Subarachnoid Hemorrhage Associated With von Willebrand's Disease

—Case Report—

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Abstract

A 59-year-old woman with type IIA von Willebrand's disease (VWD) presented with subarachnoid hemorrhage (SAH). Computed tomography showed SAH in the right sylvian fissure and intracranial hemorrhage in the right temporal lobe. Angiography demonstrated an aneurysm at the bifurcation of the right middle cerebral artery. Neck clipping was performed on the 3rd day after the onset with intra- and postoperative administration of factor VIII/von Willebrand factor concentrate. No excessive bleeding occurred. Patients with prolonged bleeding time should be screened for VWD before surgery. This is a rare case of VWD presenting with SAH secondary to ruptured intracranial aneurysm. The clinical characteristics and the management of SAH in a patient with VWD are discussed.

Key words: von Willebrand's disease, subarachnoid hemorrhage, intracranial aneurysm

Introduction

Von Willebrand's disease (VWD) is an autosomal inherited hemorrhagic disorder characterized by a prolonged bleeding time due to decreased activity of the von Willebrand factor (VWF). VWF facilitates platelet adhesion and aggregation to the subendothelium under conditions of high shear in the microcirculation. VWF has a complex multimer structure consisting of a series of disulfide-linked proteins that range in size from 860,000 to over 10 million daltons. Deficiency of large VWF multimers in the plasma and platelet granules is recognized as a variant of VWD, type IIA.

The hemorrhagic symptoms of VWD are generally mild and mucosal bleeding is common, but intracranial bleeding in this condition is rare. Experience with cases of VWD associated with intracranial hemorrhage has suggested that many cases of intracranial hemorrhage with VWD are overlooked due to inadequate screening on admission.^{2,8,11)} Further workup to exclude VWD may be necessary for patients with normal platelet count and prolonged bleeding time.²⁾

We recently experienced a rare case of subarachnoid hemorrhage (SAH) secondary to ruptured intracranial aneurysm associated with type IIA VWD, and describe the management and the causal relationship of SAH in a patient with VWD.

Case Report

A 59-year-old woman complained of sudden onset of severe headache on October 26, 2003. Next day she had severe headache again and nausea. She was admitted to Komatsu Municipal Hospital. Computed tomography showed SAH in the right sylvian fissure and intracerebral hemorrhage in the right temporal lobe (Fig. 1). Selective cerebral angiography demonstrated an aneurysm of the right middle cerebral artery (MCA) with a dumbbell shape and length of 7 mm (Fig. 2).

The diagnosis was hemostatic disorder without family history. She had experienced repeated nosebleed, hypermenorrhea, and subcutaneous hematoma. As she was required to have further examinations for disorders of hemostasis, she was transferred to Kanazawa University Hospital on

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Fig. 1 Computed tomography scans showing subarachnoid hemorrhage in the right sylvian fissure and intracerebral hemorrhage in the right temporal lobe.

Fig. 2 Preoperative right carotid angiograms (A: anteroposterior view, B: lateral view) showing an aneurysm of the right middle cerebral artery.

October 28.

On admission she was a little drowsy but well oriented. She had motor weakness of the right arm. The severity of her SAH was Hunt and Kosnik grade II.

Blood examination showed that the platelet count was normal but the bleeding time was prolonged to about 7.5 minutes (Table 1). The activated partial thromboplastin time on the day of admission was within normal limits, but after 3 months had prolonged to 44.4 seconds. Factor VIII activity was 34%, factor VIII-related antigen was 40%, and VWF was less than 6%. The diagnosis was VWD based on these findings. Replacement therapy with intravenous bolus infusion of 2000 units of factor VIII/VWF concentrate (Confact F®; Fujisawa, Tokyo) was performed before the operation. Later multimeric analysis of VWF by electrophoresis of plasma showed loss of large VWF multimers (Fig. 3). These findings indicated type IIA VWD.

Fig. 3 Electrophoretic pattern of plasma von Willebrand factor multimers showing deficiency of large multimers (L and M) in the plasma of the present patient (A) compared to control plasma (N).

Table 1 Hemostatic findings on the day of admission

Test	Result	Normal range
Bleeding time (min)	7.5*	1-3
Platelet count ($\times 10^4/\mu\text{l}$)	21.1	13-35
Prothrombin time (sec)	11.1	9.4-11.1
Activated partial thromboplastin time (sec)	39.8	27.5-42.1
Fibrinogen (mg/dl)	274	206-369
Factor II activity (%)	87	70-130
Factor V activity (%)	121	70-130
Factor VII activity (%)	75	70-130
Factor VIII activity (%)	34*	70-130
Factor VIII-related antigen (%)	40*	50-155
Von Willebrand factor (%)	<6*	60-170
Factor IX activity (%)	112	70-130
Factor X activity (%)	90	70-130
Factor XI activity (%)	97	70-130
Factor XII activity (%)	110	70-130
Factor XIII activity (%)	126	70-130

*Out of normal range.

Right frontotemporal craniotomy was performed on the day of admission. The hematoma was mainly located in the sylvian fissure and was removed as far as possible. A saccular aneurysm was found at the bifurcation of the right MCA and clipped successfully using a Sugita titanium right curved clip. The

Table 2 Clinical features of spontaneous intracranial hemorrhage secondary to von Willebrand's disease

Author (Year)	Age (yrs), Sex	Bleeding site	Operation	Outcome
Mizoi et al. (1984) ⁸⁾	4, F	intracerebral	+	alive
Almaani and Awidi (1986) ²⁾	22, F	intracerebral	—	alive
	18, M	intraventricular	+	dead
	65, M	intracerebral	—	dead
	23, F	intracerebral	—	dead
Osenbach et al. (1989) ¹¹⁾	13, F	intracerebral	+	alive
Mullaart et al. (1991) ⁹⁾	0, F	intraventricular	—	alive
Present case	59, F	subarachnoid	+	alive

bone was not returned for external decompression. Daily administration of 2000 units of factor VIII/VWF concentrate was continued for 3 days after the operation to maintain factor VIII activity at greater than 50% (110% on postoperative day 1, 120% on day 2, 66% on day 7). No abnormal bleeding was observed perioperatively.

Her postoperative course was uneventful. Postoperative angiography revealed complete clipping of the aneurysm. Subsequently cranioplasty was performed with administration of factor VIII/VWF concentrate. The patient was discharged without neurological deficits.

Discussion

This patient with VWD suffered SAH secondary to ruptured intracranial aneurysm. Aneurysm neck clipping was performed in the acute phase after infusion of factor VIII/VWF concentrate and no abnormal bleeding was encountered during or after the operation. Surgery is often reported in patients with VWD.^{1,7,13)} Excessive hemorrhage during surgery occurred in 40% of patients if special hemostatic management was not performed, but in only 8% if steroids or fresh human plasma was administered preoperatively.¹⁾ Both VWF ristocetin cofactor and factor VIII activity may be useful in evaluating the necessity for replacement therapy.⁷⁾ Administration of factor VIII/VWF concentrate based upon VWF ristocetin cofactor activity was successful in patients with VWD undergoing urgent surgery.¹³⁾ Surgery for an arteriovenous malformation in a patient with hemophilia resembling VWD was performed with the aid of factor VIII/VWF concentrate, and perioperative maintenance of factor VIII activity at 50% or more of the normal level was recommended.¹⁰⁾ We also used factor VIII/VWF concentrate and evaluated the response to replacement therapy using factor VIII activity. Factor VIII activity was 34% before using factor VIII/VWF concentrate, but was maintained at 66–120% for 1

week perioperatively after using the agent.

Numerous vascular diseases have been reported to be associated with VWD but no clear causal relationship has been demonstrated.^{3–6,12,14–16)} VWD may be related to cardiovascular abnormalities including mitral valve prolapse or cerebral aneurysm based on abnormal production of type III collagen.³⁾ Mitral valve prolapse occurs more than four times more frequently in patients with VWD than in controls.¹²⁾ Decreased levels of VWF were found in 59% of patients with mitral valve prolapse compared to only 7% of controls.⁶⁾ In our case, mitral valve prolapse was not present. The pathogenic link between type III collagen and VWD remains unexplained.

Patients lacking large VWF multimers may also suffer from aortic stenosis and bleeding gastrointestinal angiodysplasia.^{5,14,15)} In such cases, gastrointestinal bleeding was cured after aortic valve replacement. The pathological sequence may involve decrease of the shear stress to endothelial cells after correction of aortic stenosis, and recovery of production of VWF after improvement of endothelial cell function. A case of ruptured leg aneurysm in a patient with acquired VWD may have been caused by malfunction of endothelial cells.¹⁶⁾ Actually, type IIA VWD is caused by decreased synthesis of large plasma VWF multimers by endothelial cells or increased proteolysis of these multimers.

In our case, histological analysis revealed that the condition of the endothelial cells was compatible with a saccular aneurysm, and no significant findings related to VWD were found. Therefore, no causal relationship between VWD and the cerebral aneurysm could be identified.

The clinical features of eight patients with spontaneous intracranial hemorrhage secondary to VWD reported in the last 20 years are listed in Table 2.^{2,8,9,11)} Six of the eight patients suffered hemorrhage at ages less than 30 years. The bleeding site was intracerebral or intraventricular, and one case was secondary to ruptured arteriovenous malformation.¹¹⁾

This is the first case of SAH secondary to ruptured intracranial aneurysm. Administration of factor VIII/VWF concentrate was effective to prevent excessive perioperative bleeding in a patient with type IIA VWD. The association of cerebral aneurysm and VWD may have been coincidental. Further examinations for VWD in patients with prolonged bleeding time may help to reveal the etiology of this rare condition.

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