ORIGINAL CONTRIBUTION

The Coagulation-Fibrinolysis System in Patients With Leukoaraiosis and Binswanger Disease

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Background: Hypercoagulability is observed in vascular dementia, including Binswanger disease. However, the correlation between hypercoagulability, leukoaraiosis, and dementia remains unclear.

Objective: To examine how activation of the coagulation fibrinolysis correlates with leukoaraiosis and dementia.

Patients and Methods: Thrombin-antithrombin complex (TAT), prothrombin fragment$_{1+2}$ (F_{1+2}) and cross-linked D-dimer (XDP) were measured consecutively in 18 subjects without dementia and with leukoaraiosis, and in 29 subjects with subcortical vascular dementia and severe leukoaraiosis (Binswanger disease) at either stable or deteriorating stages. They were compared with 19 patients with old lacunar infarctions and 24 patients with other neurological diseases. We also examined the indices of cognitive impairment and brain atrophy. In each group, the ventricular area–cranial space area ratio was measured by an image analyzer.

Results: Patients with Binswanger disease who were exclusively at deteriorating stages showed increased TAT and XDP levels and an increased ventricular area–cranial space area ratio, as compared with the patients with other neurological diseases ($P<.001$). The index of cognitive impairment in patients at a deteriorating stage showed a decreasing trend vs that of patients in the stable stage. Among the variables that were significantly associated with a hypercoagulable condition (ie, age, scores on Mini-Mental State Examination or the Hasegawa Dementia Rating Scale, Revised [MMSE/HDRS], white matter lesions, ventricular area–cranial space area ratio, and C-reactive protein), age (odds ratio [OR], 2.82) and MMSE/HDSR scores (OR, 0.43) survived as predictors for coagulation activation, and C-reactive protein survived for fibrinolysis activation (OR, 4.63) in multivariate analysis.

Conclusion: Hypercoagulability in a subgroup of patients with Binswanger disease and with more severe cognitive impairment and brain atrophy does not support a triggering role for a coagulation-fibrinolysis system, although it may contribute to worsening of neurological deficits.

Arch Neurol. 2001;58:1620-1625

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BINSWANGER DISEASE (BD) is a form of vascular dementia characterized by diffuse white matter lesions and a varying degree of lacunar infarction in the basal ganglia and white matter.[1] Its pathogenesis still remains uncertain, but fibrohyalinosis of the medullary arteries resulting from long-standing hypertension has been thought to cause the white matter lesions.[2,3]

Previous investigations have revealed hematological disorders in patients with BD. β-Thromboglobulin, a marker of platelet activation, increases in blood samples obtained from the internal jugular veins of patients with BD, indicating the activation of platelets in the cerebral circulation.[4] In patients with dementia, the coagulation-fibrinolysis system is also activated,[5] especially in those with vascular dementia.[6] Although there has been no established therapy until recently, these observations may open a new avenue for the treatment of vascular dementia with antiplatelet or antithrombin drugs.[7,8]

White matter lesions in small-artery diseases have previously been shown to correlate with von Willebrand factor activity, but inversely with antithrombin III, an inhibitory factor of the coagulation system regardless of cognitive impairment.[9] In our previous study,[10] the coagulation markers were increased at the later stages of BD; however, it remains unclear whether white matter lesions without cognitive impairment are also associated with hypercoagulability. Our hypothesis is that there may be a causal relationship between hy-

PATIENTS AND METHODS

PATIENTS AND CONTROL SUBJECTS

The study population consisted of 90 patients who were treated at our institute and at affiliated hospitals from March 1997 to December 1999 (**Table 1**). These patients included 18 individuals without dementia with diffuse white matter lesions (leukoaraiosis without dementia group) and 29 patients with BD who had been assigned to this study consecutively. The inclusion for the leukoaraiosis without dementia group was based on the results of the clinical dementia rating (CDR) scale[11] and magnetic resonance imaging (MRI) scans. All subjects in the leukoaraiosis without dementia group had grade 2 or grade 3 white matter lesions irrespective of the number of lacunar infarctions. The diagnosis of BD was based on the clinical diagnostic criteria proposed by Bennett et al.[12] Briefly, all of the patients had dementia, bilateral diffuse subcortical hyperintense lesions (grade 3) on T2-weighted MRI scans, and at least 2 of the following 3 clinical findings: (1) a vascular risk factor or evidence of systemic vascular disease; (2) evidence of focal cerebrovascular disease; and (3) evidence of "subcortical" cerebral dysfunction such as gait disorders, parkinsonism, or incontinence. According to the neurological status, the patients with BD were classified into either the stable or deteriorating group. If there had been focal or subcortical cerebral dysfunction, as described earlier, within the previous 3 months, then those patients were defined as "deteriorating" based on their history, clinical profiles, and a follow-up of their neurological findings.

The lacunar infarction group consisted of 15 symptomatic patients at the chronic stage and 4 asymptomatic patients. The other neurological disease (OND) group consisted of 24 age-matched patients, excluding those with cerebrovascular diseases (6 patients with cervical spondylosis: 3 each with vasovagal syncope and neurosis; 2 each with dizziness, depression, essential tremor, and peripheral neuropathy; and 1 each with migraine, brain tumor, restless leg syndrome, and epilepsy). No one in the lacunar infarction or OND groups had significant white matter lesions classified as grade 2 or grade 3 by the scale devised by Schmidt et al.[13]

INVESTIGATIONS

The psychometric assessment consisted of CDR and Mini-Mental State Examination administered in Japanese or the Hasegawa Dementia Rating Scale, Revised (MMSE/HDSR). Peripheral blood samples were drawn from the antecubital vein of the nonparalyzed arm, with minimal stasis, by means of a clean venipuncture. The blood samples were collected into siliconized tubes that contained one-tenth volume of 3.8% trisodium citrate, and were then centrifuged at 2300*g* for 15 minutes at room temperature. These plasma samples were stored at –70°C until used. The concentration of thrombin-antithrombin complex (TAT), prothrombin fragment$_{1+2}$ (F_{1+2}), and cross-linked D-dimer (XDP) was measured by enzyme-linked immunosorbent assays. Samples with TAT values above the detection limit of the assays (60 ng/mL) were excluded from further analysis because they were considered to be likely artifacts. In each patient, brain MRI scans were performed to measure the size of the brain.

IMAGE ANALYSIS

Using computer-assisted image analysis of the MRI, the ventricular area–cranial space area ratio was measured as an index of brain atrophy as previously described.[14] Briefly, monochromatic photo images of the MRI at the level of the basal ganglia and thalamus were digitized on a Macintosh computer (PC7500; Apple Computers, Cupertino, Calif) with an LS-1000 film scanner (Nikon, Tokyo, Japan) at a resolution of 1350 dots per inch. The images were stored as 8-bit gray scale JPEG files (256 shades of gray), and the image files were analyzed using National Institutes of Health image analyzer software (National Institutes of Health, Bethesda, Md).

STATISTICAL ANALYSIS

The statistical significance of the intergroup differences was assessed by the χ^2 test for categorical variables and by the Kruskal-Wallis and Mann-Whitney *U* tests for continuous variables using StatView II software (version 5.0 for Macintosh; SAS Institute, Cary, NC). The association between the hemostatic markers and other variables was first tested by a univariate logistic regression analysis. Covariates significant at the $P<.05$ critical level were entered into the multivariate model.

percoagulability and dementia. To understand whether this may be a trigger or epiphenomenon during cognitive decline, it is important to assess the coagulation-fibrinolysis system during the preclinical or early stages of subcortical vascular dementia. In the present study, we determined the causes of coagulation-fibrinolysis system activation in patients with white matter lesions, manifesting dementia, or no dementia and compared them with those in subjects with normal white matter as the control group.

RESULTS

The 29 patients with BD all showed confluent or irregular periventricular hyperintensities on their MRI scans, with varying degrees of lacunar infarction in the basal ganglia and white matter. The severity of the dementia was mild to severe, with CDR scores ranging from 1 to 3 and with MMSE/HDSR scores between 8/30 and 22/30. Other abnormal neurological findings included abulia, unsteady gait, dysarthria, incontinence, sensory deficits, and hemiparesis. None of the patients with BD fulfilled the modified version of the clinical criteria on disseminated intravascular coagulation established by the Research Committee of the Japanese Ministry of Health and Welfare (Tokyo).[15] Family history was unremarkable in these patients.

The patients with BD were classified into the stable group (11 patients) or the deteriorating group (18 patients who showed subacute aggravation of either focal or "subcortical" cerebral dysfunctions) (Table 1). In the stable group, no obvious focal neurological deficits had emerged during the past 3 months, whereas 6 of the 18 deteriorating patients with BD had evidence of recent lacunar in-

Table 1. Demographic Features of the Patients Evaluated*

Variable	WM Lesion Group			No WM Lesion Group		
	Leukoaraiosis Without Dementia	BD Stable	BD Deteriorating	Lacunar Infarction	Other Neurological Disease	*P* Value†
No. of patients	18	11	18	19	24	
Mean age (range), y	73 (58-85)	71 (54-86)	75 (67-83)	72 (62-82)	72 (65-85)	.53
Proportion of women, %	67	45	56	40	75	.11
Cigarette smoking, No. (%)	1 (6)	2 (18)	3 (17)	5 (26)	3 (13)	.51
Hypertension, No. (%)	17 (94)§	9 (82)	16 (89)‡	14 (74)	10 (42)	<.001
BP control, systolic BP >140 mm Hg, No. (%)	10 (56)	4 (38)	10 (56)	7 (37)	5 (21)	.11
Microalbuminuria, No. (%)	4 (22)	6 (55)‡	8 (44)‡	6 (32)	2 (8)	.03
Diabetes mellitus, No. (%)	3 (17)	1 (9)	5 (28)	4 (21)	3 (13)	.68
Previous stroke, No. (%)	8 (44)‡	4 (36)	14 (78)§	15 (79)§	0 (0)	<.001
Previous MI, No. (%)	4 (22)	1 (9)	2 (11)	2 (11)	1 (4)	.50
Comorbidity that may enhance coagulability, No. (%)	7 (39)	6 (55)	5 (28)	9 (47)	5 (21)	.22
Use of antiplatelet drugs, No.	3 (17)	3 (27)	2 (11)	9 (47)	4 (17)	.21
Use of anticoagulants, No.	1 (6)	0 (0)	0 (0)	1 (5)	0 (0)	.20
Use of statins, No.	8 (44)	2 (18)	4 (22)	4 (21)	6 (25)	.43
Total cholesterol, mg/dL	203 ± 37	175 ± 28	202 ± 44	192 ± 25	207 ± 29	.19
Triglyceride, mg/dL	120 ± 33	91 ± 36	112 ± 52	119 ± 53	155 ± 112	.41
Hematocrit, %	38.5 ± 5.4	38.0 ± 4.6	36.0 ± 5.8	39.5 ± 5.8	36.0 ± 5.8	.27
White blood cell count, /μL × 10^3	5.8 ± 2.5	6.1 ± 1.1	6.4 ± 1.8	5.8 ± 1.6	6.1 ± 1.8	.72
CRP, μg/mL	0.4 ± 0.6	2.5 ± 5.1	1.9 ± 2.5	0.8 ± 1.1	0.3 ± 0.3	.02

*Data are presented as mean ± SD unless otherwise indicated. The lacunar infarction group includes 4 patients with asymptomatic cerebral infarction. WM indicates white matter; BD, Binswanger disease; BP, blood pressure; MI, myocardial infarction; and CRP, C-reactive protein.
†The Kruskal-Wallis test was used for continuous variables; χ^2 test for categorical variables.
‡$P<.01$ vs other neurological disease group by the Mann-Whitney *U* test and the χ^2 test.
§$P<.001$ vs other neurological disease group by the Mann-Whitney *U* test and the χ^2 test.

Table 2. Indices of the Coagulation-Fibrinolysis System Among Different Groups*

Level	WM Lesion Group			No WM Lesion Group		
	Leukoaraiosis Without Dementia (n = 18)	BD Stable (n = 11)	BD Deteriorating (n = 18)	Lacunar Infarction (n = 19)	Other Neurological Disease (n = 24)	*P* Value†
TAT, ng/mL	3.3 ± 2.0	3.5 ± 1.6	19.7 ± 17.6‡	3.7 ± 2.0	3.2 ± 1.4	<.001
F_{1+2}, nmol/mL	1.0 ± 0.6	1.5 ± 0.8	2.1 ± 1.9	1.4 ± 0.4	1.3 ± 0.4	.02
D-dimer, ng/mL	140 ± 76	138 ± 41	584 ± 493‡	128 ± 88	123 ± 89	<.001
Fibrinogen, mg/mL	277 ± 39	382 ± 141	361 ± 127	307 ± 67	295 ± 53	.01

*Data are presented as mean ± SD. WM indicates white matter; BD, Binswanger disease; TAT, thrombin-antithrombin complex; F_{1+2}, prothrombin fragment$_{1+2}$; and XDP, cross-linked D-dimer.
†The Kruskal-Wallis test was used.
‡$P<.001$ vs other neurological disease group by Mann-Whitney *U* test.

farctions, and 4 of those showed mild hemiparesis. The lacunae observed on the MRI scan were judged to be responsible for the deterioration if they appeared to be fresh or if they corresponded with the emerging neurological deficits or "subcortical" dysfunction. Antiplatelet drugs were prescribed in 3 of the 11 stable patients with BD, and in 2 out of the 18 deteriorating patients with BD before the aggravation. Anticoagulants were not used in either group.

There were no significant differences in age between the leukoaraiosis without dementia, BD, lacunar infarction, and OND groups (Table 1). Among demographic variables, hypertension and previous stroke were more frequent in the former 3 groups, and microalbuminuria and the elevated C-reactive protein (CRP) values were more frequent in the BD group (Table 1).

The number of lacunae did not differ among the groups, except for the OND group. No significant white matter lesions were observed in either the OND or lacunar infarction group. The scores on the MMSE/HDSR and CDR remained within the normal range in the leukoaraiosis without dementia, lacunar infarction, and OND groups. On the contrary, the mean±SD MMSE/HDSR scores were 16.9±4.9 and 12.2±5.8 in the stable and deteriorating BD groups, respectively, and the mean±SD CDR scores were 1.50±0.58 and 2.31±0.86, respectively, showing a trend toward worsening in the latter BD group ($P=.09$ for the MMSE/HDSR and $P=.09$ for the CDR). The mean±SD ventricular area–cranial space area ratios were 9.9±3.2 in the leukoaraiosis without dementia group, 10.3±2.7 in the stable BD group, 12.6±4.5 in the deteriorating BD group, 9.5±2.2 in the lacunar infarction group, and 7.0±2.3 in the OND group. There were intergroup differences in this ratio, with the deteriorating BD group's being higher ($P<.01$) than that of the OND group.

Table 3. Factors Associated With Activation of the Coagulation-Fibrinolysis System Using a Logistic Regression Model*

Analysis Variables	TAT>7.0 ng/mL		XDP>300 ng/mL	
	OR† (95% CI)	*P* Value	OR† (95% CI)	*P* Value
Univariate analysis‡				
Age	2.29 (1.20-4.70)	.01	2.04 (0.96-4.73)	.05
MMSE/HDSR score	0.37 (0.23-0.64)	<.001	0.45 (0.26-0.83)	.01
Leukoaraiosis	1.91 (1.11-5.09)	.005	2.27 (1.01-16.48)	.02
V/CS ratio	2.63 (1.38-5.64)	<.001	1.95 (1.04-4.16)	.03
CRP level	3.60 (1.10-18.58)	.02	13.72 (1.74-361.04)	<.001
Multivariate analysis				
Age	2.82 (0.80-13.20)	.05	. . .	. . .
MMSE/HDSR score	0.43 (0.18-1.29)	.09	. . .	. . .
CRP level		. . .	4.63 (0.86-67.49)	.04

*TAT indicates thrombin-antithrombin complex; XDP, cross-linked D-dimer; OR, odds ratio; CI, confidence interval; MMSE, Mini-Mental State Examination; HDSR, Hasegawa Dementia Rating Scale, Revised; V/CS, ventricular area–cranial space area; CRP, C-reactive protein; and ellipses, not significant.

†The OR for continuous variables refers to a change in each quintile.

‡Age, female sex, cigarette smoking, hypertension, poor blood pressure control, microalbuminuria, diabetes mellitus, previous stroke, previous myocardial infarction, comorbidity that may enhance coagulability, use of antiplatelet drugs, anticoagulants or statins, total cholesterol level, triglyceride level, hematocrit, white blood cell count, CRP level, number of lacunae, leukoaraiosis, V/CS ratio, and the MMSE/HDSR score were included in this model. The variables were retained in the multivariate analysis when $P<.10$.

In the leukoaraiosis without dementia, stable BD, and lacunar infarction groups, the TAT, F_{1+2}, and XDP levels did not differ from those in the OND group (**Table 2**). In contrast, the patients with deteriorating BD showed higher TAT and XDP levels ($P<.001$) as compared with patients in the OND group. There were intergroup differences, with higher F_{1+2} and fibrinogen values in the patients with BD (Table 2).

The multivariable relationship between the 5 predictor variables and the 2 outcome variables is presented in **Table 3**. Age, the MMSE/HDSR score, leukoaraiosis, ventricular area–cranial space area ratio, and CRP levels were significant predictors for activation of the coagulation-fibrinolysis system as determined by a TAT level of greater than 7.0 ng/mL and and an XDP level of greater than 300 ng/mL. Age was a significant predictor for an F_{1+2} level of greater than 1.8 nmol/mL. For more definitive analysis, these parameters were entered into a multivariate model as predictors of a TAT level of greater than 7.0 ng/mL and an XDP level of greater than 300 ng/mL. Only age and the MMSE/HDSR scores were retained in this model, with $P<.10$ as a predictor for the TAT values and the CRP levels as a predictor for the XDP values.

COMMENT

The white matter lesions are characterized pathologically by incomplete infarction, état criblé , perivascular demyelination, and gliosis; they correspond mostly to leukoaraiosis on radiological diagnosis.[16,17] A clinicopathologic correlation using MRI and autopsy specimens underscores the validity of the diagnostic criteria for BD,[18] although the autopsy findings are generally more comprehensive and decisive for the diagnosis of BD.

During the group comparisons, the coagulation-fibrinolysis system remained normal in the leukoaraiosis without dementia group, but was activated in a subgroup of the patients with BD (Table 2), who had been shown to have brain atrophy and more severe dementia. On multivariate analysis, age and cognitive impairment were predictors for coagulation activation, and the CRP levels were predictors for fibrinolysis activation. Brain atrophy and leukoaraiosis were significantly correlated with coagulation-fibrinolysis system activation on the univariate analysis; however, these 2 factors were not independent predictors on the multivariate analysis.

On the diffusion-weighted MRI scans, hyperintense lesions frequently emerged in patients with a stepwise decline in vascular dementia.[19] Therefore, the frequency of fresh lacunar infarctions in the patients with deteriorating BD (33%) may vary depending on the sensitivity of the detection method. However, since neurological deterioration frequently occurs throughout an extended period, and the coagulation-fibrinolysis system is not activated even at the acute stage of lacunar infarction without extensive white matter lesions,[20] the deterioration may not necessarily result from the lacunar infarctions per se. It is more likely that the deterioration observed in BD is related to diffuse small-artery disease and subsequent microcirculatory disturbances, with or without lacunar infarction.

There may be a concern for artifactual increases in the TAT levels or high variability resulting from its short half-life. However, this possibility seems unlikely since the outlier TAT values were eliminated from the present analysis, and the TAT levels strongly correlated to the D-dimer levels, which have a much longer half-life. The hemostatic markers may be elevated in disseminated intravascular coagulation, peripheral arterial disease, pancreatitis, pregnancy, and metastatic carcinoma; however, none of these conditions were found in a significant proportion in the present study. Hypercoagulability may also be encountered in very elderly people, without any complications,[21] but this possibility has been excluded. Considering that hypercoagulability was not observed in the leukoaraiosis without dementia group and was associated with brain atrophy or more severe dementia in the BD group, other factors besides the coagulation-fibrinolysis system may be a trigger for this pathologic process.

Cerebral blood flow is decreased, with oxygen extraction fraction being elevated, in subjects with leukoaraiosis without dementia.[22] Therefore, chronic cerebral ischemia may initiate the pathologic process of white matter lesions. In a rat model, white matter lesions can be induced by chronic cerebral hypoperfusion after clipping the common carotid arteries bilaterally.[23] Astroglia and microglia, being activated in white matter lesions in both rat and humans,[23,24] may mediate the inflammatory response by secreting cytotoxic substances such as proinflammatory cytokines, reactive oxygen intermediates, and nitric oxide, and may thus contribute to their pathogenesis.

Both CRP and fibrinogen are acute phase–reactant in inflammation. C-reactive protein enhances the production of tissue factor and proinflammatory cytokines, interleukin 1, and tumor necrosis factor α by monocytes and macrophages.[25,26] High CRP values in association with elevated XDP levels in the patients with BD may result from subclinical infection, but may alternatively reflect an inflammatory response after cerebrovascular disease.[27-29] An increase of fibrinogen has been previously reported in patients with BD.[30,31] It is generally agreed that high levels of fibrinogen, one of the major determinants of plasma viscosity, have a hemorheological effect, and may lead to a state of hypoperfusion that results in impaired cerebral microcirculation.[32] This effect may be especially true in brains with BD, in which the medullary arteries, arterioles, and capillaries are thickened by fibrohyalinosis.[3]

Although it may occur at the later stages of BD, thrombin generation is likely to cause microcirculatory disturbances by way of endothelial activation.[33] Thrombin may also damage neural tissues directly by enhancing vascular permeability,[34] inducing apoptosis in the neurons[35] and nitric oxide in the glial cells, as well as by a suppression of neurite outgrowth.[36] Several lines of clinical evidence also suggest that activation of the coagulation-fibrinolysis system may further aggravate the neurological status of patients with BD. First, white matter lesions and dementia are frequently observed in hypercoagulable conditions related to activated protein C resistance.[37,38] Second, its sustained activation may be a risk for recurrence of ischemic cerebrovascular diseases.[39] Finally, antithrombin drugs seemed to be effective in the treatment of vascular dementia, including BD, in preliminary trials.[9,40] Therefore, further studies seem warranted to determine whether coagulation-fibrinolysis system activation may exacerbate the neurological dysfunction in patients with BD, and whether those patients with coagulation-fibrinolysis system activation have a poorer prognosis.

Accepted for publication May 14, 2001.

This work was supported by a grant from the Takeda Medical Research Foundation (Osaka, Japan) and a grant from the Sasagawa Foundation (Tokyo).

We are grateful to Midori Yotsutsuji, BA, Satoshi Ogura, MD (Koseikai Takeda Hospital, Kyoto), and Masamiori Hayashi, MD (Kyoto Second Red Cross Hospital, Kyoto) for their help in sampling the data.

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