ORIGINAL CONTRIBUTION

Coagulation Activation in Patients With Binswanger Disease

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Background: A hypercoagulable state is often associated with an acute stroke in cerebrovascular disease (CVD). However, in Binswanger disease (BD), no information is available on the coagulation-fibrinolysis pathway except for the presence of high plasma fibrinogen levels.

Objective: To determine the association of BD and coagulation-fibrinolysis pathway activation.

Patients and Methods: We examined the levels of fibrinogen, thrombin-antithrombin complex, prothrombin fragment$_{1+2}$, and cross-linked D-dimer in 17 patients with BD, 24 neurologic patients without CVD, and 26 patients with lacunar infarction in either the acute or chronic stage.

Results: As compared with the non-CVD and lacunar infarction groups, the patients with BD had significantly elevated levels of thrombin-antithrombin complex ($P<.001$), prothrombin fragment$_{1+2}$ ($P<.05$), and cross-linked D-dimer ($P<.01$). There was also a significant increase in fibrinogen levels compared with the non-CVD group ($P<.05$). In the BD group, 8 patients in stable condition (ie, those without obvious neurologic deficits in the past 3 months) showed normal levels or a mild increase in their fibrinogen, thrombin-antithrombin complex, prothrombin fragment$_{1+2}$, or cross-linked D-dimer levels. In contrast, 9 patients with BD with a subacute aggravation of their focal or subcortical cerebral functions (deteriorating group) showed a significant increase in their thrombin-antithrombin complex levels compared with the stable patients ($P<.01$). Similarly, the fibrinogen, prothrombin fragment$_{1+2}$, and cross-linked D-dimer levels were elevated in the deteriorating patients, but this trend did not reach statistical significance.

Conclusions: These results indicate that the coagulation-fibrinolysis pathway is activated in patients with BD with a subacute aggravation. Coagulation activation may result in the formation of microthrombi and microcirculatory disturbances in the brains of these patients, and thus promote further biological and neurologic insults.

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A HYPERCOAGULABLE state is often encountered in the acute stages of cerebrovascular disease (CVD). Studies in which hemostatic markers were used have shown a rapid activation of the coagulation-fibrinolysis pathway after a stroke.[1-4] The degree of activation differs between different types of stroke, with cerebral embolism being the most marked followed by atherothrombotic infarction.[5] However, some investigators have shown that abnormalities in the coagulation-fiblinolytic pathway are not as important in patients with penetrating artery disease.[6,7]

Binswanger disease (BD) is a condition characterized by prominent brain atrophy with ventricular dilation, diffuse white matter lesions, and a scattering of lacunar infarcts in the basal ganglia and white matter. Patients with BD have dementia, and often have vascular risk factors, focal cerebrovascular deficits, and subcortical cerebral dysfunction.[8] Although hypertensive small artery disease and medullary artery sclerosis have been implicated in the pathogenesis of these white matter lesions, as well as multiple lacunae,[9-12] only a few authors have addressed the alterations in the hemorheological parameters that may affect the cerebral microcirculation in BD. The release of β-thromboglobulin into the cerebral circulation, which is an indicator of platelet activation, is increased in patients with BD.[13] Plasma hyperviscosity and elevated fibrinogen levels are striking abnormalities in patients with BD, and are believed to deteriorate to chronic ischemia, thus promoting the process of demyelination.[11,14] However, a therapeutic approach using ancrod, a defibrinating agent, has proven ineffective.[15] To our knowledge, there have been no reports on the coagulation-fibrinolysis pathway in patients with BD.

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PATIENTS AND METHODS

PATIENTS AND CONTROL SUBJECTS

The study population consisted of 67 patients treated at Kyoto University, Kyoto, Japan, and affiliated hospitals from March 1996 to February 1998. These included 17 patients with BD who were assigned to this study consecutively. The diagnosis of BD was based on the clinical diagnostic criteria proposed by Bennett et al.[8] Briefly, all of the patients had dementia, bilateral diffuse subcortical hyperintense lesions on T_2-weighted magnetic resonance imaging (MRI), 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 CVD; and (3) evidence of subcortical cerebral dysfunction such as gait disorders, parkinsonism, or incontinence. The neurologic status of patients with BD was judged to be deteriorating or stable; ie, if there was either focal or subcortical cerebral dysfunction, as described above, within the past 3 months, the patients were classified as deteriorating based on the history of their clinical profile and a follow-up of their neurologic findings; otherwise the patient was defined as stable.

The control population consisted of 24 age-matched neurologic patients with nonvascular diseases (non-CVD group) such as cervical spondylosis, peripheral neuropathy, Parkinson disease, Alzheimer disease, spinocerebellar ataxia, depression, and essential tremor. The lacunar infarction group included 26 age-matched patients whose diagnoses were based on neurologic examination and MRI findings. All of the patients in this group showed a few lacunae but no significant white matter lesions. The interval between the stroke and the blood sampling was 1 month in 10 patients, 1 to 3 months in 3 patients, and 3 to 55 months in 13 patients.

INVESTIGATIONS

The psychometric assessment consisted of a Mini-Mental State Examination (MMSE) or a Hasegawa Dementia Rating Scale–Revised administered in Japanese.[16] Brain computed tomography and MRI were performed to determine the presence of diffuse white matter lesions and lacunar infarcts. Peripheral blood samples were drawn by venipuncture from an antecubital vein of the nonparalyzed arm, with minimal stasis. They were collected in siliconized tubes that contained a one-tenth volume of 3.8% trisodium citrate, centrifuged at 2300*g* for 15 minutes at room temperature, and stored at −70°C until used. The concentration of the coagulation markers (thrombin-antithrombin complex [TAT] and prothrombin fragment$_{1+2}$ [F_{1+2}]) and the fibrinolytic marker (cross-linked D-dimer [XDP])[17] were measured by enzyme-linked immunosorbent assays. The normal values were as follows: TAT concentration, lower than 3.0 ng/mL; F_{1+2}, lower than 1.2 nmol/mL; and XDP, lower than 150 ng/mL.

STATISTICAL ANALYSIS

Differences between the ages of each group were determined by a 1-factor analysis of variance followed by the Fisher protected least significant difference procedure between each group using StatView II software, version 4.5, 1995 (Abacus Concepts Inc, Berkeley, Calif), for a Macintosh computer. The differences between the groups for the fibrinogen, TAT, F_{1+2}, and XDP levels were determined by the Mann-Whitney *U* test. The association between the TAT values and the patient characteristics was analyzed using multiple regression analysis. A P value $<.05$ indicated statistical significance.

In the present investigation, we examined the plasma levels of several hemostatic markers in patients with BD and compared them with those of neurologic patients without CVD as well as patients with lacunar infarction.

RESULTS

The 17 patients with BD all showed confluent or irregular periventricular hyperintensities on their MRI scans judged to be grade 3 by the Schmidt scale,[18] with varying degrees of lacunar infarction in the basal ganglia and white matter. The severity of the dementia was mild to moderate, with the MMSE/Hasegawa Dementia Rating Scale–Revised scores ranging from 8/30 to 21/30. Other abnormal neurologic findings included abulia, an unsteady gait, dysarthria, incontinence, sensory deficits, and hemiparesis. None of the patients with BD fulfilled the modified version of the criteria established by the Research Committee on Disseminated Intravascular Coagulation (DIC) of the Japanese Ministry of Health and Welfare.[19] The mean (range) prothrombin time was 12.8 (11.1-21.0) seconds; activated partial thromboplastin time, 31.0 (22.2-48.4) seconds; and platelet count, 0.21 (0.13-0.32) $\times$ 10^9/L.

The patients with BD were subdivided into 8 neurologically stable patients (stable group) and 9 patients who showed a subacute aggravation of either focal or subcortical cerebral dysfunctions (deteriorating group). No obvious focal neurologic deficits had been noted within the past 3 months in the stable patients, whereas 4 of the 9 deteriorating patients had evidence of recent lacunar infarctions (**Table 1**; patients 9, 10, 15, and 16) and 3 of these patients showed mild hemiparesis. Since patients with BD usually have lacunar infarcts visible on MRI scans, the lacunae were thought to be responsible for the deterioration if the MRI studies indicated a recent infarction or the location of the lacunae corresponded to the emerging neurologic deficits or subcortical dysfunction. Antiplatelet drugs were prescribed in 3 of 8 stable patients and in 1 of 9 deteriorating patients before the aggravation. An anticoagulant was not used in either group.

There was no significant difference in age between the non-CVD, lacunar infarction, and BD groups. Although hypertension was more frequent in the lacunar infarction and BD groups than in the non-CVD group, there were no significant differences in other risk factors between these groups (**Table 2**). In the lacunar infarction group, there were no significant increases in the fibrinogen, TAT, F_{1+2}, or XDP levels compared with the non-CVD group. This was also true of the patients with lacunar infarction in the acute stage who had strokes

Table 1. Clinical Profiles and Levels of Hemostatic Markers in Patients With Binswanger Disease*

Patient No./ Age, y/Sex	Complication	CRP, mg/dL	Plt, $\times 10^9$/L	FDP, ng/mL	Fibrinogen, mg/dL	TAT, µg/mL	F_{1+2}, nmol/L	XDP, ng/mL
			Stable					
1/62/F	HT	<0.3	0.22	<10.0	704	3.9	1.41	ND
2/75/M	AP	<0.3	0.20	<10.0	310	3.0	1.65	121
3/77/F	HT, OMI	<0.3	0.23	<10.0	367	2.6	2.44	180
4/77/F	hx HT, Af	<0.3	0.20	<10.0	283	2.6	1.10	129
5/57/M	hx HT	<0.3	0.26	<10.0	260	2.3	0.82	200
6/71/M	hx HT	ND	0.22	<10.0	437	3.1	ND	155
7/76/F	hx HT, epilepsy	<0.3	0.18	ND	251	4.1	3.05	ND
8/66/M	Colon cancer (postoperative)	<0.3	0.15	<10.0	220	2.9	0.74	103
Mean ± SD age, 70 ± 8			0.21 ± 0.03		354 ± 158	3.1 ± 0.6	1.6 ± 0.9	148 ± 37
			Deteriorating					
9/70/F	HT, hx thalamic hemorrhage	<0.3	0.27	<10.0	287	3.1	0.94	121
10/69/F	hx HT, DM	<0.3	0.17	<10.0	248	4.3	1.42	107
11/78/F	HT, OMI, AA	<0.3	0.21	<10.0	248	17.9	1.99	351
12/73/F	HT, hyperlipidemia	8.74	0.25	14.5	715	10.1	1.77	1225
13/72/M	HT, Ménière disease	<0.3	0.17	<10.0	439	5.3	0.63	ND
14/79/F	HT, AA	0.66	0.13	12.2	386	10.1	3.01	403
15/68/M	HT	ND	0.18	20.0	494	23.2	2.77	554
16/76/M	OMI	5.2	0.32	<10.0	405	28.7	ND	355
17/80/F	HT	0.34	0.13	<10.0	305	38.3	8.02	1021
Mean ± SD age, 74 ± 5			0.20 ± 0.07		392 ± 149	15.7 ± 12.3†	2.6 ± 2.4	517 ± 405

CRP indicates C reactive protein; Plt, platelet count; FDP, fibrinogen degradation products; TAT, thrombin-antithrombin complex; F_{1+2}, prothrombin fragment$_{1+2}$; XDP, cross-linked D-dimer; AP, angina pectoris; HT, hypertension; hx, history of; Af, atrial fibrillation; ND, not done; DM, diabetes mellitus; OMI, old myocardial infarction; and AA, aortic aneurysm.

†P<.01 *for the difference from the stable subgroup by the Mann-Whitney* U *test.*

Table 2. Summary of the Patient Profiles and Laboratory Findings*

Characteristic	Non-CVD	Lacunar Infarction	Binswanger Disease
No. of Patients	24	26	17
Mean age, y	67	68	72
Sex (male/female)	8/16	18/8	7/10
Hypertension	10/24 (42)	22/26 (81)	15/17 (88)
Diabetes mellitus	4/24 (17)	7/26 (26)	1/17 (6)
Noncerebral vascular lesions†	5/24 (21)	5/26 (19)	5/17 (29)
Total cholesterol, >5.69 nmol/L (220 mg/dL)	7/24 (29)	5/26 (19)	2/17 (12)
Triglycerides, 1.69 mmol/L (150 mg/dL)	7/24 (29)	9/26 (35)	2/17 (12)
Hematocrit, >0.45	3/24 (13)	4/26 (15)	2/17 (12)
White blood cell count, $>9.0 \times 10^9$/L	1/24 (4)	0/26 (0)	2/17 (12)
C-reactive protein, >1.0	1/23 (4)	1/26 (4)	2/15 (13)

Unless otherwise indicated, data are given as the number of patients with the given characteristic/the number of patients evaluated (percentage). CVD indicates cerebrovascular disease.

†*Noncerebral vascular lesions include aortic aneurysms, old myocardial infarctions, and peripheral arterial diseases.*

within the past month, with the mean ± SD level for fibrinogen being 326.9 ± 74.6 mg/dL; TAT, 1.8 ± 0.7 mg/mL; F_{1+2}, 0.7 ± 0.1 nmol/L; and XDP, 83.0 ± 35.2 ng/mL.

The patients with BD showed significantly higher TAT ($P<.001$), F_{1+2} ($P<.05$), and XDP ($P<.01$) levels compared with the non-CVD and lacunar infarction groups (Mann-Whitney *U* test; **Table 3**). The association between TAT values and patient characteristics, including disease category, age, sex, smoking history, hypertension, diabetes mellitus, antiplatelet therapy, noncerebral vascular lesions, total cholesterol and triglyceride levels, hematocrit, leukocyte count, and C-reactive protein, was assessed by multiple linear regression analysis. The coefficient of determination (R^2) was 0.541, and the multiple correlation coefficient was 0.735. Among the 13 explanatory variables, only the disease category correlated significantly with the TAT value ($P<.05$). The patients with BD also showed significantly higher fibrinogen levels than the non-CVD group ($P<.05$, Mann-Whitney *U* test). The stable patients with BD often showed slightly elevated levels of fibrinogen, TAT, F_{1+2}, and XDP compared with the non-CVD group, but this was not significant. The deteriorating patients with BD occasionally showed abnormally high values for these 4 hemostatic markers, regardless of the presence or absence of fresh lacunar infarctions. The concentration of TAT in the deteriorating group was significantly higher than in the stable group ($P<.01$, Mann-Whitney *U* test; Table 1).

Table 3. Hemostatic Markers for the Subgroups*

Marker	Non-CVD	Lacunar Infarction	Binswanger Disease
Fibrinogen, mg/mL	273 ± 56	311 ± 70	374 ± 149†
TAT, ng/mL	2.8 ± 1.4	2.8 ± 1.8	9.7 ± 10.8‡
F_{1+2}, nmol/mL	1.2 ± 0.6	1.1 ± 0.5	2.1 ± 1.8§
XDP, ng/mL	106 ± 76	100 ± 70	315 ± 350‖

*All data are given as means ± SDs. CVD indicates cerebrovascular disease; TAT, thrombin-antithrombin complex; F_{1+2}, prothrombin fragment$_{1+2}$; and XDP, cross-linked D-dimer.
†P<.05 compared with the non-CVD group.
‡P<.001 compared with the lacunar infarction and non-CVD groups.
§P<.05 compared with the lacunar infarction and non-CVD groups.
‖P<.01 compared with the lacunar infarction and non-CVD groups.

Similarly, the fibrinogen, F_{1+2}, and XDP levels were elevated in the deteriorating group, but this trend did not reach statistical significance.

COMMENT

Recent advances in radiological diagnosis have demonstrated that BD is far more common than originally thought, and increasing attention has been paid to BD not only in Europe and Japan, but also in North America.[1,15,20] The pathogenesis of BD and the difference between BD and the multiple lacunar infarctions that accompany the white matter lesions remain unclear.[9] However, it is likely that chronic cerebral ischemia is common to these 2 diseases.[21] In addition, it has been suggested that these white matter lesions may be caused by arterial hypertension and a subsequent dysfunction of the blood-brain barrier.[22-24] A compromised blood-brain barrier may permit the entry of macromolecules and other blood constituents into the vascular wall and perivascular neural parenchyma,[25] and these serum components may subsequently damage the myelin structures.

In the present study, the patients with BD showed significantly higher fibrinogen, TAT, F_{1+2}, and XDP values, especially in the deteriorating group. Activation of the coagulation-fibrinolysis pathway has been observed during the acute stage of cardioembolic stroke and aneurysmal subarachnoid hemorrhage.[4-6,26] In some studies, the levels of TAT and other molecular markers were reported to be increased in poststroke patients, suggesting a sustained enhancement of the coagulation system in the chronic stages of stroke.[27,28] Activation of the coagulation-fiblinolysis pathway may have unfavorable effects on cerebral microcirculation through a hemorheological mechanism rather than clotting the vessels. This mechanism may exert particular effect on thickened small arteries, in which any form of hemostasis can easily cause microcirculatory failure.

Levels of fibrinogen, one of the major determinants of plasma viscosity, are elevated in patients with marked white matter lesions compared with those with slight abnormalities.[1] The plasma viscosity also has an important hemorheological impact on the cerebral microcirculation.[29] Therefore, high fibrinogen levels may contribute to the chronic cerebral ischemia observed in BD, although the neurologic deterioration seems to occur regardless of the plasma fibrinogen levels.

The hemostatic markers are also elevated in disseminated consumption coagulopathy,[17] metastatic carcinoma,[30] pancreatitis,[30] pregnancy,[31] peripheral arterial disease,[32] and acute atrial fibrillation after pharmacological cardioversion.[33] Although the hemostatic markers were elevated in those patients with BD with a subacute aggravation, most patients did not experience such problems. In addition, the frequency of noncerebral vascular lesions was not increased in the patients with BD compared with the other 2 groups. Although the fresh lacunar infarctions may have some effect on hemostatic markers, coagulation system activation was not observed even in the acute stages of lacunar infarction, and also was not related to their concomitant presence in deteriorating patients with BD. Therefore, the increase in hemostatic markers observed in the deteriorating patients with BD can be attributed to an activation of the coagulation-fibrinolysis pathway occurring more diffusely in the brain. Coagulation-fibrinolytic activation is presumed to have more hemorheological effect on small penetrating arteries in the white matter.

A marked increase in the TAT, F_{1+2}, and XDP levels was observed only in the patients with BD experiencing a subacute aggravation. The prothrombotic state indicated by these hemostatic markers may be merely the result of cerebral tissue damage. Alternatively, it may play a causative role in cerebral microembolization and subsequent neurologic exacerbation.

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