

Association of Prothrombotic Status With Markers of Cerebral Small Vessel Disease in Elderly Hypertensive Patients

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BACKGROUND

Aging and hypertension are well-known risk factors for cerebral white matter lesions. Prothrombotic status has been shown to be a risk factor for cardiovascular disease. In this study, we investigated the relationships among prothrombotic status, ambulatory blood pressure (ABP), and white matter hyperintensity (WMH) in elderly hypertensives.

METHODS

Measurement of prothrombin fragments 1+2 (F1+2), von Willebrand Factor (vWF) and plasminogen activator inhibitor-1 (PAI-1), ABP monitoring (ABPM), and brain magnetic resonance imaging (MRI) were performed in 514 Japanese elderly hypertensives (72.3 years old, male 37%). WMH cases were further divided into deep subcortical white matter lesion (DWML) or periventricular hyperintensity (PVH).

RESULTS

Deep WMH (DWMH) had significant positive correlations with age, use of antiplatelet agents, log F1+2, log vWF, log PAI-1, and

24-h systolic BP (SBP). PVH had significant positive correlations with age, male gender, smoking, use of antiplatelet agents, white coat hypertension (WCH), log vWF, and 24-h SBP. Severe PVH had significant positive correlations with age, use of antiplatelet agents, WCH, and 24-h SBP, and that was marginally correlated with log F1+2. In the logistic linear regression analysis, log F1+2 was significantly associated with DWMH ($P < 0.01$) and severe PVH ($P < 0.05$) adjusted for age and 24-h SBP. Log PAI-1 was significantly associated with DWMH ($P < 0.05$) adjusted for age and 24-h SBP.

CONCLUSIONS

In the present study, F1+2 and PAI-1 were positively associated with WMH after adjustment for 24-h SBP in elderly hypertensives. In addition to the conventional risk factors, prothrombotic status might serve as a significant determinant for WMH.

Keywords: blood pressure; cerebral small vessel disease; hypertension; prothrombotic status; white matter hyperintensity

American Journal of Hypertension, advance online publication 28 June 2012; doi:10.1038/ajh.2012.85

Vascular disease of the brain is a major cause of death and disability.¹ Magnetic resonance imaging (MRI) has revealed that white matter lesions (WMLs) are common in the elderly.² And white matter hyperintensity (WMH) has been shown to be associated with stroke.³ WMH cases were divided into deep WMLs (DWMLs) and periventricular hyperintensity (PVH).

Hypertension is a well-known risk for WMH.^{4,5} In addition, ambulatory blood pressure (ABP) has been shown to have a closer correlation with target organ damage including WMH than clinic BP.⁶

Prothrombotic state has been shown to be a risk for cardiovascular disease.⁷ Prothrombin factor 1+2 (F1+2) is a peptide released during the conversion of prothrombin into thrombin.⁸ The von Willebrand Factor (vWF) is expressed by endothelial cells after tissue damage, and it triggers aggregation of platelets.⁷ Plasminogen activator inhibitor-1 (PAI-1) is

an important inhibitor of fibrinolysis.⁹ In the earlier literature, several studies reported that coagulation or prothrombotic markers were associated with carotid artery atherosclerosis,¹⁰ atherothrombotic infarction,¹¹ or WMH.^{12,13} Specifically, in multivariate analyses, F1+2, vWF, and PAI-1 had significant correlations with silent cerebral ischemia, whereas the other markers did not.^{12,14–16}

However, there have been few studies to investigate the relationship between these markers and WMH in a larger population. The aim of this study was to investigate the relative contribution of prothrombotic status to WMH in a selected population at high risk of cerebral small vessel disease, i.e., elderly hypertensive patients. In this study, we investigated the associations of F1+2, vWF, and PAI-1 with WMH in elderly hypertensives.

METHODS

Patients. We initially enrolled 821 older hypertensive outpatients (clinic BP >140/90 mm Hg and age >50 years) in the Jichi Medical School Ambulatory Blood Pressure Monitoring (JMS-ABPM) study, wave one from six participating institutions (three

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Received 23 December 2011; first decision 26 January 2012; accepted 5 May 2012.

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clinics, two hospitals, and one outpatient clinic of a medical school) between 1 January 1992 and 1 January 1998.¹⁴ Patients who had a history of stroke, ischemic heart disease, chronic heart failure, peripheral vascular disease, renal failure (serum creatinine level >2.0 mg/dl), or any clinically relevant arrhythmia (including atrial fibrillation) at baseline were excluded from this study. Measurement of blood sample at baseline was performed in 811 patients (99% of the patients). Among them, analysis was performed for 514 patients after we excluded the patients who did not agree to undergo brain MRI (296 patients) or had incomplete data (one patient). Clinic BP was measured after resting for at least 5 min in a sitting position. Diabetes mellitus was defined as a fasting glucose level >140 mg/dl, a random non-fasting glucose level >200 mg/dl, hemoglobin A_{1c} >6.2%, or the use of an oral hypoglycemic agent or insulin.^{17–19} Hyperlipidemia was defined as a total cholesterol level >240 mg/dl or the use of an oral lipid-lowering agent.²⁰ Current smokers were defined as having smoked daily during the past month regardless of the quantity. Body mass index was calculated as weight (in kilograms)/height² (in meters squared). This study was approved by the independent research ethics committee, Jichi Medical University School of Medicine, Japan, in 1998. All participants gave written informed consent. Some of the data from the JMS-ABPM study have been published previously.^{21,22} This article is a subanalysis of the study.

Blood samples. Blood samples were drawn from the cubital vein in the fasting state within 2 months of the day of ABP monitoring (ABPM). In almost all subjects, blood sampling was performed within 1 month before or after the ABPM was conducted and antihypertensive agents discontinued. F1+2 and vWF were determined by using ELISA kits (Diagnostic Stago, Asnieres, France). Plasma levels of PAI-1 were determined using ELISA kits (TDC-88; Teijin, Tokyo, Japan) and were expressed in nanograms per milliliter. The interassay coefficient of variation was 3.6% for F1+2, 4.2% for vWF, and 5.4% for PAI-1.

Brain MRI. Brain MRI was carried out using a superconducting magnet with a main strength of 1.5 T (MRT200FXII; Toshiba, Tokyo, Japan, SIGNA Horizon Ver. 5.8; General Electric, Milwaukee, WI, or Vision; SIEMENS, Erlangen, Germany) within 3 months of the JMS-ABPM. T1- and T2-weighted images were obtained in the transverse plane with 7.8–8.0 mm thick sections. We further defined WMH as occurring in the area under the cortex (DWML) or the area adjacent to the ventricles (PVH) in the MRI images, because earlier studies have shown that the etiology, progression rate, and clinical consequences of these subtypes may differ.^{23,24} Hyperintense punctate lesions on T2-weighted images were not counted as lacunae if they were not visible as low-intensity areas on T1-weighted images. Proton density images were evaluated for the extent of patchy or diffuse PVHs. The PVH lesions were classified into four grades as previously described.²⁵ Grade I was defined as no WMLs except for small triangular foci surrounding the frontal horns; grade II was defined as caps in both anterior and posterior horns of the lateral ventricles or additional discrete patchy subcortical WMLs beside

or above the lateral ventricles. More extensive punctate periventricular WMLs and their early confluent stages were classified as grade III. Marked areas of high signal intensity that reached confluence completely surrounding the lateral ventricles were defined as grade IV. Grades III and IV were defined as severe PVH. Because the histological changes underlying mild PVH are not always caused by ischemia, we additionally focused on the group with severe PVH.⁴ The MRI images of the subjects were randomly stored and interpreted by neurologists who were blind to the subjects' names and characteristics.¹⁸ In our laboratory, the inter-reader and intra-reader κ -statistics for the PVH grade were 0.812 and 0.851, respectively. The inter-reader and intra-reader κ -statistics for the DWMH were 0.721 and 0.745, respectively.

ABPM. ABPM was measured using a validated machine: ABPM-630 (Nippon Colin, Komaki, Japan),²⁶ TM-2421, or TM-2425 (A&D, Tokyo, Japan).²⁷ Patients stopped antihypertensive medication for at least 14 days before the ABPM study, and 56.7% of the patients had a history of antihypertensive medication use. Measurements were performed at 30-min intervals for 24 h on a weekday. Hypertensives whose 24-h systolic BP (SBP)/24-h diastolic BP was <130/80 mm Hg were described as having white coat hypertension (WCH).

Statistical analysis. Statistical analyses were conducted for 514 patients. Data are shown as the mean (\pm s.d.), median, or percentages. One-way analysis of variance was used to determine difference in prothrombotic markers among patients with and without DWMH, PVH, and severe PVH. Correlations between variables were performed using Spearman's correlation. Logistic linear regression analysis was performed with DWML, PVH, or severe PVH as a dependent variable (scored 1 when present, and 0 when absent). This model included factors that had correlations with a *P* value threshold <0.1 for DWML, PVH, or severe PVH as determined by Spearman's correlation test. Differences/associations with a *P* value <0.05 were considered statistically significant. All analyses were performed with SPSS version 11.5J statistical software (SPSS, Chicago, IL).

RESULTS

We compared the baseline characteristics of the 514 patients with MRI and 297 patients without MRI. In the unpaired *t*-test or χ^2 test, there were significant differences in the baseline characteristics in body mass index (24.2 vs. 23.5 kg/m², *P* < 0.01), diabetes mellitus (14.4 vs. 8.45%, *P* < 0.05), hyperlipidemia (21.8 vs. 13.2%, *P* < 0.01) and the use of antihypertensive agents (56.7 vs. 45.3%, *P* < 0.01), and antiplatelet agents (27.1 vs. 35.3%, *P* < 0.01). Continuous variables of F1+2, vWF, and PAI-1 were tested to detect substantial deviations from the norm by computing the Kolmogorov-Smirnov test. The assumptions of satisfactory normal distribution were not met for all of the examined continuous variables (*P* < 0.001, *P* < 0.001, and *P* < 0.001, respectively). All of the patients included in this study were free from neurological deficits. The mean age of the patients was 72.3 \pm 6.4 years (male 37%). **Table 1** presents the clinical characteristics of the patients, laboratory parameters,

and MRI data for WMH. The prevalence of DWMH, PVH, and severe PVH were 34.4, 74.0, and 16.6%, respectively.

In one-way analysis of variance, patients with DWMH had significantly higher mean values of log F1+2, log vWF, and log PAI-1 than those without DWMH. Patients with PVH had a significantly higher mean value of log vWF than those without PVH, whereas patients with severe PVH had significantly higher mean values of log F1+2 than those without severe PVH (Figure 1a–c).

DWMH was significantly positively correlated with PVH and severe PVH, whereas PVH was significantly positively correlated with severe PVH. DWMH was significantly positively correlated with age, use of antiplatelet agents, log F1+2, log vWF, log PAI-1, and 24-h SBP. PVH was significantly positively

correlated with age, male gender, smoking, use of antiplatelet agents, WCH, log vWF, and 24-h SBP. Severe PVH was significantly positively correlated with age, use of antiplatelet agents, WCH, and 24-h SBP, and marginally positively correlated with log F1+2 (Table 2).

In the logistic linear regression analysis, log F1+2 and log PAI-1 were significantly associated with DWMH including age, diabetes mellitus, smoking, antiplatelet agent use, and WCH in the model. The 24-h SBP was significantly associated with PVH when including age, gender, smoking, antiplatelet agent use, and WCH in the model. Log F1+2 was significantly associated with severe PVH when including age, hyperlipidemia, antiplatelet agent use, and WCH in the model (Table 3). A significant interaction was found between antiplatelet agent use and log F1+2 for the DWMH ($P < 0.05$), while there were no significant interactions in any of the other models.

DISCUSSION

In the present study, prothrombotic status was a significant indicator for WMH in Japanese elderly hypertensives after adjustment for 24-h SBP. These findings may provide some new insights into the pathophysiology underlying the relationship of prothrombotic status with WMH even in patients with a high risk of cardiovascular disease.

In this study, univariate analysis showed that the F1+2 level was significantly correlated with DWMH, and marginally correlated with severe PVH. The association of F1+2 with DWMH and severe PVH remained significant after adjusting for confounding factors in a multiple linear regression model. In previous literature, F1+2 was significantly associated with carotid intima-media thickness in middle-aged subjects free of clinical overt atherosclerotic disease.¹⁰ In the report by Kario *et al.*, a high level of plasma F1+2 was shown to be a risk factor for stroke in elderly hypertensives.¹⁴ On the other hand, in the Austrian Stroke Prevention Study, F1+2 was not associated with WMH lesion progression.²⁸ That study mainly focused on normal elderly subjects, whereas our study was focused on high-risk older subjects. Thus, the difference in study population might have affected the results. Plasma F1+2 is a peptide released during the conversion of prothrombin into thrombin, which is the final step of the coagulation cascade. So, it was suggested that a status related with coagulation in the cerebral arteries was also associated with WMH. Recently, an immunohistochemistry study by Simpson *et al.*²⁹ showed that the lesion types differ in their cellular pathology. Specifically, those authors demonstrated that PVH appears to be primarily associated with cerebrospinal fluid leakage into the white matter and subsequent loss of ependymal lining in the ventricles. In addition, the histological changes underlying mild PVH are not always caused by ischemia.⁴ The association of F1+2 with DWMH and severe PVH suggests that high plasma F1+2 was related with cerebral ischemic injury, although that pathophysiology might differ in DWMH and severe PVH.

In our study, vWF activity was significantly correlated with DWMH and PVH in the univariate analysis but was marginally associated with PVH in the multiple regression analysis. The vWF activity has been shown to be elevated in patients

Table 1 | Baseline characteristics

Measures	Mean \pm s.d.
N	514
Age (years)	72.3 \pm 8.6
Male (%)	37.1
Body mass index	24.2 \pm 3.6
Diabetes mellitus (%)	14.4
Hyperlipidemia (%)	21.7
Smoking (%)	21.7
Antihypertensive agents (%)	56.7
Antiplatelet agents (%)	35.3
FBG (82–110 mg/dl)	94.9 \pm 25.1
Total cholesterol (130–240 mg/dl)	201.6 \pm 33.9
Triglycerides (40–130 mg/dl)	144.6 \pm 80.3
HDL cholesterol (40–119 mg/dl)	47.0 \pm 12.3
Median F1+2 (0.44–1.1 nmol/l)	1.42
Interquartile range of F1+2	1.14–1.77
Median vWF (50–150%)	160
Interquartile range of vWF	132–198
Median PAI-1 (<50 ng/ml)	35.0
Interquartile range of PAI-1	24.4–57.5
BP measures	
Clinic SBP (mm Hg)	165 \pm 19
DBP (mm Hg)	91 \pm 14
PR (bpm)	77 \pm 12
24-h SBP (mm Hg)	138 \pm 17
DBP (mm Hg)	79 \pm 10
PR (bpm)	71 \pm 8
White coat hypertension (%)	29.7
Deep white matter hyperintensity (%)	34.4
PVH (%)	74.0
Severe PVH (III,IV) (%)	16.6

The numbers in parentheses indicate the normal range. Data presented as mean \pm s.d. bpm, beats per minute; BP, blood pressure; DBP, diastolic BP; FBG, fasting blood glucose; HDL, high-density lipoprotein; PAI-1, plasminogen activator inhibitor-1; PR, pulse rate; PVH, periventricular hyperintensity; SBP, systolic BP; vWF, von Willebrand Factor.

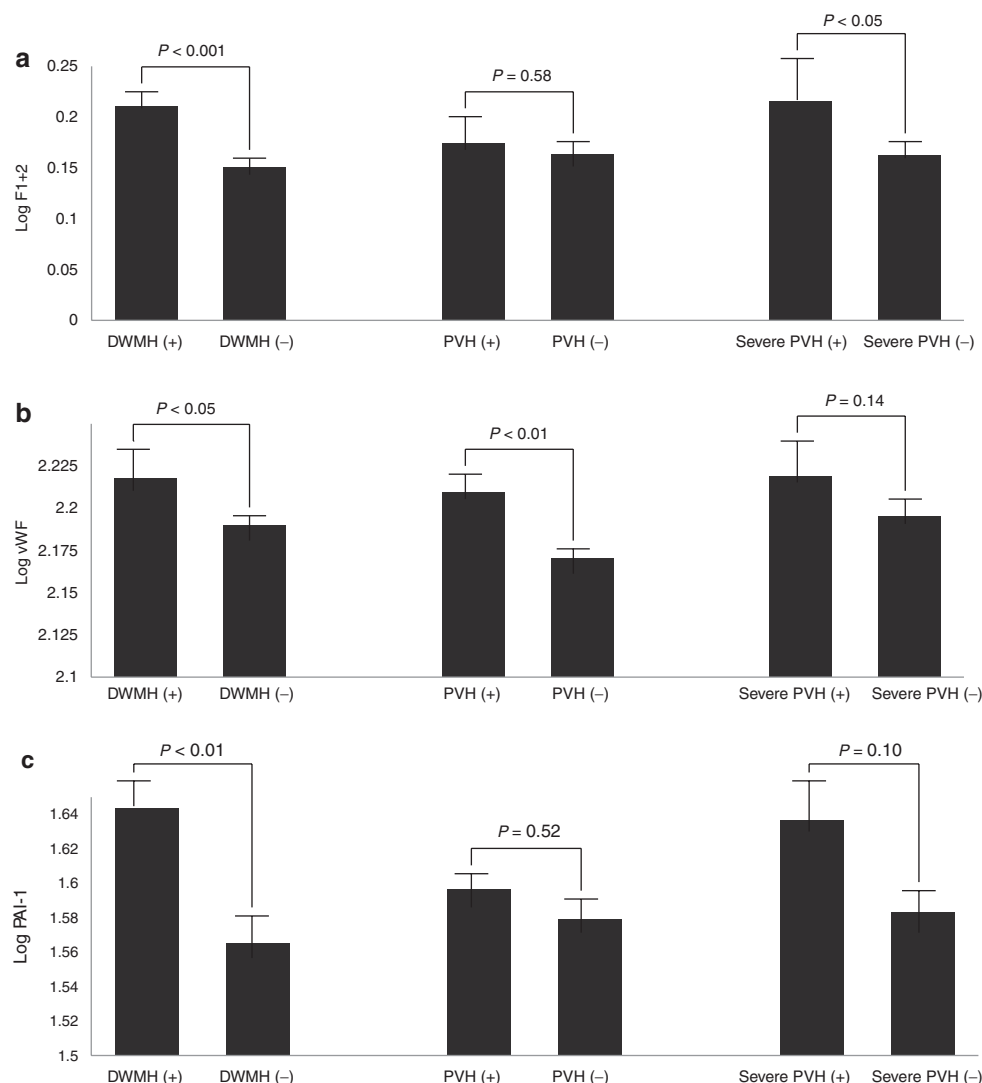


Figure 1 | Mean values of (a) log F1+2, (b) log vWF, and (c) log PAI-1 are presented in patients with and without deep white matter hyperintensity (DWMH), periventricular hyperintensity (PVH), and severe PVH. One-way analysis of variance was used to determine differences between two groups. F1+2, prothrombin fragments 1+2; PAI-1, plasminogen activator inhibitor-1; vWF, von Willebrand Factor.

with atherothrombotic infarction.¹¹ A time course study in patients with stroke suggested that vWF represented continuous and chronic endothelial dysfunction in the cerebral arteries.³⁰ Kohriyama *et al.* reported vWF activity was significantly correlated with PVH grade.¹³ And recent studies have reported the positive relationship between vWF concentration and WMH in elderly hypertensives with cognitive impairment.¹² In these points, although vWF was suggested to serve as a potential surrogate marker for endothelial function, vWF might have a weaker association with WMH in elderly hypertensives compared with those with neurological deficits.

PAI-1 is extensively present in small blood vessels in the white matter,³¹ and this protein was suggested to be involved in mediating neuronal cell damage.³² Although exact mechanisms are still unknown, low activity of PAI-1 is associated with brain tissue damage resulting from NMDA (N-methyl-D-aspartate)-induced ischemia after crossing the blood-brain barrier.^{33,34} On the other hand, in this study, PAI-1 had signifi-

cant positive correlation with DWMH and PVH, while it was significantly associated only with DWMH in the multivariate analysis. In the report by Kario *et al.*, a high level of plasma F1+2 was shown to be a risk factor of stroke in elderly hypertensives.¹⁴ An increased level of PAI-1 might be associated with stroke via cerebral small artery damage.

Hypertension was previously shown to be associated with a prothrombotic state.³⁵ In the follow-up study, Lip *et al.*³⁶ reported that patients with death or adverse cardiovascular events had high plasma vWF level. In the earlier literature, Kario *et al.* reported that the F1+2 level and vWF significantly increased according to the number of silent cerebral infarctions in the elderly at high risk of cardiovascular disease.¹⁵ The results in this study confirmed the previous reports that investigated the relationship between prothrombotic status and silent cerebral injury. Both WMH and silent cerebral infarction are suggested as indicators of microvascular brain injury. However, the pathogenesis of these abnormalities is

Table 2 | Correlation between prothrombotic markers, BP measures, and white matter lesions

		DWMH (n = 177)		PVH (n = 381)		Severe PVH (n = 85)	
		r	P value	r	P value	r	P value
Age (years)		0.174	<0.001	0.299	<0.001	0.187	<0.001
Gender (male = 1, female = 0)		0.045	0.31	0.135	<0.01	0.059	0.18
Body mass index (kg/m ²)		−0.057	0.20	−0.035	0.43	0.007	0.87
Diabetes mellitus ((+) = 1, (−) = 0)		0.077	0.08	0.054	0.22	0.027	0.55
Hyperlipidemia ((+) = 1, (−) = 0)		0.025	0.57	0.012	0.78	0.083	0.06
Smoking ((+) = 1, (−) = 0)		0.084	0.06	0.098	<0.05	0.057	0.20
Antihypertensive agents ((+) = 1, (−) = 0)		−0.003	0.95	0.044	0.31	0.051	0.25
Antiplatelet agents ((+) = 1, (−) = 0)		0.209	<0.001	0.198	<0.001	0.229	<0.001
FBG (mg/dl)		0.004	0.92	0.001	0.51	−0.028	0.53
Total cholesterol (mg/dl)		−0.004	0.92	0.008	0.86	0.022	0.62
Triglycerides (mg/dl)		−0.024	0.59	0.028	0.52	0.058	0.19
HDL cholesterol (mg/dl)		−0.062	0.16	−0.073	0.10	−0.057	0.20
Log F1+2		0.158	<0.001	0.019	0.66	0.086	0.051
Log vWF		0.106	<0.05	0.136	<0.01	0.070	0.11
Log PAI-1		0.139	<0.01	0.021	0.64	0.077	0.08
BP measures							
Clinic	SBP (mm Hg)	0.111	<0.05	0.157	<0.001	0.105	<0.05
	DBP (mm Hg)	0.053	0.23	0.133	<0.01	0.123	<0.01
	PR (bpm)	0.022	0.62	0.010	0.82	0.065	0.24
24-h	SBP (mm Hg)	0.111	<0.05	0.261	<0.001	0.182	<0.001
	DBP (mm Hg)	0.080	0.07	0.195	<0.001	0.160	<0.01
	PR (bpm)	−0.026	0.56	−0.021	0.64	0.045	0.31
White coat hypertension ((+) = 1, (−) = 0)		−0.077	0.08	−0.215	<0.001	−0.163	<0.001
DWMH ((+) = 1, (−) = 0)		—	—	0.308	<0.001	0.394	<0.001
PVH ((+) = 1, (−) = 0)		0.308	<0.001	—	—	0.264	<0.001
Severe PVH ((+) = 1, (−) = 0)		0.394	<0.001	0.264	<0.001	—	—

Correlation coefficients (r) by Spearman's test are shown.
bpm, beats per minute; BP, blood pressure; DBP, diastolic BP; DWMH, deep white matter hyperintensity; F1+2, prothrombin fragments 1+2; FBG, fasting blood glucose; HDL, high-density lipoprotein; PAI-1, plasminogen activator inhibitor-1; PR, pulse rate; PVH, periventricular hyperintensity; SBP, systolic BP; vWF, von Willebrand Factor.

Table 3 | Logistic regression analysis with white matter lesions as dependent factors

	DWMH	PVH	Severe PVH
	Regression coefficient (95% CI), P value	Regression coefficient (95% CI), P value	Regression coefficient (95% CI), P value
Age/year	1.09 (1.06–1.12), <0.001	1.09 (1.06–1.12), <0.001	1.06 (1.02–1.09), <0.001
Gender, male	—	1.63 (0.95–2.81), 0.08	—
Diabetes mellitus	1.20 (0.70–2.08), 0.51	—	—
Hyperlipidemia	—	—	1.76 (0.99–3.12), 0.054
Smoking	1.29 (0.81–2.06), 0.29	1.40 (0.73–2.69), 0.31	—
Antiplatelet agents use	2.23 (1.49–3.33), <0.001	2.28 (1.36–3.83), <0.01	3.02 (1.81–5.04), <0.001
Log F1+2	4.30 (1.49–12.4), <0.01	0.890 (0.27–2.97), 0.89	4.38 (1.12–17.1), <0.05
Log vWF	2.37 (0.53–10.5), 0.26	4.99 (0.99–25.1), 0.051	1.47 (0.20–10.7), 0.70
Log PAI-1	2.26 (1.07–4.74), <0.05	0.695 (0.29–1.66), 0.41	1.46 (0.57–3.72), 0.43
White coat hypertension	1.06 (0.57–1.95), 0.86	0.70 (0.35–1.39), 0.31	0.41 (0.17–0.97), <0.05
24-h SBP (mm Hg)	1.01 (0.995–1.03), 0.16	1.03 (1.01–1.05), <0.05	1.01 (0.99–1.03), 0.24

Parameters were added simultaneously to the regression models.
CI, confidence interval; DWMH, deep white matter hyperintensity; F1+2, prothrombin fragments 1+2; PAI-1, plasminogen activator inhibitor-1; PVH, periventricular hyperintensity; SBP, systolic blood pressure; vWF, von Willebrand Factor.

not fully understood; a diffuse arteriopathy affecting the deep, small, perforating cerebral vessels has been proposed as the mechanism underlying chronic ischemia, ischemic demyelination, axonal loss, and gliosis.^{37,38} Prothrombotic status was suggested as an additional indicator for silent cerebral injury among the elderly at high risk of cardiovascular disease.

Study limitations

This was a post-hoc analysis of the JMS-ABPM study previously conducted for reasons other than examining the relationship between prothrombotic status and WMH. Subjects with MRIs were at higher risk of cardiovascular disease compared with those without MRIs. This study was based on a cross-sectional design. Thus, it is difficult to conclude exactly which measures are causes of WMH. Further prospective studies are needed to investigate whether the increased levels of prothrombotic markers are risk factors of WMH progression. There is a possibility that prothrombotic status was altered secondarily to the cerebral lesions rather than the other way around. In addition, blood samples were not measured repeatedly; thus, there may have been a lack of reproducibility and an underestimation of the true associations of these markers with WMH. Because blood sampling was conducted on a different day from the ABPM, the associations among the prothrombotic status, 24-h SBP, and WMLs might be underestimated in this study. There would be circadian variations in the measurement of prothrombotic markers; unfortunately, there is a lack of data on circadian variation. Measures of F1+2, vWF, and PAI-1 do not constitute all of the markers of prothrombotic status. However, in the earlier literature, those studies that investigated the relationship of prothrombotic status with target organ damage were based on only one marker.^{10,12} Results based on F1+2, vWF, and PAI-1 in this study would thus be more robust regarding the relationship between prothrombotic status and WMH. A significant interaction was found between antiplatelet agent use and log F1+2 for DWMH. Antiplatelet agent use might have affected the relationship between prothrombotic status and WML.

Perspectives

In the present study, F1+2 and PAI-1 were significantly positively associated with WMH after adjustment for 24-h SBP in elderly hypertensives. In addition to conventional risk factors, prothrombotic status might serve as a significant determinant for WMH. Further studies seem warranted to determine whether elderly hypertensives with increased prothrombotic status have a poorer prognosis.

Acknowledgments: This study was supported by a Research Grant for Geriatrics and Gerontology (22-5) from the Ministry of Health, Labor, and Welfare, Japan

Disclosure: The authors declared no conflict of interest.

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