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Homocysteine and risk of cerebrovascular lesions: The PRESENT project

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Abstract

Objective: Cerebral white matter changes (WMCs) and silent brain infarcts (SBIs) are common radiological findings in neurologically asymptomatic elderly people. Their presence is associated with an increased risk of stroke or dementia. Homocysteine (Hcy) can cause atherosclerosis and may thus act as a useful marker of stroke prior to symptom onset. This study aimed to evaluate the utility of Hcy as a surrogate marker for early intervention for stroke in community-dwelling healthy elderly persons with cerebrovascular lesions such as WMCs and SBIs. *Methods:* We assessed the relationship between the Hcy level and presence of WMCs/SBIs on brain computed tomography (CT) in 554 elderly individuals aged ≥65 years with no history of stroke or dementia. *Results:* The mean age of the participants was 74.43±7.32 years. Of the 554 patients, 106 (19.1%) had WMCs and/or SBI findings on brain CT. The mean Hcy level was higher in participants with WMCs/SBIs (P=0.001). The WMCs/SBIs group had a significantly greater number of participants with high Hcy levels than the non-WMCs/SBIs group (P<0.001). High Hcy levels (≥12.3 μmol/L) was significantly associated with WMCs and SBIs even after adjusting for age, Korean Mini Mental Status Examination score, education level, and vascular risk factors such as hypertension, diabetes, hyperlipidemia and smoking status.
Conclusion: The result of our study suggests that regular monitoring of homocysteine level as a modifiable risk factor may be helpful for predicting the association of cerebrovascular lesions such as WMCs and SBIs for the prevention of future ischemic stroke and cognitive impairment.

Keywords: White matter changes, silent brain infarcts, homocysteine, elderly, stroke, dementia

INTRODUCTION

White matter changes (WMCs) and silent brain infarcts (SBIs) are common imaging-defined cerebral vascular lesions in elderly persons without neurological abnormalities.[1-5] The presence of WMCs and SBIs is associated with cognitive dysfunction, and act as risk and prognostic factors for future stroke.[2,3,6] To date, there are no definitive treatment for WMCs and SBIs, but it is accepted that early detection of WMCs and SBIs at the asymptomatic stage is advantageous for the prevention of stroke.[3,7]

WMCs and SBIs have similar pathogenic mechanisms and are associated with cerebrovascular risk factors such as age, hypertension, and homocysteine (Hcy) in previous studies of ischemic stroke patients.[1,8-11] However, the relationship between Hcy as a modifiable controllable risk factor and the presence of WMCs and SBIs, particularly in community-dwelling healthy elderly adults, is controversial. We aimed to determine whether the Hcy level is related to the presence of WMCs and SBIs in community-dwelling elderly persons, with the hope of identifying a predictable marker of controllable risk factors that could prevent future vascular-related cognitive impairment or stroke.

METHODS

Study design and participants

The Prevention of Stroke and Dementia (PRESENT) project, for people aged 50 years or older, is an ongoing regional government project initiated in Korea in July 2007 for the prevention of stroke and dementia via public education,

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public relations, early medical check-ups, and research.[5] Data were collected over 3 years between January 2007 and December 2009. As part of the PRESENT project, elderly participants (aged ≥65 years) with no history of stroke or dementia were recruited by random sampling or voluntarily. We recruited 554 healthy elderly participants in this study. All procedures were performed after obtaining written permission from the participants. All participants assessed a medical questionnaire, laboratory evaluation, and brain CT, which were all performed on the same day. The study protocol was approved by the Wonkwang University Institutional Review Board (IRB No. 2016-11-BM-071).

Clinical and laboratory data

All participants completed a medical questionnaire, which included questions regarding smoking habits, alcohol consumption, hypertension, diabetes, hyperlipidemia, and history of stroke and dementia. Hypertension was defined as systolic blood pressure of ≥140 mmHg and diastolic blood pressure of ≥90 mmHg; participants undergoing treatment for hypertension were considered to be hypertensive.[12] Diabetes mellitus was defined as a fasting glucose level of ≥126 mg/dL or when treatment for diabetes was reported.[13] Hyperlipidemia was defined as a total cholesterol level ≥240 mg/L, low-density lipoprotein cholesterol level of ≥160 mg/L, or triglyceride level of ≥200 mg/dL, or when treatment was reported for elevated cholesterol.[14] Smoking was defined as a current smoking habit. All participants were assessed for cognitive functions using Korean mini-mental status examination (K-MMSE).

Venous blood samples were collected after an overnight fast, and lipid profiles, homocystein using an automated chemistry analyzer (Modular P 800, Roche Diagnostics, Indianapolis, IN, USA) and measurement of stroke biomarkers[15] were performed.

Definition of cerebral WMCs and SBIs on brain CT

Brain CT was performed with a Phillips Brilliance CT 6-Slice scanner. All scans were performed with the same scanner, using the same scanning procedure, with 6 mm continuous slices, and without contrast enhancement. The CT results were independently evaluated by two expert and highly experienced neurologists who were blinded to the clinical condition and laboratory assessment of the participants. Based on the brain CT results, participants were assigned to either the WMCs/SBIs or non-WMCs/SBIs group. The WMCs/SBIs group included participants with either WMCs or SBIs, or both because each have similar cerebrovascular risk factors and pathogenic mechanisms.[8,9] WMCs were defined as the presence of at least 5 mm wide unclear or moderately hypodense areas located in the periventricular or subcortical areas. SBIs were defined as the presence of >2 mm wide well-defined areas that exhibited attenuation without relevant clinical neurologic events.[5,16,17] We conducted a review and discussion session to reach a consensus regarding inconsistent CT findings between raters.

Statistical analyses

Data are presented as means ± standard deviation for continuous variables, and as numerals and percentages for categorical variables. Significant differences were tested using the χ^2 test, independent-test, and multiple regression analysis in the Statistical Package for the Social Sciences (SPSS) Ver. 18.0 for Windows (SPCC Inc., Chicago, IL. USA). We divided the Hcy level into tertiles; T 1, <9.90μmol/L; T 2, 9.90-12.3μmol/L; and T 3, >12.3μmol/L. A logistic regression analysis was conducted to determine the independent factors of WMCs/SBIs after adjustment for potential confounders, including sex, age, hypertension, diabetes, current smoking status, education, and Hcy level. All differences were considered statistically significant at $P<0.05$.

RESULTS

The baseline characteristics of the participants are presented in Table 1. A total of 554 elderly persons aged ≥65 years (306 females and 248 males) completed all evaluation processes. The mean age of the participants was 74.43±7.32 years. We divided the participants into two groups based on brain CT findings. Of the 554 patients, 106 (19.1%) had WMCs/SBI findings on brain CT. The concordance rate between the two observers was good ($k = 0.89$; 91% concordance). Patient's age (73.3±6. vs 78.9±7.9 years, P<0.001), rate of hypertension (50.0 vs 85.8%, P<0.001), diabetes mellitus (16.8 vs 33.9%, P=0.001), education level (9.6±4.4 vs 7.5±5.1 years, P<0.001), K-MMSE score (26.4±3.2 vs 24.45±4.5, P<0.001), and mean Hcy level (11.5±3.7 vs 12.9±3.5 μmol/L, P=0.001) were significant in the WBCs/SBIs group compared to the non-WBCs/SBIs group.

Table 1: Baseline characteristics between subjects with normal brain CT findings and those with white matter changes (WMCs) and silent brain infarcts (SBIs)

	Normal brain CT (n =448)	WMCs/SBIs findings on brain CT (n = 106)	P value
Age, years	73.36 ± 6.75	78.97 ± 7.94	<0.001
Male, n (%)	197 (44.0)	51 (48.1)	0.441
Education, years	9.6 ± 4.4	7.5 ± 5.1	<0.001
Hypertension, n (%)	224 (50.0)	91 (85.8)	<0.001
Diabetes, n (%)	75 (16.8)	36 (33.9)	0.001
Dyslipidemia, n (%)	146 (32.5)	39 (36.8)	0.380
Current smoking, n (%)	77 (17.3)	18 (17.4)	0.989
K-MMSE	26.44 ± 3.23	24.45 ± 4.54	<0.001
Mean homocystein (μmol/L)	11.57 ± 3.71	12.95 ± 3.57	0.001
T 1 (< 9.90)	147(32.8)	17 (16.0)	<0.001
T 2 (≥9.90, <12.3)	162 (36.2)	35 (33.0)	
T 3 (≥12.3)	139 (31.0)	54 (50.9)	

Data are presented as mean ± standard deviation, CT: computed tomography, WMC: White matter changes, SBI: Silent brain infarcts, K-MMSE: Korean mini-mental status examination

When the participants were divided into tertiles (T) according to the Hcy level, the participants with 3rd Hcy level (T3) were significantly more common in the WBCs/SBIs group than the non-WBCs/SBIs group (P<0.001).

Table 2 indicates the association of Hcy and brain CT findings. An unadjusted analysis revealed that the odds ratio (OR) for cerebral WMCs/SBIs on brain CT was 1.86 for participants in the 2nd Hcy tertile (T2) [95% confidence interval [CI], 1.00-3.47, P=0.049], and 3.35 for participants in the 3rd Hcy tertile (T3) [95% CI, 1.85-6.07, P<0.001]. After adjustment for age, sex, education, and other confounding factors such as hypertension, diabetes mellitus, hyperlipidemia and current smoking, the relationship remained statically significant. OR was 1.99 for participants in 3rd Hcy tertile (T3) [95% CI, 0.99-3.96, P=0.05].

DISCUSSION

Our study results revealed a significant association between the Hcy level and cerebral WMCs/SBI findings on brain CT in healthy elderly persons aged ≥65 years with no history of dementia or stroke, after adjusting for confounding factors. Furthermore, this study reanalyzed only elderly participants (aged ≥65 years) who are more vulnerable to future stroke or cognitive dysfunction. In our previous PRESENT study[3], Hcy level was associated with cerebral WMCs/SBIs on brain CT findings in all participants aged 50 years or older (P=0.001), but this correlation was not observed in aged <65 years healthy adults (P=0.59). This finding suggests that controlling the Hcy level could be helpful for preventing cerebral WMCs/SBIs in elderly, which may play a role in preventing stroke or cognitive dysfunction. A

Table 2: Logistic regression analysis of demographic variables on brain CT

Variables	OR (95% CI)	*P* value
Homocystein level (Reference : < 9.90)		
Unadjusted		
T 2	1.868 (1.004-3.476)	0.049
T 3	3.359 (1.858-6.074)	<0.001
Homocystein level (Reference : < 9.90)		
Adjusted for age, sex, K-MMSE, education level and vascular risk factors*		
T 2	1.441 (0.726-2.857)	0.296
T 3	1.990 (0.999-3.965)	0.050

OR: Odds Ratio, CI: Confidence interval, CT: computed tomography, K-MMSE: Korean mini-mental status examination, *Hypertension, diabetes, dyslipidemia and current smoking

possible explanation for the association of Hcy with WMCs/SBIs is that a high Hcy level can lead to atherosclerosis via various mechanisms such as activating platelets, promoting coagulation (formation of a red thrombus), increasing the production of free oxygen radicals causing oxidative stress, decreasing vasomotor function, endothelial dysfunction, and axonal demyelination in periventricular and subcortical white matter via the neuronal injury of oligodendrocytes.[18-22] Recent studies have reported the correlation of hyperhomocysteinemia and WMCs in ischemic stroke patients, as well as the relationship with age and hypertension, as in our study.[1,10,11] In addition, several studies investigating the concentration of Hcy also reported a significant correlation in the highest Hcy concentration group, as in our study, although the highest Hcy concentration varies from 10.25-22.13 μmol/L among studies.[11,23] This is due to racial diversity, genetic factors, and nutritional state; thus, the level of hyperhomocysteinemia needs to be clearly defined.

The purpose of our study was to evaluate the Hcy level as a modifiable risk factor for WBCs/SBI findings in healthy elderly persons. Our results indicated a significant association between the Hcy level and cerebral WMCs/SBIs. However, there are several limitations to this study that need to be addressed. This was a cross-sectional study rather than a large prospective study based on only brain CT. Brain CT is not as accurate as MRI for evaluating cerebral WMCs and SBIs.[24-26] Thus, the prevalence (19.1%) of cerebral WMCs/SBIs observed in this study may have been underestimated compared to the rates reported in MRI studies of the general elderly population, which ranged from 26.5 to 87%.[24,27] Nonetheless, the findings of this study are valuable because brain CT is still widely used due to its cost effectiveness and its utility in detecting age-related lesions as previous studies.[3,5,24] In addition, we do not have data on nutritional status or renal impairment affecting level of Hcy because this was a cross-sectional analysis based on baseline data. Further studies assessing vitamin deficiency or renal state are needed.

In conclusion, we found that the Hcy level is correlated with WMCs/SBIs in community-dwelling, stroke-free, dementia-free healthy elderly persons aged ≥65 years. On the basis of these findings, we propose that Hcy screening might play an important role in the early detection of WMCs/SBIs, leading to early intervention for the prevention of future vascular-related cognitive impairment or ischemic stroke.

DISCLOSURE

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Conflict of interest: None

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