Case Report

A Case of Reversible Posterior Leukoencephalopathy Syndrome Caused by Transient Hypercoagulable State Induced by Infection

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We report a normotensive case of reversible posterior leukoencephalopathy syndrome caused by transient hypercoagulable state. Hypertension is the main risk factor for reversible posterior leukoencephalopathy syndrome, which is believed to occur as a result of high blood pressure-related dysfunction of cerebrovascular endothelial cells, because it commonly appears in hypertensive emergency. However, in this completely normotensive case, the typical clinical findings of reversible posterior leukoencephalopathy syndrome were triggered by transient hypercoagulable state without any blood pressure variation. The case was successfully treated with anticoagulation therapy using heparin. Thus, this case indicates that reversible posterior leukoencephalopathy syndrome is induced by cerebrovascular endothelial dysfunction, which is induced not only by high blood pressure but also hemostatic dysfunction. (*Hypertens Res* 2005; 28: 619–623)

Key Words: reversible posterior leukoencephalopathy syndrome, endothelial dysfunction, normotensive, hypercoagulable state

Introduction

Reversible posterior leukoencephalopathy syndrome was first described by Hinchkey *et al.* (1) in 1996, and occurs exclusively in patients with and frequently occurs in patients with hypertensive encephalopathy (2). The normal response of the cerebral arterioles to acute rising blood pressure is sympathetic nerve-mediated vascular constriction to prevent increasing blood flow (autoregulation). But in the case of reversible posterior leukoencephalopathy syndrome, the response does not work well when there is excess high pressure or recent onset of a modest increase in blood pressure,

and excess dilatation of the arterioles following disruption of cerebral small vessel endothelial cells (*i.e.*, the blood-brain-barrier) can occur, resulting in vasogenic brain edema. Therefore, disruption of cerebral vascular endothelial cells plays a critical role in the pathogenesis of reversible posterior leukoencephalopathy syndrome. Recently, there have been several case reports indicating that not only high blood pressure, but also other factors, like cytotoxic drug using, connective tissue diseases (1, 3, 4) can contribute to the development of this syndrome *via* damage to cerebral vascular endothelial cells with no relation to blood pressure.

The endothelium are now considered as the largest “organ” in the body, and play a critical role not only in separating the

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Table 1. Variation of the Hematologic and Chemical Values during Hospitalization

Variable	On presentation	Four days after presentation (on attack)	On discharge
Hematocrit(%)	49.7	44.7	37.9
White blood cell (/mm ³)	5,500	11,500	4,400
Platelets (/mm ³)	161,000	106,000	183,000
Glucose (mg/dl)	99	116	87
Sodium (mmol/l)	143	140	144
Potassium (mmol/l)	4.37	4.14	3.94
Urea nitrogen (mg/dl)	12.4	15.7	9.6
Creatinine (mg/dl)	0.7	0.6	0.7
Total protein (g/dl)	8.1	6.8	6
C-reactive protein (mg/dl)*	0.26	1.5	0.26
PT-INR†	1.03	1.31	1.63
Fibrinogen (mg/dl)‡	390	129	252
TAT(ng/ml)§	2.5	16.5	2.2
PIC (µg/ml)¶	1.3	12.2	0.8
D-Dimer (µg/ml)¶	0.8	3.8	0.7
Anticardiolipin antibody: IgG (U/ml)**	<8	<8	<8
Anticardiolipin antibody: IgM (U/ml)††	0.8	1.7	0.8

It shows the variation of the hematologic and chemical values during hospitalization. *Normal range: <0.30 mg/dl. †PT-INR: prothrombin time-international normalized ratio. ‡Normal range: 111–333. §Thrombin-antithrombin III complex; normal range: ≤3.0. ¶Plasmin-α₂plasmin inhibitor complex; normal range: ≤0.8. ¶Normal range: ≤1.0, **Normal range: ≤10.0. ††Normal range: ≤1.0.

Fig. 1. Neuroimaging of the brain. *a*: T₂-weighted magnetic resonance imaging. *b*: Diffusion-weighted magnetic resonance imaging. *a* and *b*, obtained on the day 8 after admission, show pale hyperintensity in both the frontal and posterior lobes involving both the subcortical white matter and gray matter. *c*: Apparent diffusion coefficient maps demonstrating hyperintensity in the same lesion.

vascular wall from circulation, but also in regulating blood pressure and inhibiting platelet aggregation, coagulation, inflammation, oxidative stress, and cell migration and proliferation (5). Hypertension, diabetes, dyslipidemia, smoking, obesity and aging are well known risk factors for impairment of endothelial cells (6–9), which in turn contributes to vascular constriction, thrombosis, vascular inflammation, pro-oxidation, atherosclerosis, and cardiovascular diseases (10–14).

Hypertension is the most significant frequent problem resulting from cerebral endothelial cell dysfunction, and can introduce ischemic stroke (15), lacunar infarction, vascular dementia, and reversible posterior leukoencephalopathy syndrome. But there are many cases of such cerebrovascular disease of undetermined cause (16, 17). So, understanding more about these is very important for preventing and treating cerebrovascular disease.

Fig. 2 a: T₂-weighted magnetic resonance imaging. b: Diffusion-weighted magnetic resonance imaging. a and b, obtained on day 36 after admission, show complete resolution of the lesions.

Here, we report a completely normotensive patient with reversible posterior leukoencephalopathy syndrome whose typical clinical and morphological abnormalities were triggered by transient hypercoagulable state induced by infection. Although there have been previous reports of normotensive individuals with this syndrome, this is the first report characterized by a hypercoagulable state. This case indicates that the hypercoagulable state and related cerebrovascular endothelial dysfunction played a role in the pathogenesis of reversible posterior leukoencephalopathy syndrome independent of blood pressure level.

Case Report

A 65-year-old woman was admitted to the hospital because of dyspnea on exertion. From 55 years old, she had noticed that her digits appeared to be cyanotic when exposed to cold. At age 59, she felt shortness of breath on light exertion, and this symptom gradually worsened. Two weeks before admission, she was diagnosed with limited systemic sclerosis with pulmonary hypertension at another hospital based on clinical symptoms and the results of blood analysis (positive for anti-nuclear antibodies and anticentromere antibodies), and transferred to our hospital.

On admission, her blood pressure was 102/68 mmHg, her pulse was 98 beats/min, and her respiration was 24 breaths/min. Her oxygen saturation was 88% while breathing ambient air, and reached 95% after supplementation of 2 l/min oxygen. On physical examination, the jugular vein was prominent. The breath sounds were normal, but a blowing holosystolic murmur was heard along the lower left sternal margin which was intensified during inspiration. The abdo-

men was normal, and there was peripheral edema (2+) at both lower extremities. Sclerodactyly and cyanosis were seen at her digits. The urine was normal and the results of hematologic and other laboratory tests are shown in Table 1. An electrocardiogram showed sinus tachycardia at a rate of 102 beats/min with right axis deviation and inverted T-wave from V1 to V4. Chest radiograph showed cardiomegaly and enlarged central pulmonary arteries. The echocardiogram demonstrated right ventricular enlargement pushing into the left ventricular cavity. Doppler studies revealed severe tricuspid regurgitation (pressure gradient: 75 mmHg). CT examination of the chest with contrast material and a perfusion lung scan were normal. An inserted Swan-Ganz catheter showed that the pulmonary arterial pressure was 83/40 mmHg, the pulmonary-capillary wedge pressure was 6 mmHg, and the cardiac output was 3.4 l/min.

After hospitalization her symptoms gradually improved by rest. On the fourth day, she complained of a sudden loss of vision without any vital changes, and just a few minutes later, she became uncommunicative. Because her respiration had weakened with severe hypoxia, intubation was required. During this attack, her blood pressure was 119/73 mmHg without abnormal elevation (<130/80 mmHg) and her pulmonary arterial pressure was 95/43 mmHg. Blood tests revealed a white blood cell count of 11,500/mm³, platelets of 106.0 × 10³/mm³, C-reactive protein of 1.5 mg/dl, thrombin-antithrombin III complex of 16.5 ng/ml, plasmin-α₂plasmin inhibitor complex of 12.2 μg/ml, D-dimer of 3.8 μg/ml, and an anticardiolipin antibody (IgM) titer of 1.7 U/ml (Table 1). Brain CT showed no abnormality. T₂-weighted and diffusion-weighted MRI showed a relatively hyperintense region in both the frontal and posterior lobes involving both subcortical

white matter and gray matter. Apparent diffusion coefficient (ADC) maps demonstrated hyperintensity in these lesions (Fig. 1). The findings of magnetic resonance (MR) angiography were normal. Initially, central nervous system involvement through small vessel vasculitis was suspected, but because of its characteristic clinical features and radiological findings, a provisional diagnosis of reversible posterior leukoencephalopathy syndrome was considered. Antibiotics, continuous intravenous heparin and epoprostenol were started to treat her inflammation, hypercoagulable state and pulmonary hypertension. Her consciousness and vision recovered gradually and completely normal. Extubation was done 7 days later. A follow-up MRI performed on day 36 after admission showed complete resolution of the affected lesions (Fig. 2), and the elevated C-reactive protein, thrombin-antithrombin III complex, plasmin- α_2 plasmin inhibitor complex, and D-dimer level had subsided to normal levels (Table 1). On 71 days after administration, she was discharged under warfarin treatment.

Discussion

We here report a case of reversible posterior leukoencephalopathy syndrome caused by hypercoagulable state without hypertension. This case indicates that reversible posterior leukoencephalopathy syndrome is induced by cerebrovascular endothelial dysfunction, which is induced not only by high blood pressure but also hemostatic dysfunction.

Reversible posterior leukoencephalopathy syndrome is characterized clinically by altered mental status, headache, seizures, and visual disturbances, and T_2 -weighted and diffusion-weighted MRI findings of a hyperintense region in the parietal-occipital lobe involving lesions of the white matter, basal ganglia, brain stem, cerebellum, and gray matter (1, 18). Analysis of ADC maps suggests that such abnormalities are caused by vasogenic edema rather than by ischemia (18). In the past, reversible posterior leukoencephalopathy syndrome has been considered to occur mainly in the posterior lobe and to be reversible disease as per its name. More recently, however, the syndrome has been considered irreversible in the manner of cerebral infarction or hemorrhages if the underlying causes are not treated, and the involved lesions are no longer considered specific to the posterior region (19). Our case also demonstrated that the abnormality is not restricted to the white matter or posterior lobe, but also occurs in the gray matter and anterior lobe. For this reason, we should reconsider the definition of reversible posterior leukoencephalopathy syndrome and decide on more appropriate terms described precisely.

Reversible posterior leukoencephalopathy syndrome is mostly associated with abrupt and severe hypertension occurring at eclampsia or acute renal failure, *etc.* However, it is also seen in patients treated with immunosuppressive or cytotoxic agents such as cyclosporine or tacrolimus (1), and in patients with connective tissue diseases such as systemic

lupus erythematosus (3), and thrombotic microangiopathic states such as thrombotic thrombocytopenic purpura (4). Because some cases of the latter (1, 3, 4) occur even in the absence of hypertension, the pathogenesis of reversible posterior leukoencephalopathy syndrome is multifactorial, although the most fundamental mechanism is disruption of cerebral vascular endothelial cells.

The endothelium are now considered as the largest "organ" in the body, and play a critical role not only in separating the vascular wall from circulation, but also in regulating blood pressure and inhibiting platelet aggregation, coagulation, inflammation, oxidative stress, and cell migration and proliferation (5). Because endothelium are distributed systemically, such abnormalities are participating diffuse vascular beds damages (12, 13) even though specific site is prone to be more or less (20). Because the cerebral endothelial cells form a blood-brain-barrier for preventing excess flux of ions, amino acids, and peptides into the brain through adherens and tight junctions (21), the interaction between endothelial cells and other factors could be more complex than at other sites. There are several well known risk factors for cerebral endothelial cell damage, including hypertension, diabetes, hyperlipidemia, smoking, aging, and obesity (6, 7, 22). Recently, several other possible factors have been suggested to play a role—*i.e.*, hyperhomocysteinemia, inflammation, infection, and hypercoagulability (23, 24)—although further evidence will be needed to confirm these relations. Nevertheless there are still many deteriorating factors to be remained undetermined (16, 17), so we have to break such enigmas and promote the strategies for preventing and treating cerebrovascular disease (25).

In our case, there were no well known cardiovascular risk factors and used no cytotoxic agents, but there was only a transient hypercoagulable state corresponding with the event. Because the patient was complicated with systemic sclerosis with pulmonary hypertension, we think that systemic endothelial dysfunction played an important role in the pathogenesis (26), but the event synchronized with inflammatory symptoms followed by a hypercoagulable state. Although we were unable to determine the trigger for such process, infection was perhaps the most likely candidate, since the symptoms and all of the inflammatory markers were ameliorated by using antibiotics. Such synergic effects produced a transient hypercoagulable state, as shown by the elevations in thrombin-antithrombin III complex, plasmin- α_2 plasmin inhibitor complex, and D-dimer level. Because thrombocytopenia and a reduction in the fibrinogen level were also seen concomitantly, we conjecture that the underlying pathogenesis involved disseminated intravascular coagulation. Although there have been previous reports of normotensive reversible posterior leukoencephalopathy syndrome, this is the first case to be involved in coagulation abnormality (4, 27). Our case was successfully treated with anticoagulation therapy using heparin, but since we have no control case, the usefulness of this regimen cannot be conclusively deter-

mined. But now reversible posterior leukoencephalopathy syndrome is considered to be possibly irreversible damaged without treatment, we have to keep in mind that it could be induced by hypercoagulable state, and cope with it by anticoagulation therapy to avoid any hangover.

In this completely normotensive case, the typical clinical findings of reversible posterior leukoencephalopathy syndrome were triggered by a hypercoagulable state without any blood pressure variation, and the case was successfully treated with anticoagulation therapy using heparin. Thus, this case indicates that reversible posterior leukoencephalopathy syndrome is induced by cerebrovascular endothelial dysfunction, which is induced not only by high blood pressure but also hemostatic dysfunction.

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