Neurology Asia 2014; 19(4) : 351 – 356

Prevalence and risk factors of cerebral white matter changes and silent infarcts on brain computed tomography scans among community-dwelling healthy adults: The PRESENT project

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Abstract

Cerebral white matter changes (WMCs) and silent brain infarcts (SBIs) are common radiologic findings in neurologically asymptomatic elderly people, but are associated with an increased risk of subsequent stroke. We investigated the prevalence and risk factors for these cerebral changes on brain computed tomography (CT) in 480 community-dwelling healthy Korean adults without stroke or dementia, who were recruited for an early health program. Cerebral WMCs were defined as the presence of approximately 5 mm wide ill-defined and moderately hypodense lesions, and SBIs were defined as the presence of >2 mm wide well-defined hypodense lesions. Of the 480 patients, 49 (10.2%) had cerebral WMCs and SBIs findings on brain CT. The prevalence of WMCs and SBIs increased with age: the prevalence was 2.4%, 9%, and 32% for subjects in their 50, 60s, and 70s, respectively. In addition, hypertension, abdominal obesity, increased levels of homocysteine and high sensitivity C-reactive protein were significantly associated with cerebral WMCs and SBIs. Our study suggests that regular monitoring of risk factors is required to prevent cerebral WMCs and SBIs and decrease the incidence of stroke and dementia in healthy individuals.

INTRODUCTION

Cerebral white matter changes (WMCs) and silent brain infarcts (SBIs) are the most common radiological findings in the elderly population without neurological abnormalities.[1-3] In addition, cerebral WMCs and SBIs are associated with cognitive decline, gait impairment, and urinary dysfunction with or without dementia and are known risk factors for dementia or symptomatic ischemic stroke in the healthy mid-aged population.[4-7] Cerebral WMCs can occur due to ischemic, inflammatory, toxic, metabolic, or degenerative causes and are mainly associated with cerebral ischemia related to cardiovascular diseases in the elderly population.[8] SBIs are cerebral ischemic lesions identified with brain computed tomography (CT) or brain magnetic resonance imaging (MRI) in patients with no history of ischemic stroke or transient cerebral ischemic attack, and show no neurological abnormalities such as changes in tendon reflexes or dementia.[9-10]

MRI is more sensitive than CT and provides a more detailed observation of cerebral WMCs and SBIs. Therefore, most studies on the prevalence of cerebral WMCs and SBIs in population-based samples have been conducted with MRI. However, brain CT is still widely used due to its cost-effectiveness and its usefulness in detecting age-related lesions such as basal ganglia calcification, ventricular enlargement, and cortical atrophy.[7,11] Very few studies have explored cerebral WMCs and SBIs using brain CT in terms of their frequency and risk factors in the healthy adult population in Korea. In addition, the reported prevalence of these lesions has varied between 5–68.5%.[2,3,7,12] We analyzed the brain CT scans of healthy adults aged ≥50 years without history of ischemic stroke or dementia and determined the incidence and risk factors for cerebral WMCs and SBIs in this population.

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METHODS

Study design and subjects

The Prevention of Stroke and Dementia (PRESENT) project is an ongoing regional government project that began in July 2007 that aims to help prevent stroke and dementia by providing public education, enhancing public relations, promoting early medical check-ups, and supporting research in Ansan City, Gyeonggi province, Korea.[13] As a part of the PRESENT project, stroke-free and dementia-free adults (aged 50–75 years) were recruited by random sampling or volunteering. Data were collected over 2 years between January 2008 and December 2009. Systematic random sampling was performed with administrative support from the regional government. Using the official registered list provided by the regional government office, we contacted every 100th person in the baseline cohort aged ≥50 years (n = 32,324) to participate in a telephone interview conducted by a trained nurse. If a potential participant could not be contacted, refused to participate, had relocated, or had a history of stroke or dementia, we contacted the next person on the list. We attempted to contact 1,603 people; of these, 594 could not be contacted, 413 refused to participate, 16 had died, 74 had relocated, and 26 had a history of stroke or dementia. Thus, we finally recruited 480 healthy adults. All procedures were performed after obtaining written permission from the subjects. In addition, all participants performed medical questionnaire, laboratory evaluation, and brain CT, which were all performed in the same day.

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 by a systolic pressure was ≥140 mmHg and diastolic pressure was ≥90 mmHg; participants undergoing treatment for hypertension were considered to be hypertensive.[14] Diabetes mellitus was defined by a fasting glucose level of ≥126 mg/dL or when treatment for diabetes was reported.[15] Hyperlipidemia was defined as total cholesterol ≥240 mg/L, low-density lipoprotein cholesterol ≥160 mg/L, or triglyceride level ≥200 mg/dL, or when treatment was reported for elevated cholesterol.[16] Abdominal obesity was defined as waist diameter >90 cm for males and >80 cm for females.[17] Smoking was defined as a current smoking habit.

Sample were collected from venous blood after overnight fast, and lipid profiles and stroke biomarkers[18] as erythrocyte sedimentation rate (ESR), high sensitivity C-reactive protein (hs-CRP), fibrinogen, D-dimer, and homocysteine were performed. ESR was measured by TEST 1 method using photometrical capillary stopped flow kinetic analysis (ALIFAX, Padova, Italy); hs-CRP (SS type pure auto S-CRP) level was measured using an automated chemistry analyzer (Hitachi High-Technologies Co., Tokyo, Japan); fibrinogen and D-dimer (SIMENS, Simens Health care Diagnostics Inc., Deerfeild, IL, USA) level was measured using an automated coagulation analyzer (SYSMEX, CA-7000, Sysmex Co., Kobe, Japan); and homocysteine (Hisens, HBI Inc., Anyang, Korea) using an automated chemistry analyzer (Modular P 800, Roche Diagnostics, Indianapolis, IN, USA).

Definition of cerebral WMCs and SBIs in brain CT

Brain CT was performed with a Phillips Brilliance CT 6-Slice. 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 2 neurologists who were blinded to the participants' clinical condition and laboratory data. Based on the brain CT results, subjects were assigned to either the normal or the WMCs/SBIs group. The WMCs/SBIs group included participants with either WMCs or SBIs, or both. SBIs were defined as the presence of >2 mm wide well-defined areas that showed attenuation without relevant clinical neurologic events. WMCs were defined as the presence of at least 5 mm wide unclear or moderately hypodense areas located in the periventricular or subcortical areas (Figure 1).[13,19,20] We conducted a review and discussion session to reach a consensus regarding inconsistent CT findings between raters.

Statistical Analyses

The results are presented as the mean ± standard deviation. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) Ver.13.0 for Windows (SPCC Inc., Chicago, IL. USA). Significant differences were tested using χ^2 tests for categorized variables, whereas independent *t*-tests were

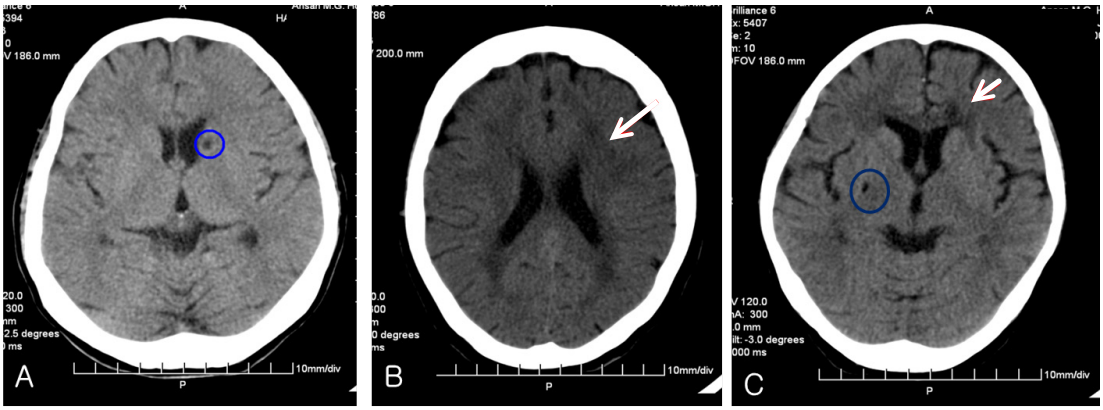

Figure 1. Representative examples of silent brain infarcts (SBIs, circle in A), cerebral white matter changes (WMCs, arrow in B), and both SBIs and cerebral WMCs (C) on brain CT.

performed for continuous variables. Univariate analyses were performed to compare baseline characteristics between patients with and without cerebral WMCs/SBIs. Multivariate analyses were conducted to determine the independent risk factors for cerebral WMCs/SBIs after adjustment for other significant risk factors used as covariates. Statistical significance was identified at $P < 0.05$.

RESULTS

The baseline characteristics of the subjects are shown in Table 1. Among the 480 subjects, 431 showed normal brain CT findings whereas 49 showed WMCs/SBIs findings. The concordance rate between the 2 observers according to the Kappa statistic was 91%. We found that the prevalence of WMCs/SBIs increased with age:

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 = 431)	WMCs/SBIs findings on brain CT (n = 49)
Age, year	59.8 ± 7.9	71.0 ± 7.9
Age ≥65 years, n (%)[1]	117 (27.1)	41 (83.7)
Male, n (%)	209 (48.5)	26 (53.1)
Hypertension, n (%)[1]	265 (61.5)	43 (87.8)
Diabetes, n (%)	223 (51.7)	32 (65.3)
Abdominal obesity, n (%)[2]	228 (52.9)	36 (73.5)
Current smoking, n (%)	101 (23.4)	9 (18.4)
Metabolic syndrome, n (%)	185 (42.9)	28 (57.1)
Mean total cholesterol (mg/dL)	209.9 ± 39.8	202.4 ± 46.2
Mean triglyceride (mg/dL)	168.0 ± 100.9	166.2 ± 85.2
Mean LDL-Cholesterol (mg/dL)	114.8 ± 32.8	105.9 ± 40.7
Mean HDL-Cholesterol (mg/dL)	62.0 ± 15.1	63.7 ± 20.8
Mean CRP (mg/L)[3]	0.21 ± 0.33	0.39 ± 0.50
Mean homocysteine (μmol/L)[3]	11.3 ± 4.4	12.8 ± 2.6

Data are mean ± SD values, [1]P < 0.001, [2]P < 0.01, [3]P < 0.05, WMC: White matter changes, SBI: Silent brain infarcts, LDL: low-density lipoprotein, HDL: high-density lipoprotein, CRP: C-reactive protein

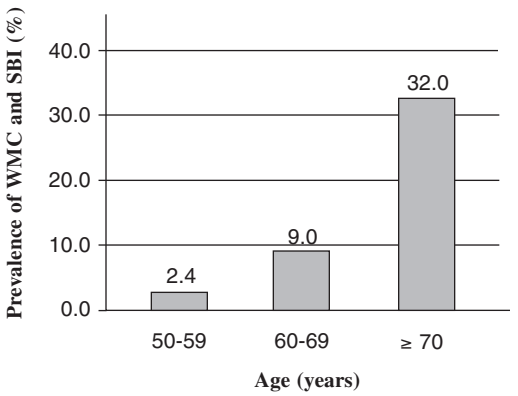

Figure 2. Prevalence of white matter changes (WMCs) and silent brain infarcts (SBIs)

the prevalence was 2.4% (6/249), 9% (12/134), and 32% (31/97) for subjects in their 50s, 60s, and 70s, respectively (Figure 2). Age (≥65 years), incidence of hypertension, levels of hs-CRP and homocysteine, and obesity were significantly higher in the WMCs/SBIs group than in the normal brain CT group.

Hypertension and abdominal obesity were significant in both the univariate variable analysis (hypertension, odds ratio 4.49, $P < 0.001$; abdominal obesity, odds ratio 2.47, $P < 0.001$) and the multivariate analysis (hypertension, odds ratio 3.0, $P = 0.018$; abdominal obesity, odds ratio 2.3, $P = 0.035$). The highest quartile for hs-CRP and the second quartile for homocysteine also showed a significant difference between the 2 groups in the multivariate analysis when they were compared with the lowest quartiles (Table 2).

DISCUSSION

Our study demonstrated that the prevalence of WMCs/SBIs increased markedly with age, hypertension, abdominal obesity, and elevated levels of homocysteine and hsCRP, which were significantly higher in the WMCs/SBIs group than in the normal brain CT group. Compared to the normal brain CT group, the WMCs/SBIs group showed a greater incidence of diabetes mellitus and metabolic syndrome, but this difference was not significant after adjusting for other significant risk factors. However, we acknowledge that education and awareness of the subject is necessary as metabolic syndrome is getting increased based on food habit and change in different life style. Also, this indicates a higher prevalence rate than previous Korean study which

Table 2: Risk factors analysis of cerebral lesions in brain CT

	Univariate analysis OR (95%CI)	Multivariate analysis OR (95% CI)
Age ≥65 years	13.75 (6.26-30.21)[1]	10.2 (4.43-23.26)[1]
Male	0.83 (0.46-1.51)	
Hypertension	4.49 (1.87-10.78)[1]	3.0 (1.20-7.24)[3]
Diabetes	1.75 (0.94-3.26)	1.1 (0.47-2.41)
Abdominal obesity	2.47 (1.27-4.78)[2]	2.30 (1.06-4.97)[3]
Current smoking	0.73 (0.34-1.56)	
Metabolic syndrome	1.77 (0.97-3.22)	
Total cholesterol≥240 mg/dL	0.71 (0.31-1.64)	
Triglyceride≥200 mg/dL	1.16 (0.61-2.25)	
LDL-Cholesterol≥160 mg/dL	0.63 (0.18-2.13)	
HDL-Cholesterol<40 mg/dL	0.98 (0.12-7.89)	
CRP (mg/L)[+]	3.27 (1.79-5.98)[1]	2.20 (1.07-4.37)[2]
Homocysteine (μmol/L)[++]	5.97 (2.74-13.04)[1]	5.20 (2.20-12.09)[1]

[1]P < 0.001, [2]P < 0.01, [3]P < 0.05, OR: Odds Ratio, CI: Confidence interval, LDL: low-density lipoprotein, HDL: high-density lipoprotein, CRP: C-reactive protein
Abdominal obesity: Waist circumference, men ≥90 cm, women ≥80 cm
[+]CRP: ≥ 0.25 mg/dL (≥75th percentile)
[++]homocysteine: ≥ 10.665 μmol/L (≥50th percentile)

requires further research whether this difference diverges from district where the subjects are or age or insufficient exercise, or various causes.[21,22]

WMCs showed evidence of ischemia, represented by a loss of cells and axons in ischemic lesions and the associated influx of glia and macrophages. Furthermore, WMCs were significantly associated with the prevalence of SBIs.[8,23] Thus, these white matter lesions are a risk factor for symptomatic ischemic stroke and dementia.[4,5] We considered WMCs and SBIs as comparable risk factors for stroke or dementia and did not analyze WMCs and SBIs separately. The most predominant risk factors for the presence of WMCs/SBIs were age and hypertension, and results are similar to those of previous studies.[23-26] However, potential risk factors for cerebrovascular disease, such as elevated homocysteine and hs-CRP levels or abdominal obesity, remain controversial. It is worthwhile to evaluate these controversial risk factors because cerebral WMCs and SBIs often precede the occurrence of stroke and cognitive decline and can predict future occurrences of more severe cerebral infarctions.[6,26] The PRESENT project aims to prevent stroke and dementia; therefore, our study did not include individuals that were diagnosed with stroke or dementia. We believe that community-based, early-life, and regular risk factor education and campaign programs can decrease the incidence of stroke and dementia in the community-dwelling elderly.

This study was a cross-sectional study rather than a large prospective study based on brain CT. Because brain CT is not as accurate as MRI for evaluating cerebral WMCs and SBIs[7-8,23,27], the prevalence of cerebral WMCs and SBIs observed in this study may have been underestimated when compared with the rates reported with MRI studies in the general elderly population, which ranged from 26.5%–87%.[7,28] We also could not evaluate the risk factors related to severity of cerebral WMCs. Nonetheless, the findings of the present study are valuable because brain CT is still widely used in clinics, and this study is the extending to younger elderly adults(≥50 years of age) in Korea to analyze the prevalence and risk factors of cerebral WMCs and SBIs using brain CT.

In conclusion, our results suggest that age is the most important risk factor, whereas hypertension, abdominal obesity, and elevated levels of homocysteine and hs-CRP were significantly associated with cerebral WMCs and SBIs in healthy community-dwelling adults aged ≥50 years. We think that it is necessary to control the risk factors related to cerebral WMCs and SBIs to prevent the occurrence of stroke or dementia in younger elderly healthy adults.

ACKNOWLEDGEMENTS

This research was supported in part by funding from the PRESENT (Prevention of Stroke and Dementia) project from Ansan City, Gyeoggi-do, South Korea

DISCLOSURE

Conflicts of interest: None

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