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Delayed Progression of Edema Formation Around a Hematoma Expressing High Levels of VEGF and MMP-9 in a Patient With Traumatic Brain Injury: Case Report

Tomoya HIROSE,[1] Naoya MATSUMOTO,[1] Osamu TASAKI,[2] Hajime NAKAMURA,[3] Fuyuko AKAGAKI,[1] and Takeshi SHIMAZU[1]

Departments of [1]Traumatology and Acute Critical Medicine and [3]Neurosurgery, Osaka University Graduate School of Medicine, Suita, Osaka; [2]Department of Emergency Medicine, Unit of Clinical Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Nagasaki

Abstract

The mechanisms accounting for the development of tissue damage following traumatic brain injury (TBI) have been studied for several decades. A variety of mediators, such as vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9), which play a crucial role in edema formation after TBI, have been identified. We experienced a case of brain edema that progressed continuously at least until 13 days after head injury. The brain edema occurred around the hemorrhage from an intracerebral contusion. The evacuated hematoma was investigated based on the inference that the unexpected expansion of edema was induced by the mediators within the hematoma itself. A 64-year-old woman was admitted to our hospital following a traffic injury. Left brain contusion was revealed by head computed tomography (CT) on admission. Three hours later, formation of an intracerebral hematoma became evident. Serial CT examination revealed that brain edema had developed progressively till 13 days after the injury. A hematoma removal operation was performed on Day 13. The hematoma was centrifuged and the supernatant was analyzed for the expression of VEGF and MMP-9. The values of both (4400 pg/ml and 920 ng/ml, respectively) were extremely high compared with values reported previously in serum and cerebrospinal fluid collected from patients with intracranial infection or injury. This case suggested that the delayed exacerbation of edema following traumatic intracranial hemorrhage was possibly induced by secretory factors such as VEGF and MMP-9 released from within and around the hematoma.

Key words: traumatic brain injury, hematoma, vascular endothelial growth factor, matrix metalloproteinase-9, brain edema

Introduction

The mechanisms associated with the development of tissue damage following traumatic brain injury (TBI) have been studied, and it has been demonstrated that formation of cerebral edema is one of the major factors leading to high mortality from TBI.[10] Cerebral edema is classified into two main categories, cytotoxic edema and vasogenic edema.[3,14] Cytotoxic edema is essentially a water compartment shift with no change in tissue water content or volume. In contrast, vasogenic edema increases tissue water content, leading to swelling. Tissue swelling thus requires a vascular contribution if it is to occur.[3]

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The time course of intracranial hypertension after TBI was reported by Stocchetti et al.[11] They showed that 56% (113/201) of patients experienced their highest mean intracranial pressure (ICP) during the first 3 days after the injury, and the highest mean ICP peaked within 10 days after the injury in 99% (199/201) of patients.

We recently experienced a case of TBI in which brain edema had continuously progressed in proximity to the hematoma over 10 days after the injury. Recently, a number of mediators, such as vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9), have been identified as key molecules associated with enhanced edema formation after TBI.[3] We speculated that these mediators were released from the hematoma and attributed to the progression of edema. The hematoma evacuated in this case contained high concentrations

of VEGF and MMP-9. This is the first report, to our knowledge, to suggest clinically that VEGF and MMP-9 stemming from within and around the hematoma could be the cause of late-onset brain edema after TBI.

Case Report

A 64-year-old woman was admitted to our hospital following a road accident. Her only notable past history was hypertension. Her consciousness was impaired (Glasgow coma scale [GCS], 4-4-6), and a brain contusion was detected in the left temporal lobe by head computed tomography (CT) (Fig. 1a). Her disturbance of consciousness gradually exacerbated, and a head CT 3 hours after admission revealed the formation of an intracerebral hematoma (Fig. 1b). Body temperature control was performed with the administration of sedative agents under ICP monitoring by placing the sensor in the vicinity of the contusional region. As the level of ICP remained stable at around 10 mmHg and device-related intracranial infection was suspected, the ICP sensor was removed on day 10, although the brain edema was slightly increased compared with that on hospital day 7 (Fig. 1c, d). On hospital day 13, the edema increased further (Fig. 1e), and an enhanced CT showed ring enhancement of the hematoma (Fig. 1f). We then considered the possibility of brain abscess, and craniotomy and hematoma removal procedure were conducted. Eventually, intracranial infection was ruled out on the basis of negative culture and Gram staining results of the hematoma. Next, to explore the causality between the existence of the hematoma and the progression of the adjacent brain edema, we analyzed the expression of VEGF and MMP-9, both of which are known to induce vasogenic edema, in the hematoma. For this purpose, the hematoma was centrifuged, and the supernatant was evaluated to measure the concentrations of VEGF by enzyme-linked immunosorbent assay and MMP-9 by enzyme immunoassay (SRL, Osaka). The value of VEGF was 4400 pg/ml and that of MMP-9 was 920 ng/ml, indicating that a high concentration of these mediators were present in the hematoma. In addition, Gram staining of the hematoma contents revealed substantial infiltration of foamy phagocytes (data not shown). On hospital Day 25, head magnetic resonance imaging (MRI) showed the edematous lesion mainly in white matter as a high-intensity signal on fluid-attenuated inversion recovery (FLAIR) imaging (Fig. 2) but not on diffusion-weighted imaging (data not shown), indicating that the edema was vasogenic. On hospital Day 40, the patient was transferred to a rehabilitation hospital, and her consciousness level at that time was Glasgow outcome scale 3 (severe disability).

Discussion

Reported cases of cerebral edema in which the edema progresses over 10 days after the injury are rare.[11] Various molecules playing a pivotal role in edema formation after

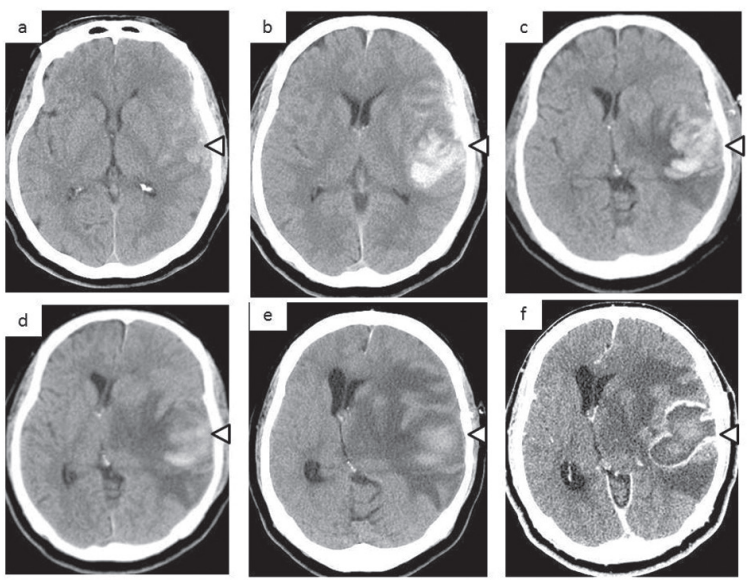

Fig. 1 Serial changes in head computed tomography (CT). Head CT revealed the formation of hematoma (*arrowheads*). Brain edema had progressed continuously at least until 13 days after the injury. a: on admission; b: 3 hours after admission; c: hospital day 7; d: day 10; e and f: day 13 (plain and enhanced CT, respectively).

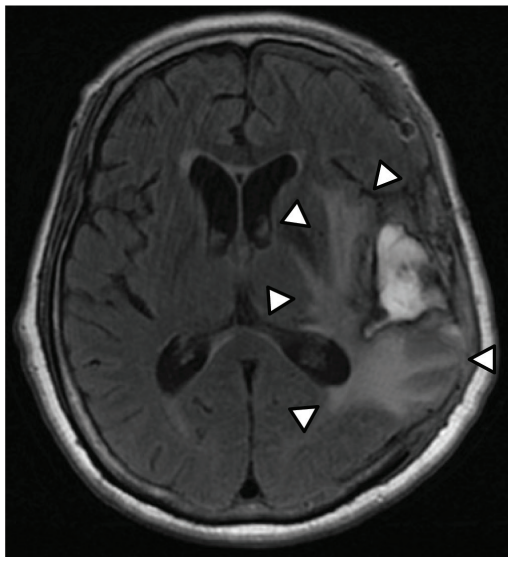

Fig. 2 Head magnetic resonance imaging (MRI) on day 25. Brain edema is shown as a high signal intensity (*arrowheads*) on fluid-attenuated inversion recovery (FLAIR) imaging.

TBI, e.g., secretory factors such as VEGF, MMP-9, interleukin (IL-1β, IL-6, IL-10), and tumor necrosis factor-α, and aquaporin water channels,[3] have been identified. In the present case, we demonstrated that the values of VEGF and MMP-9 in the hematoma collected 13 days after the injury were extremely higher in this case than levels previously reported in the blood and cerebrospinal fluid in cases of meningitis or TBI.[2,5]

It was reported that VEGF is expressed from astrocytes surrounding brain contusion in humans.[12] In the cat model of cerebral hemorrhage, macrophage infiltration and astrocyte proliferation were recognized around the hematoma, and VEGF was strongly expressed from these astrocytes 7 days after the formation of hematoma.[13] Hohenstein et al. reported that the mRNA expression of VEGF within chronic subdural hematoma was increased, so hematoma cells might be the primary source of VEGF.[7] VEGF induces angiogenesis, and we suspected that the ring-enhanced lesion in this case would indicate a neovascular area and that newly formed endothelial cells would be another source of VEGF secretion.[9]

Many types of extracellular matrix proteins are degraded by MMPs, including the neurovascular basal lamina and tight junction proteins of the blood-brain-barrier (BBB).[5,6,15] The up-regulation of MMP-9, in particular, is associated with BBB disruption and edema formation,[1,4] and MMP-9 is vigorously released from activated macrophages.[8] These findings, together with the fact that the brain edema in this case ameliorated after removal of the hematoma, suggest that MMP-9 secreted from infiltrated macrophages to phagocytose hematoma debris, in conjunction with VEGF derived from astrocytes and/or endothelial cells at the margin of hematoma, could induce brain edema around hematoma. The delayed progression of edema might be caused by a time lag between hematoma formation and cell activation to release these mediators.

In this case, we examined only VEGF and MMP-9 concentration due to shortage of sample. To clarify the mechanism more precisely, the expression of other MMPs, the endogenous tissue inhibitors of metalloproteinases, and the factors which are involved in vascular permeability should be evaluated simultaneously in future researches.

Further clarification regarding the functional roles of VEGF and MMP-9 in hematomas of TBI patients would lead to new therapeutic strategies, including use of VEGF and MMP-9 inhibitors, and hematoma evacuation to suppress secondary brain edema.

Acknowledgment

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Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Address reprint requests to: Tomoya Hirose, MD, Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine, 2-15 Yamadaoka, Suita, Osaka 565-0871, Japan. *e-mail*: htomoya1979@hp-emerg.med.osaka-u.ac.jp