—Review—

Cerebral Endothelial Damage after Severe Head Injury

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Abstract

We demonstrate that in head injuries the degree of cerebral endothelial activation or injury depends on the type of brain injury and the patient's age, and that in severe head injuries measuring the serum levels of thrombomodulin (TM) and von Willebrand factor (vWF) is useful in evaluating cerebral endothelial injury and activation. The values of vWF in the cases of focal brain injury were significantly higher than in the cases of diffuse axonal injury. The serum levels of TM in focal brain injuries were higher than in diffuse axonal injuries, but the differences were not statistically significant. In patients with delayed traumatic intracerebral hematoma (DTICH), vWF levels were much higher than in patients without DTICH. The values of TM and vWF in elderly patients were significantly higher than in younger patients. These findings indicate that: 1) the degree of endothelial activation in focal brain injury is significantly higher than in diffuse brain injury; 2) the degree of cerebral endothelial injury in patients with DTICH is much higher than in those without DTICH; and 3) the degree of cerebral endothelial activation and injury in elderly head injury patients is significantly higher than in younger patients.
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Key words: cerebral endothelial injury, head injury, thrombomodulin, von Willebrand factor, delayed traumatic intracerebral hematoma, elderly patients

Introduction

Head injuries accompanied by coagulation abnormalities might be associated with cerebral endothelium activation and injury[6,22]. Several molecules have been proposed as markers of endothelial activation and endothelial injury[12,13].

Thrombomodulin (TM), which is located in the surface endothelium of the arteries, veins and capillaries of major organs such as the brain, lungs, liver, kidneys, skeletal muscles, and gastrointestinal tract, is a good indicator of endothelial injury[10]. TM is a glycoprotein released from the injured endothelial cell surface that acts as a receptor for thrombin and neutralizes the clotting activity of thrombin.

Von Willebrand factor (vWF), which is synthesized by endothelial cells, is also an endothelium-specific glycoprotein. The serum level of vWF increases in response to various stimuli even without endothelial injury[20], but elevated serum levels of vWF suggest endothelial activation in severe head injuries[19].

Measuring TM and vWF may be useful for evaluating endothelial injury or activation caused by cerebral contusion, and for predicting the delayed

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traumatic intracerebral hematoma (DTICH) produced by weakness of the vessel walls in the cerebral parenchyma, a cause of poor outcome in elderly patients.

The purpose of this paper is to demonstrate the usefulness of measuring TM and vWF in patients with head injuries.

Serum Levels of TM and vWF in Head Injury

The local disturbance of intravascular coagulation accompanying local injury of the endothelium in association with brain injury has been demonstrated in anatomical and carotid-jugular coagulation studies[11,16,17]. The results suggest that the abnormal levels of TM or vWF seen after head injury were caused by injury to or activation of cerebral endothelial cells.

Gourin et al. demonstrated endothelial injury after head injury in a study using cultured human cerebral microvascular endothelium (HCME)[6]. They reported the production of inflammatory cytokines from HCME after traumatic brain injury, which was independent of systemic influences. In situ cytokine production by HCME after percussion trauma might mediate the increased cerebral leukocyte accumulation and cerebrovascular dysfunction observed after focal brain injury. Intracerebral cytokine production was thought to be partially responsible for brain edema, and increased leukocyte adhesion was observed after head injury, both as a direct effect on vascular permeability and as a cause of leukocyte activation. The cerebrospinal fluid concentrations of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 were elevated after traumatic brain injury. These researchers concluded that cerebral endothelial injury was a concomitant of head injury.

Ikegami et al. demonstrated the relationship between endothelial injury and the serum level of TM[9]. The TM that acts as a receptor for thrombin and neutralizes the clotting activity of thrombin consists of various molecular weight fragments (75,000 to 105,000) that are probably degraded from cellular TM. Its plasma half-life is reported to be 10 to 15 minutes, and it is partly excreted by the kidney[10]. Ikegami concluded that the serum level of TM was a good indicator of endothelial injury and that it was correlated with the severity of blunt trauma[9]. TM is a glycoprotein that is located in the endothelial surface of the arteries, veins and capillaries of major organs such as the brain, lungs, liver, kidneys, skeletal muscles, and gastrointestinal tract[10]. There are 50,000 to 100,000 molecules in every endothelial cell, compared with 60 molecules in every platelet. The amount of TM in monocytes and neutrophils is about 20% of that found in endothelial cells. This suggests that the increased serum level of TM after head injury derives from the injured cerebral endothelial cells rather than from platelets, monocytes, or neutrophils[9]. TM is secreted by injured endothelial cells but is not released from activated or stimulated endothelial cells. Many authors have demonstrated that the increased serum level of TM derives from the injured endothelium[25]. The level of TM is therefore regarded as a molecular marker of endothelial injury[9].

vWF synthesized by endothelial cells and stored in Weibel-palade bodies is also an endothelium-specific glycoprotein that allows platelets to remain attached to the vessel wall[27]. vWF activity is distributed among a series of plasma multimers with molecular weights ranging from 400,000 to 20 million. A single large vWF precursor subunit is synthesized in endothelial cells[8]. The serum level of vWF increases in response to various stimuli, even in the absence of overt endothelial injury[19]. The release of vWF caused by the stimulation of endothelial cells, not by damage or injury to them, induces platelet agglutination and thrombus formation at the sites of vascular stimulation. Local endothelial secretion of vWF may occur at the site of inflammation or stimulation.

These facts suggest that an elevated serum level of TM is a good indicator of injury to cerebral endothelial cells, and that an elevated vWF level reflects the activation of cerebral endothelial cells in head injuries without injury to any other site (**Fig. 1**).

The mechanisms of cerebral endothelial injury and/or activation are not clear, but we think that

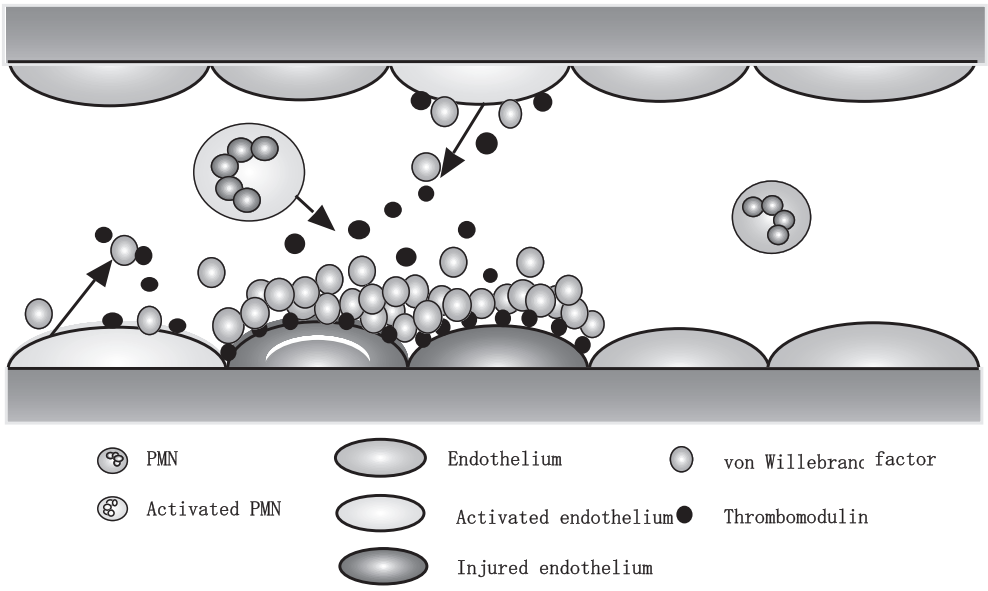

Fig. 1 Schema of endothelial injury, von Willebrand factor and thrombomodulin

many direct or indirect results of injury, such as impact on cerebral vessels, hemodynamic stress, hypoxia, cerebral ischemia, or brain edema, may cause cerebral endothelial injury and/or activation. Cerebral endothelial injury or activation promotes the release of inflammatory cytokines[6], and the promotion of an inflammatory process in the cerebral endothelium may amplify the endothelial injury or activation[9].

When hemostatic parameters including TM and vWF are used to evaluate cerebral damage, extracerebral factors that influence the level of TM and/or vWF should be considered. In our series, patients with multiple trauma and an underlying disease (syncope, heart disease, malignant tumor, renal disease or dysfunction, or epilepsy), and/or with a pre-existing systemic disease that might be associated with a coagulation disorder were excluded. Therefore, the serum levels of TM and vWF in our series were good indicators of cerebral endothelial injury and activation.

Differences in Cerebral Endothelial Injury between Diffuse Axonal Injury and Focal Brain Injury

Adams and Gennarelli attributed practical significance to diffuse axonal injury in their clinical and pathological investigation[1,4], and we reported that diffuse axonal injury gave characteristic findings in the cerebral white matter, basal ganglia, corpus callosum, or the dorsal part of the brainstem on Magnetic Resonance Imaging (MRI)[29].

In our series, the values of vWF in the cases of focal brain injury (ranging from 332.5 ± 52.8 to 361.7 ± 86.2%) were significantly higher than those in the cases of diffuse axonal injury from 2 hours to 7 days after the injury (ranging from 201.6 ± 59.5 to 242.5 ± 51.7%). The serum levels of TM in focal brain injury (from 3.84 ± 1.54 to 4.12 ± 1.46 U/mL) were higher than those in diffuse axonal injury (from 2.96 ± 1.70 to 3.67 ± 1.70), but these differences were not statistically significant[30] (**Table 1**).

The fact that the serum levels of vWF in focal brain injury were significantly higher than in diffuse axonal injury demonstrated the difference between the two types of injury in the mechanism by which the impact affects the brain parenchyma, including the cerebral vessels. The impact and mechanical forces on the cerebral vessels inflicted by a coup injury or contre-coup injury and leading to focal brain injury might be more serious than the strain force to the brain that causes diffuse axonal injury. Focal brain injuries such as subdural hematomas, cerebral contusions, or intracerebral hematomas were accompanied not only by cerebral

Table 1 Thrombomudulin and von Willebrand factor in focal brain injury and diffuse axonal injury

	2 hours	3 days	7 days
vWF			
FBI	332.5 ± 52.8 *	361.7 ± 86.2 *	333.8 ± 42.1 *
DAI	201.6 ± 59.5	242.5 ± 51.7	241.3 ± 64.2
TM			
FBI	3.84 ± 1.54	3.86 ± 1.34	4.12 ± 1.46
DAI	3.60 ± 1.92	3.67 ± 1.70	2.96 ± 1.70

* significantly different compared to DAI ($p<0.05$)
FBI: focal brain injury; DAI: diffuse axonal injury; TM: thrombomudulin; vWF: von Willebrand factor

Table 2 Thrombomudulin and von Willebrand factor with DTICH and without DTICH

vWF	
DTICH (+)	6.63 ± 1.05 *
DTICH (−)	3.20 ± 0.68
TM	
DTICH (+)	262.6 ± 106.1
DTICH (−)	221.2 ± 78.5

* significantly different compared to DAI ($p<0.05$).
DTICH: delayed traumatic intracerebral hematoma; TM: thrombomudulin; vWF: von Willebrand factor

parenchymal injury, but also by endothelial activation and destruction.

Although the serum levels of vWF in focal brain injury were significantly higher than in diffuse axonal injury, TM levels did not differ significantly between the two types of injury. Our observations suggest that endothelial activation in focal brain injury was much more serious than in diffuse axonal injury from 2 hours through 7 days after injury.

Prediction of Delayed Traumatic Intracerebral Hematoma (DTICH)

The concept of DTICH was first introduced by Bollinger in 1891[3]. Bollinger's original criteria have been modified by various authors, particularly since the introduction of computed tomography (CT). Recently, the term DTICH has been applied when a hematoma is demonstrated on sequential CT without any hematomas appearing on the initial CT performed on admission[23].

DTICH, which is very difficult to predict, is a cause of morbidity in patients suffering from severe head injuries, and its prediction might be effective in reducing both morbidity and mortality in such patients. Selladurai et al. suggested that measuring hemostatic parameters was useful in predicting DTICH[21]. They commented that DTICHs greater than 25 mL were found in patients with significantly abnormal DIC scores.

Various etiologic mechanisms have been proposed for the appearance of DTICH, most invoking weakness of the vessel wall as a direct effect of the injury[2,14,15]. Such being the case, a nonhemorrhagic contusion would create the necessary conditions for DTICH within the brain. We previously reported that MRI, which is capable of revealing nonhemorrhagic contusions, might be useful for predicting DTICH[29]. The sites of these contusions may reveal cerebral endothelial injuries. However, it is not always possible to transfer severe head injury victims for MRI because of their unstable vital signs and the difficulty of providing appropriate critical care. As previously described, the number and severity of cerebral endothelial injuries may be reflected in the serum level of TM. In patients with DTICH, vWF levels were much higher than in patients without DTICH ($p<0.01$). The values of TM and vWF at 2 hours after injury in elderly patients were significantly higher than those in younger patients (**Table 2**). The results of our series demonstrate that patients with high levels of vWF and TM are at risk of DTICH (30) (**Table 2**).

Recent evidence suggests that the endothelium plays an active role in coordinating the inflammatory response to endothelial injury[2]. Endothelial injury aggravates inflammation by producing proinflammatory cytokines such as IL-1, IL-6, and IL-8[18]. Injured endothelial cells lose their ability to maintain a balance between coagulation and anticoagulation factors, to regulate the tone of smooth muscle, and to control vascular permeability. Increased vascular permeability in the cerebral parenchyma may result in DTICH. These facts and our results suggest that measuring the serum level

Table 3 Serum levels of TM and vWf in three groups

	J-group	M-group	E-group
・Thrombomodulin (U/mL)			
2 hours after injury	2.8 ± 0.4	2.8 ± 2.0	5.4 ± 1.1 *
3 days after injury	3.2 ± 1.4	4.4 ± 1.8	4.5 ± 1.2
7 days after injury	4.1 ± 1.7	3.5 ± 0.7	2.7 ± 1.0
・von Willebrand factor (%)			
2 hours after injury	205.0 ± 57.1	225.0 ± 56.0	375.3 ± 78.2 *
3 days after injury	233.0 ± 86.0	285.2 ± 85.4	281.3 ± 76.8
7 days after injury	297.0 ± 71.0	306.0 ± 47.6	312.0 ± 50.4

TM: thrombomodulin; vWF: von willebrand factor
Juvenile (J)-group with the age of 16 ～ 30 years, mid-aged (M)-group with the age of 31 ～ 65 years, and the elderly (E)-group with the age over 66 years.
*: significantly different compared to J-group and M-group ($p<0.05$)

of TM in the acute stage of head injury may be useful for predicting the occurrence of DTICH.

Cerebral Endothelial Injury and Activation in Elderly Patients

Age is one of the most significant and reliable prognostic indicators after traumatic injury. Multiple studies have documented that outcomes for geriatric trauma patients are worse than those for their younger counterparts[5,7,24,26]. Von der Sande et al. suggested that abnormal hemostatic parameters may be a more sensitive indicator of cerebral contusion than CT, especially in the early stages of acute head injury[18]. Their studies revealed that the severity of a head injury and the degree of endothelial injury were reflected in the disturbance of coagulation in a closed head injury.

In our series, the values of vWF at 2 hours after injury in elderly patients were significantly higher than in the two younger groups. However, there were no significant differences in the serum levels of vWF in the three groups at 3 days and 7 days after injury (**Table 3**). Similarly, the TM values at 2 hours after injury were significantly higher in the elderly patients, but there were no significant differences in the serum levels at 3 day and 7 days after injury (**Table 3**).

Our study demonstrated that elderly patients are more susceptible to activation and injury of the cerebral endothelium than younger patients. Considering the short half-life of TM and vWF, our study suggests that endothelial activation and injury at 2 hours after injury is much more serious than at 3 days and 7 days after injury, and that cerebral endothelial activation and injury are caused by a primary brain injury[28].

Conclusion

In the acute stage of severe head injury, the degree of cerebral endothelial injury and activation varies according to the type of injury to the brain, and higher degrees of endothelial injury and activation are observed in patients with DTICH than in patients without. Cerebral endothelial activation and injury occur more easily in elderly patients than in younger patients, and this leads to poor outcomes and a high incidence of DTICH. Measuring the serum levels of TM and vWF is very important in evaluating endothelial damage in the acute stage of severe head injury.

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