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Relationship between White Matter Lesions and Self-reported Chewing Difficulty in Japanese Adults: A Cross-sectional Study

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This cross-sectional study investigated the relationship between white matter lesions (WMLs) and self-reported chewing status among Japanese adults. The participants were 570 individuals (369 males, 201 females; mean age, 54.0 years) who underwent brain dock checkups at Asahi University Hospital Human Health Center between April 2019 and March 2020. The presence of WMLs was confirmed by brain magnetic resonance imaging (MRI) in brain dock checkups. Chewing status was evaluated using a self-reported questionnaire. WMLs were found in 272 participants (48%). Presence of WMLs was positively related with age (older; odds ratio [OR], 1.130; 95% confidence interval [CI], 1.100 to 1.161), body mass index (BMI) (higher; OR, 1.103; 95%CI, 1.038 to 1.171), and chewing status (difficulty; OR, 2.794; 95%CI, 1.617 to 4.827) after adjusting for gender, HbA1c, hypertension, heart disease, and medication history. Furthermore, the proportion of participants with chewing difficulty increased according to WML grade ($p < 0.001$). In conclusion, presence of WMLs in Japanese adults showed a relationship with self-reported chewing difficulty.

Key words : white matter lesions, brain dock checkups, chewing status, cross-sectional studies

INTRODUCTION

White matter lesions (WMLs) indicate ischemic foci in cerebral white matter of the deep brain and are classified as a cerebral microvascular disease [1)]. WHLs are caused by chronic cerebral ischemia due to reduced cerebral blood flow and damage to the blood-brain barrier [1)], and contribute to the initiation of Alzheimer's disease [2)]. It is also known that WMLs can cause stroke and cerebrovascular dementia [3-5)]. The treatment and prevention of WMLs usually involve the administration of antihypertensive and anticoagulant drugs [6-8)], but a complete cure is difficult after WMLs have developed. Therefore, it is very important to understand the risk factors for WMLs and determine appropriate preventive measures.

The risk of developing WMLs is related to lifestyle habits and is increased in smokers, for example [9)]. Heavy alcohol intake is known to cause hypertensive microangiopathy that reduces cerebral blood flow and causes WMLs [10)]. A relationship is also reported between WMLs and poor sleep quality with less stable resting activity rhythms [11)]. In the search for effective preventive measures for WMLs, it is therefore also essential to explore habits related to lifestyle.

In Japan, the Ministry of Health, Labour and Welfare requires medical insurers to provide insured persons aged 40 to 74 years with specific medical checkups focused on lifestyle diseases [12, 13)]. The medical questionnaires used for specific medical checkups include sections on lifestyle habits. In 2018, a new item on chewing status was added to this questionnaire.

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A cross-sectional study reported that chewing is useful for maintaining and promoting hippocampus-dependent cognitive function in elderly people [14]. Another cross-sectional study also showed that chewing difficulty is related to the presence of WMLs in the left hemisphere [15]. These observations indicate a relationship between brain health and chewing status. In addition, it is reported that self-reports were considered valid alternatives to clinical measures to estimate chewing status in the Japanese adult population [16]. Therefore, there is a potential relationship between WMLs and self-reported chewing status.

The system of specific health checkups is a core health policy in Japan. It is helpful to utilize these existing data to ensure that findings of checkups are transferred to policy. As more than 30 million people in Japan receive specific health checkups annually, screening for WHLs using the same questions used in the checkups could have great social significance. In the present study, we hypothesized that a relationship exists between WMLs and self-reported chewing status in specific medical checkups. Because brain dock checkups in our hospital include people who have received specific medical checkups, it is convenient to match the results of the brain dock checkups with questionnaire data obtained from the specific medical checkups. Therefore, we conducted a cross-sectional study to determine the relation between WMLs and self-reported chewing status among Japanese adults who underwent brain dock checkups at Asahi University Hospital Human Health Center.

MATERIALS AND METHODS

1. Participants

All study participants had undergone a brain dock checkup at Asahi University Hospital Human Health Center between April 2019 and March 2020. A total of 623 people were recruited. Of these, 53 were excluded because the MRI findings or information about lifestyle habits were missing. Accordingly, 570 participants (369 males, 201 females; mean age, 54.0 years) were included in the final analysis.

2. Evaluation of the Presence of WMLs

A neurologist evaluated all magnetic resonance imaging (MRI) brain scans for the presence of WMLs. An axial T2-weighted fluid-attenuated inversion recovery sequence was acquired using a 3.0 or 1.5 T scanner. An independent internist and a neuroradiologist performed MRI assessment by brain lesion division (21 areas; online supplement file – MRI). WMLs were categorized into grades 1–4, as follows. Grade 1: punctate lesions <3 mm in diameter or enlarged perivascular space; grade 2: mottled and scattered subcortical deep white matter lesions >3 mm; grade 3: lesions in deep subcortical white matter showing a tendency to fuse with blurred borders; and grade 4: fused lesions widely distributed over most of the white matter [17, 18].

3. Assessment of Body Composition

At the brain dock checkups, nurses measured each participant's height and body weight. Body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2).

4. Measurement of Hemoglobin A1c (HbA1c)

HbA1c values were measured using high-performance liquid chromatography in venous blood samples collected after an overnight fast [19].

5. Evaluation of Chewing Status

We used the questionnaire used for specific medical checkups in Japan [20]. The questionnaire items included chewing status ("I can eat anything", "Sometimes it is difficult to chew because of dental problems such as dental caries and periodontal disease" or "I can hardly chew") [21, 22]. Respondents who answered "I can hardly chew" were considered to have chewing difficulty [23].

6. Presence of Systemic Diseases and Medication History

A comprehensive search was conducted of all participants' electronic health records at the time of brain dock checkups for the presence of hypertension, diabetes, psychiatric disease, cerebrovascular disease, heart disease, neurological disease, eating disorder, and medication history. Medication history was defined as currently taking one or more medications.

7. Other Items Surveyed from the Self-administered Questionnaire

The self-administered questionnaire used in specific medical checkups was used to collect the participants' gender, age, smoking habit, drinking habit, amount of alcohol, exercise habit, and sleep status. Smoking and drinking habits were classified as being present if the participant smoked at least one cigarette per day [24], and regularly consumed alcohol at least once a week [25], respectively; otherwise, they were deemed absent. Participants who drank >180 ml of sake or >500 ml of beer or >80 ml of shochu or >60 ml of whiskey double or >240 ml of wine were defined as heavy drinkers [12]. Sleep status was categorized as being poor or well [20].

8. Statistical Analysis

Because continuous variables (age, BMI, and HbA1c) are not normally distributed, data were presented as the median (25%, 75% percentiles). Among participants with WMLs, few (n= 3) answered "Sometimes it is difficult to chew because of dental problems such as dental caries and periodontal disease". Thus, the participants were divided into two categories: chewing difficulty or not chewing difficulty. Differences in the presence or absence of WMLs were evaluated by the Mann-Whitney U test for continuous variables and by the Chi-squared test for categorical variables. Univariate and multivariate logistic regression analyses were performed with presence of WMLs as the dependent variable. Chewing status was set as the independent variable in univariate and multivariate logistic regression analyses, as chewing status (not difficulty or difficulty). Age, gender, BMI, HbA1c, smoking habit, drinking habit, amount of alcohol, presence or absence of hypertension, presence or absence of psychiatric disease, presence or absence of heart disease, medication history, and sleeping status were selected as the third category. Variables with p < 0.10 were excluded in the model, the third category of variables related to the sample (age, gender) and variables with significant differences in univariate logistic analysis, which were adjusted for in these analyses. Differences in the proportion of the participants with chewing difficulty relative to WML grade were assessed using Chi-squared test, and statistically significant difference at the α = 0.05 level was adjusted with Bonferroni's correction. All data were analyzed using statistical analysis software (SPSS statistics version 27; IBM Japan, Tokyo, Japan). A p-value < 0.05 was considered statistically significant.

9. Research Ethics

This study was approved by the Ethics Committee of Asahi University (No. 27010), and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

RESULTS

WMLs were present in 272 participants (48%). Among these, 99 participants had WML grade 1, 134 had WML grade 2, 39 had WML grade 3, and none had WML grade 4. Participants whose medical history corresponded to a neurological disease or eating disorder were not observed.

Table 1 shows the characteristics of participants with and without WMLs. Compared to those without WMLs, participants with WMLs had significantly higher mean age (p < 0.001), BMI (p < 0.001), and HbA1c (p < 0.001); and significantly higher rates of hypertension (p = 0.010), heart disease (p = 0.045), and chewing difficulty (p < 0.001), and were also more likely to have a medication history (p < 0.001).

The results of univariate logistic regression analysis with WMLs as the dependent variable are shown in Table 2. The presence of WMLs was significantly related to age (older; OR, 1.136; 95%CI, 1.109 to 1.164), BMI (higher; OR, 1.074; 95%CI, 1.026 to 1.125), HbA1c (higher; OR, 1.711; 95%CI, 1.194 to 2.451), hypertension (presence; OR, 2.877; 95%CI, 1.246 to 6.645), heart disease (presence; OR, 1.856; 95%CI, 1.006 to 3.426), medication history (presence; OR, 2.216; 95%CI, 1.457 to 3.370), and chewing status (difficulty; OR, 4.612; 95%CI, 2.898 to 7.340).

Table 3 shows the adjusted odds ratios and 95%CI for WMLs according to the participant factors that were analyzed. After adjusting for gender, HbA1c, hypertension, heart disease, and medication history, the presence of WMLs was significantly related to age (older; OR, 1.130; 95%CI, 1.100 to 1.161), BMI (higher; OR, 1.103; 95%CI, 1.038 to 1.171), and chewing status (difficulty; OR, 2.794; 95%CI, 1.617 to 4.827).

Table 4 shows the difference in the proportion of participants with chewing difficulty for each WML grade. The proportion was 9% (28/298) among participants with WML grade 0, 27% (27/99) among participants with WML grade 1, 34% (45/134) among participants with WML grade 2, and 41% (16/39) among participants with WML grade 3. The proportion

Table 1. Participant characteristics according to the presence or absence of white matter lesions.

Factor	WMLs Absence (*n* = 298)	WMLs Presence (*n* = 272)	*p*-value*
Male [a]	187 (63%)	182 (67%)	0.299
Age (years)	51 (47, 57)	59 (54, 65)	< 0.001
BMI (kg/m^2)	22.1 (20.1, 24.5)	23.8 (21.6, 26.3)	< 0.001
HbA1c (%)	5.4 (5.3, 5.6)	5.6 (5.3, 5.8)	< 0.001
Smoking habit [b]	38 (13%)	24 (9%)	0.132
Drinking habit [b]	135 (45%)	126 (46%)	0.807
Amount of drink [c]	74 (25%)	106 (27%)	0.654
Hypertension [b]	8 (3%)	20 (7%)	0.010
Psychiatric disease [b]	14 (5%)	11 (4%)	0.703
Heart disease [b]	18 (6%)	29 (11%)	0.045
Medication history [b]	43 (14%)	74 (27%)	< 0.001
Sleep status [d]	58 (20%)	60 (22%)	0.445
Chewing status			
Not Difficulty	270 (90%)	184 (68%)	< 0.001
Difficulty	28 (10%)	88 (32%)	

Continuous variables (age, BMI, and HbA1c) were presented as median (25%, 75% percentiles).

Abbreviations: WMLs, white matter lesions; BMI, body mass index; HbA1c, hemoglobin A1c.* $p < 0.05$, using Chi- Squared test or Mann-Whitney U test, a Male (proportion of male); b Presence (proportion of presence); c Heavy (proportion of heavy); d Poor (proportion of poor).

Table 2. Crude odds ratios and 95%CIs for white matter lesions.

Factor		ORs	95% CI	*p*-value
Gender	Female	1	(reference)	0.299
	Male	1.200	0.850–1.695	
Age (years)		1.136	1.109–1.164	< 0.001
BMI (kg/m^2)		1.074	1.026–1.125	< 0.001
HbA1c (%)		1.711	1.194–2.451	< 0.001
Smoking habits	Absence	1	(reference)	0.134
	Presence	0.662	0.386–1.136	
Drinking habit	Absence	1	(reference)	0.807
	Presence	1.042	0.749–1.449	
Amount of drink	Not heavy	1	(reference)	0.654
	Heavy	1.090	0.748–1.588	
Hypertension	Absence	1	(reference)	0.013
	Presence	2.877	1.246–6.645	
Psychiatric disease	Absence	1	(reference)	0.704
	Presence	0.855	0.381–1.917	
Heart disease	Absence	1	(reference)	0.048
	Presence	1.856	1.006–3.426	
Medication history	Absence	1	(reference)	< 0.001
	Presence	2.216	1.457–3.370	
Sleep status	Well	1	(reference)	0.445
	Poor	0.854	0.569–1.281	
Chewing status	Not difficulty	1	(reference)	< 0.001
	Difficulty	4.612	2.898–7.340	

Abbreviations: ORs, odds ratios; CI, confidence interval; BMI, body mass index; HbA1c, hemoglobin A1c.

Table 3. Adjusted odds ratios and 95%CIs for white matter lesions.

Factor		ORs	95% CI	*p*-value
Gender	Female	1	(reference)	0.393
	Male	0.832	0.545–1.270	
Age (years)		1.130	1.100–1.161	< 0.001
BMI (kg/m²)		1.103	1.038–1.171	0.001
HbA1c (%)		0.693	0.449–1.070	0.098
Hypertension	Absence	1	(reference)	0.677
	Presence	1.238	0.452–3.393	
Heart disease	Absence	1	(reference)	0.639
	Presence	1.187	0.580–2.430	
Medication history	Absence	1	(reference)	0.143
	Presence	1.456	0.881–2.407	
Chewing status	Not difficulty	1	(reference)	< 0.001
	Difficulty	2.794	1.617–4.827	

Abbreviations: ORs, odds ratios; CI, confidence interval; BMI, body mass index; HbA1c, hemoglobin A1c.

Adjustment for gender, age, BMI, HbA1c, hypertension, heart disease, medication history, and chewing status.

Table 4. Chewing status for each WML grade.

Factor	Chewing status		*p*-value
	Not difficulty	Difficulty	
WML Grade			
0 (n=298)	270 (91%)[a]	28 (9%)	< 0.001
1 (n=99)	72 (73%)	27 (27%)	
2 (n=134)	89 (66%)	45 (34%)	
3 (n=39)	23 (59%)	16 (41%)	

Abbreviations: WML, white matter lesion.

Statistically significant difference at the $\alpha = 0.05$ level was adjusted with Bonferroni's correction.

P-value listed as corrected.

[a] number (proportion of number)

of participants with chewing difficulty increased with increasing WML grade, and remained significant after Bonferroni's correction (corrected $p < 0.001$).

DISCUSSION

To the best of our knowledge, the present study is the first to examine the relation between WMLs and self-reported chewing status in Japanese adults. The results showed that participants with WMLs had a higher incidence of chewing difficulty than those without WMLs. Logistic regression analyses also revealed that the presence of WMLs was related to chewing difficulty even after adjusting for gender, age, BMI, HbA1c, hypertension, heart disease, medication history, and chewing status. Furthermore, the proportion of participants with chewing difficulty increased according to the severity of WMLs. These results suggest a relationship of both presence and severity of WMLs with chewing difficulty. In Japan, questionnaires that form part of mandatory specific health checkups for adults aged 40–74 years include a question on chewing status. This item might be useful for screening for individuals who need health guidance for prevention of WMLs.

There are several possible mechanisms for the relationship between WMLs and chewing status. A previous clinical study revealed a significant increase in middle cerebral artery blood flow velocity during gum chewing compared with the preceding rest period[26]. A relationship has been reported between chewing and cerebral blood flow or partial pressure of oxygen in the brain[27]. Therefore, there is a relationship between WMLs and chewing difficulty via modifications in cerebral blood flow or partial pressure of oxygen. Chewing difficulty has also been identified as a risk factor for arteriosclerosis[28, 29], which might also be involved in the relationship between chewing and WMLs. Conversely, as chewing can activate the hypothalamic-pituitary-adrenal axis and autonomic nervous system [30], chewing difficulty may be related to WHLs via suppression of these neurological mechanisms. However, we cannot comment on this relationship as we did not evaluate cerebral blood flow or neurological mechanisms in this study.

Previous studies have reported a relationship between lifestyle habits and WMLs [6-8], whereas our study showed a positive correlation between the presence of WMLs and chewing difficulty. Thus, previous studies and our results both support the notion that ensuring good lifestyle habits might be important for the prevention of WMLs.

The present participants with WMLs were significantly older than those without WMLs, which is in agreement with the findings of previous reports [31,32]. This might be due to the fact that small vessel disease, which is the main cause of WMLs, is an aging-related vascular risk factor [33].

We found that BMI was significantly higher in participants with WMLs than in those without WMLs, which is in agreement with a previous study reporting that higher BMI is associated with higher risk of WMLs [34]. This previous study reported that increased visceral fat due to obesity increases the inflammatory activity of IL-6 in blood, which can cause progression of WMLs [34]. Thus, the present findings also suggest that in those with high BMI, a systemic increase in inflammatory molecules might be associated with WMLs.

Mean participant age was 54.0 years, and 48% of all participants had WMLs. In several previous studies, around 45% of participants in their 50s who underwent brain dock checkups had WMLs [35,36], which is in agreement with the present results.

The present method of WML grading, as defined above, is based on the guidelines of the Japan Brain Dock Society and is not an international standard. In contrast, the internationally used Fazeka's classification is "grade 0 = absence, grade 1 = punctate foci, grade 2 = beginning confluence of foci, grade 3 = large confluence foci" [37]. Thus, the present classification criteria differ from Fazeka's classification.

Our study has some limitations. First, as our study was cross-sectional in nature, we could not demonstrate causal relations. Additional longitudinal studies are needed to investigate the relation between WMLs and chewing status. Second, we evaluated chewing status based on a questionnaire. A previous study showed that self-reported chewing status in specific medical checkups was related to the number of decayed teeth and periodontal pockets, based on Eichner's classification [21]. This indicates that chewing difficulty reflects poor oral status. However, a previous study has evaluated chewing status using the sieve method, which calculates chewing efficiency using a chewing conversion table [38]. Therefore, there may be a discrepancy between chewing awareness and actual chewing problems, which may result in false negatives or false positives. Third, as the present participants had undergone brain dock checkups for screening purposes, the presence or absence of WMLs was determined only by MRI of the brain, and there is a possibility of false-negative results. Fourth, the validity of questionnaire items in the specific health checkup is unknown, and is an issue for further study. Finally, the external validity of our study should be considered, because all the participants were recruited from Asahi University Hospital Human Health Center. Nevertheless, a strength of our study is that the sample size was sufficient to assess the prevalence of WMLs among participants in whom chewing status varied.

CONCLUSION

We found a relationship between presence of WMLs and self-reported chewing difficulty among Japanese adults who underwent brain dock checkups at Asahi University Hospital Human Health Center. The presence of WMLs was also related to age and BMI.

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