higher in MCI group than normal group (100.0% vs. 59.5%, $p = 0.014$). ESS score was lower in MCI group than normal group (3.3 ± 2.5 vs. 5.5 ± 2.9, $p = 0.032$). The TMT-B score was higher in MCI group than normal group (142.9 ± 44.9 sec vs. 104.4 ± 36.6 sec, $p = 0.006$) (Table 3).

	Normal group (n=42)	**MCI group (n=10)**	***P***
Subject characteristics			
Age (years)	70.4 ± 4.4	73.5 ± 5.6	0.063
Male (%)	52.4	60.0	0.664
Height (cm)	160.3 ± 8.3	158.4 ± 5.5	0.487
Weight (kg)	57.9 ± 9.1	53.1 ± 9.9	0.145
BMI (kg/m^2)	22.5 ± 2.5	21.1 ± 3.1	0.134
SBP (mmHg)	140.3 ± 16.1	155.6 ± 23.1	0.017
DBP (mmHg)	80.9 ± 9.9	90.8 ± 10.3	0.006
HR (bpm)	69.3 ± 9.8	73.8 ± 15.9	0.259
Smoking (%)	14.3	30.0	0.238
Alcohol intake (%)	38.1	50.0	0.490
Hypertension (%)	59.5	100.0	0.014
Diabetes mellitus (%)	4.8	10.0	0.523
Hyperlipidemia (%)	23.8	40.0	0.300
ESS	5.5 ± 2.9	3.3 ± 2.5	0.032
PSQI	5.4 ± 3.0	6.3 ± 3.2	0.387
BDI-II Score	6.4 ± 5.5	5.4 ± 5.2	0.610
Olfactory function			
OSIT-J score	8.5 ± 2.6	8.9 ± 2.5	0.621
Cognitive function tests			
HDS-R	28.5 ± 1.7	28.3 ± 1.5	0.765
MMSE Score	29.0 ± 1.5	29.0 ± 1.2	1.000
TMT-B Score (s)	104.4 ± 36.6	142.9 ± 44.9	0.006

Data are expressed as mean ± standard deviation.

TDAS = Touch Panel-type Dementia Assessment Scale, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, ESS = Epworth Sleepiness Scale, PSQI = Pittsburgh Sleep Quality Index, BDI-II = Beck Depression Inventory Second edition, OSIT-J = Odor Stick Identification Test for the Japan, HDS-R = Revised Hasegawa's Dementia Scale, MMSE = Mini-Mental State Examination, TMT-B = Trail Making Test B.

Table 3: Comparison of subject characteristics and cognitive function based on TDAS score.

4. Discussion

We found that olfactory function evaluated by the OSIT-J and HR were associated with the TMT-B score. Moreover, the TDAS score was significantly correlated with BP. Our findings suggest that screening of olfactory function and BP monitoring may facilitate the early detection of executive dysfunction in older adults.

Olfactory function evaluated by the OSIT-J was associated with the TMT-B score. Over 50% of individuals aged ≥60 years' experience difficulties with smell; the prevalence of olfactory impairment is higher in patients with AD than in the general population [27]. Olfactory loss or dysfunction can occur in AD prior to the development of neuropathology and cognitive dysfunction [28]. The OSIT-J tool uses odors that familiar to the Japanese; therefore, this test shows good sensitivity for evaluation of olfactory function in Japanese patients with AD [29]. Moreover, it is a noninvasive test and is less time consuming. Olfactory dysfunction should be considered a marker for AD and this evaluation can help to determine the level of AD. OSIT-J tool can serve as a useful tool for the early detection of cognitive decline in community-dwelling older adults.

In this study, the TDAS score was significantly associated with SBP and DBP. Moreover, both SBP and DBP were significantly higher in participants with TDAS scores ≥7, which indicates MCI. A previous study reported that elevated SBP was linked to cognitive dysfunction and cognitive decline in patients with cardiovascular disease [30]. However, the association between late-life high BP and incident cognitive decline was inconsistent [31], and could have been affected by age, duration, and administration of antihypertensive medication, among other such factors.

Hypertension has been recognized as a risk factor for cardiovascular disease [32, 33] and dementia [34]. We recently showed that hypertension negatively affected cognitive function in community-dwelling older adults [35]. A previous study reported an association between hypertension and cognitive impairment in individuals with the allele of apolipoprotein E [36]. Future studies are warranted to conclusively establish whether treatment of hypertension can help reverse cognitive decline and prevent the onset of dementia.

The TMT-B score was significantly associated with the HR. SBP variation and the mean HR were independent predictors of cognitive decline and dysfunction in patients at a high risk of cardiovascular disease [37]. A meta-analysis showed that a higher resting HR was independently associated with an increased risk of all-cause and cardiovascular mortality, which indicates that the resting HR is a predictor of all-cause and cardiovascular mortality in the general population [38]. Autonomic imbalance, characterized by a hyperactive sympathetic system and a hypoactive parasympathetic system, is associated with various pathological conditions. Cardiovascular disease is a known risk factor for the development of AD and vascular dementia. A low resting HR is usually an indicator of good health; therefore, it is reasonable to conclude that a high HR likely contributes to an increased risk of cognitive decline.

5. Limitations

Following are the methodological limitations of this study; (a) The relatively small sample size is a drawback of this study. (b) The observational design is also a limitation of this research. Future trials with larger sample sizes are warranted to conclusively establish the association between olfactory dysfunction and executive function in older adults.

6. Conclusions

Olfactory dysfunction and high SBP, DBP, and HR were associated with cognitive decline. Evaluation of olfactory function and BP could be a valuable screening tool for cognitive decline in community-dwelling older adults.

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Conflict of Interest

All authors have no conflict of interest to declare.

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