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Potential Mechanisms of COVID-19-related Intracranial Hemorrhage Due to Temporary Depletion of Vitamin K-dependent Coagulation Factors: An Illustrative Case

Narihide SHINODA,[1] Shogo TAMURA,[1] Masafumi MORI,[1] Mitsugu NAKAMURA,[1] Kazuyoshi KOROSUE,[2] and Shigeru KOSE[1]

[1]*Department of Neurosurgery, Kosei Hospital, Kobe, Hyogo, Japan*
[2]*Department of Neurosurgery, Kosei Kanoko Hospital, Kobe, Hyogo, Japan*

Abstract

Coronavirus disease 2019 (COVID-19)-related intracranial hemorrhage (ICH) is believed to be associated with at least one known risk factor for ICH, such as hypertension, hyperlipidemia, diabetes mellitus, severe pneumonia, or anticoagulation therapy. However, in this study, we report a case of ICH in a 14-year-old boy with mild COVID-19 infection without pneumonia who had no such risk factors. The only abnormal laboratory finding was temporary depletion of vitamin K-dependent coagulation factors. This case indicates that COVID-19 infection may cause simultaneous asymptomatic intracranial microhemorrhages and temporary depletion of vitamin K-dependent coagulation factors. This temporary depletion might transform the intracranial microhemorrhages into symptomatic ICH.

Keywords: Coronavirus disease 2019 (COVID-19), COVID-19-related ICH, vitamin K-dependent coagulation factors, angiotensin-converting enzyme 2 (ACE2)

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), affects the nervous system and can cause both ischemic and hemorrhagic strokes.[1)] Several mechanistic theories have been advanced regarding ischemic stroke, but much remains to be elucidated regarding the mechanism leading to cerebral hemorrhage.

Based on the previous reports,[2,3)] COVID-19-related ICH is believed to be associated with at least one known risk factor for ICH, such as hypertension, hyperlipidemia, diabetes mellitus (DM), severe pneumonia, or anticoagulation therapy. However, in this study, we report a case of ICH in a 14-year-old boy with mild COVID-19 infection without pneumonia who had none of the abovementioned risk factors or congenital or acquired angiopathy. The only abnormal laboratory finding was temporary depletion of vitamin K-dependent coagulation factors, which has not been definitively identified as a risk factor for ICH. We discuss the potential mechanisms underlying ICH in this case and the implications for clinical practice.

Case Report

Our patient was a 14-year-old boy with a 2 day history of fever, mild headache, and nausea. Although he did not have any smell and taste disorders or respiratory symptoms, he underwent polymerase chain reaction swab testing for SARS-CoV-2 RNA because of a history of contact with COVID-19-positive individuals. The test result was positive. Based on neurological examination, head computed tomography (CT) was performed and left cerebellar hemorrhage was diagnosed (Fig. 1). No acute ischemic lesion was seen on magnetic resonance imaging (MRI) of the brain, including diffusion-weighted imaging, and there were no cerebral microbleeds on T2*-weighted MRI. On fluid-attenuated inversion recovery images showed no abnormalities. Magnetic resonance angiography showed that the large vessels were intact. CT angiography of the head

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and neck with contrast showed normal vasculature and digital subtraction angiography showed no evidence of cerebral aneurysm or arteriovenous malformation (Fig. 2). Chest X-ray and CT revealed no abnormal findings (Fig. 3). Initial laboratory tests were remarkable, showing a prothrombin time (PT) of 15.1 s and an international normalized ratio (INR) of 1.30. A coagulation factor assay test identified decreases in vitamin K-dependent coagulation factors only, including factor VII (54%), factor IX (63%), and factor X (69%). No other coagulation abnormality or autoimmune disease was noted, and no inflammatory findings suggestive of bacterial coinfection were observed.

The patient had a Glasgow Coma Scale score of 15. His blood pressure was normal and systolic blood pressure was between 100 and 120 mmHg during hospitalization. Accordingly, antihypertensive treatment was not given and conservative treatment was selected. During his hospital stay, he did not develop smell and taste disorders or respiratory symptoms related to his COVID-19 infection. His respiratory rate was approximately 20 breaths/min and SpO_2 was within the normal range (96%-100%) on room air. Moreover, he had a low-grade fever for only 2 days after admission. A repeat head CT scan showed a reduction in the amount of hemorrhage. Vitamin K was not administered, but repeat laboratory tests performed 2 weeks after admission showed normal PT (INR: 1.06) and normal levels of all coagulation factors. The patient had an uncomplicated course in the hospital and made a complete recovery. His final National Institutes of Health Stroke Scale score at discharge was 0. No abnormalities were found on MRI after the disappearance of the hematoma.

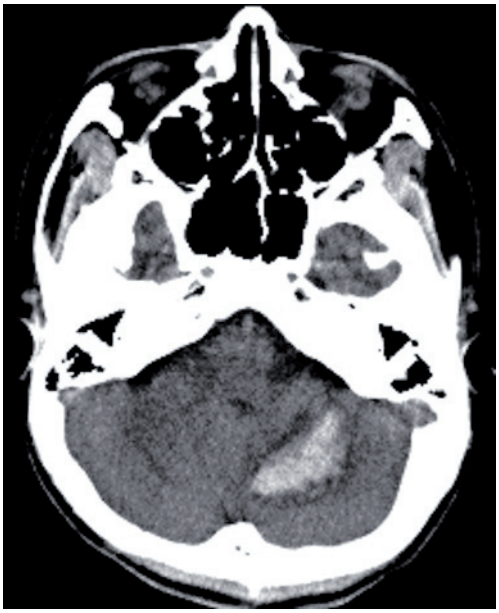

Fig. 1 Computed tomography of the head showing left cerebellar hemorrhage (hematoma diameter: 37 mm).

Discussion

Our case suggests that COVID-19-related ICH can occur even in the absence of known risk factors for ICH, and temporary depletion of vitamin K-dependent coagulation factors resulting from COVID-19 infection may be an important risk factor for COVID-19-related ICH.

Findings of magnetic resonance microscopy, histopathological examination, and immunohistochemical analysis in the brain of patients who died of COVID-19

Lee et al.[4] reported some characteristic findings in the brain of COVID-19 patients that may help to understand ICH in COVID-19. Based on findings of magnetic resonance microscopy, histopathological examination, and immunohistochemical analysis, they showed the effects of SARS-CoV-2 on the vessels of the brain. Multifocal mi-

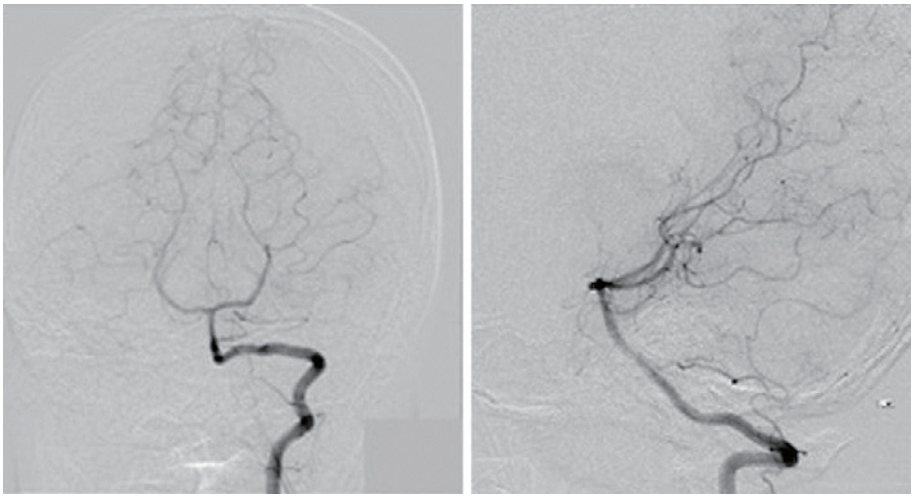

Fig. 2 Digital subtraction angiography (left vertebral artery) with no evidence of cerebral aneurysm or arteriovenous malformation.

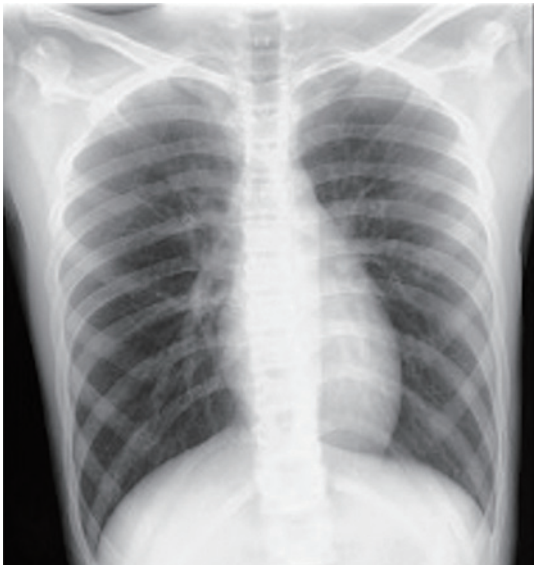

Fig. 3 Chest X-ray showing no remarkable findings.

crovascular injury was observed in the brain of patients who had died of COVID-19 without neurological symptoms. The magnetic resonance images were obtained from the brains of 13 patients with the use of an 11.7-T scanner at a resolution of 100 μm. In nine of the 13 patients, magnetic resonance microscopy showed punctate hyperintensities, which indicate areas of microvascular injury and fibrinogen leakage. These features were observed on histopathological examination of the corresponding sections performed using fluorescence imaging. Additionally, in five of these nine patients, collagen IV immunostaining revealed structural change comprising thinning of the basal lamina of the endothelial cells in the areas of the punctate hyperintensities. In 10 of the 13 patients, the punctate hypointensities observed on imaging corresponded to congested blood vessels with surrounding areas of fibrinogen leakage and relatively intact vasculature. Areas of linear hypointensities were interpreted as microhemorrhages. These findings suggest that SARS-CoV-2 may cause structural changes in the microvessels of the brain and asymptomatic intracranial microhemorrhages.

Structural change in microvessels and intracranial microhemorrhages

Angiotensin-converting enzyme 2 (ACE2) transmembrane receptor is widely recognized as the gateway of SARS-CoV-2 into human host cells.[5] Data obtained from protein-level analyses of ACE2 suggest that it is expressed on endothelial cells, and immunohistochemical staining of tissue samples obtained from a wide range of human organs (lungs, heart, kidneys, oral mucosa, stomach, small intestine, colon, and brain) has demonstrated ACE2 expression on arterial and venous endothelial cells.[6] Invasion of SARS-CoV-2 via ACE2 leads to the disruption of the endothelial cell membrane or the development of endotheliitis, resulting in increased vascular permeability.[7]

A recent study showed that SARS-CoV-2 can infect and multiply in human microvascular organoids composed of both endothelial cells and pericytes.[8] Pericytes are multifunctional mural cells that wrap around the endothelial cells in capillaries and venules, and they are crucial to the regulation of diverse microvascular functions such as angiogenesis, the blood-brain barrier (BBB), capillary blood flow, and the movement of immune cells into the brain.[9] Damage to the pericytes causes suppression of angiogenesis, dysfunction of the BBB, and disruption to the autoregulation of blood flow. These disturbances cause vascular hyperpermeability and gradual weakening of vascular integrity, eventually leading to vessel rupture and microhemorrhages.[10]

Some studies[11,12] have reported that low-level tissue inflammation in the arterioles or elevation of intraluminal arterial pressure persists over the long term in patients with hypertension, hyperlipidemia, and DM. This chronic stimulation forms microaneurysms at arteriole bifurcations, increases vascular permeability, weakens the vascular integrity of the microvessels, and may eventually cause microhemorrhages or ICH. Therefore, if patients with hypertension, hyperlipidemia, or DM are infected by SARS-CoV-2, COVID-19-related ICH will likely occur.

Other studies[13,14] have reported that in patients with severe pneumonia, COVID-19-related ICH occurs because of inflammatory hyperactivation, which is recognized as a cytokine storm or intravascular disseminated intravascular coagulation (DIC). Severe dysfunction of the immune system damages the neurovascular unit and increases BBB permeability, which in turn can cause ICH. In addition, dysfunction of coagulation systems may transform intracranial microhemorrhages to symptomatic ICH.

In a previous study,[15] the risk of ICH was increased fivefold in COVID-19 patients who were on anticoagulation therapy compared with those who were not. Beyrouti et al.[16] reported that 74.4% of cases of COVID-19-related ICH were associated with anticoagulation therapy, so it is also possible that ICH occurs in more severe COVID-19, for which anticoagulation is more likely to be given (including for extracorporeal membrane oxygenation). Thus, anticoagulation therapy may transform intracranial microhemorrhages into symptomatic ICH.

Taken together, the abovementioned studies strongly suggest that risk factors for COVID-19-related ICH include hypertension, hyperlipidemia, DM, severe pneumonia, and anticoagulation therapy. Nevertheless, additional factors may be present in healthy individuals such as in the present case.

Temporary depletion of vitamin K-dependent coagulation factors

The decline in vitamin K after COVID-19 infection was

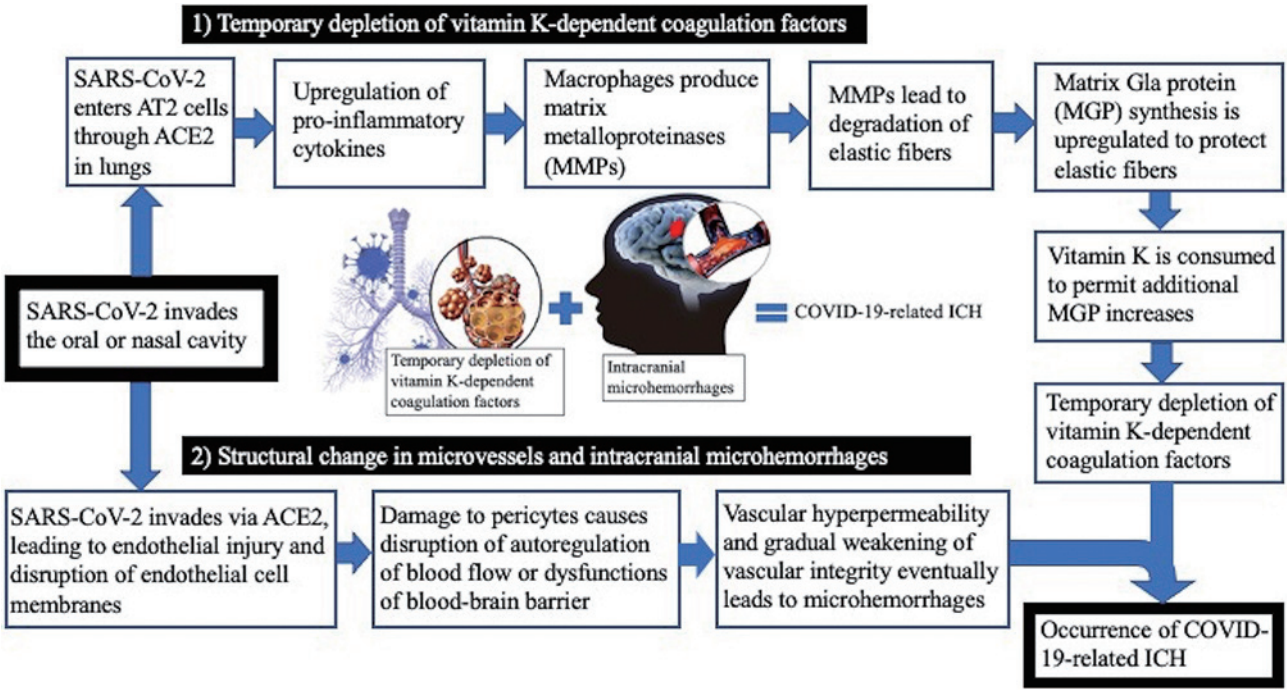

Fig. 4 Proposed mechanism of COVID-19-related intracranial hemorrhage. 1) Temporary depletion of vitamin K-dependent coagulation factors and 2) Structural change in microvessels and intracrani- al microhemorrhages.

explained by Dofferhoff et al. as follows.[17] The invasion of SARS-CoV-2 into AT2 cells of the lung through ACE2 upregulates pro-inflammatory cytokines that increase the number and activity of macrophages in the lungs. These macrophages produce matrix metalloproteinases that accelerate the degradation of elastic fibers. Matrix Gla protein synthesis is upregulated to protect elastic fibers, which consumes considerable amounts of vitamin K. This increased use of vitamin K may lead to a temporary depletion of vitamin K-dependent coagulation factors. Vitamin K is used efficiently and is stored at low levels in the body, so excessive consumption of vitamin K leads to depletion of vitamin K-dependent coagulation factors.

Recent data suggest that COVID-19-related thrombosis is associated with decreased levels of vitamin K and increased severity of pneumonia,[17] but there are few reports of cerebral hemorrhage in patients with no or mild respiratory symptoms. Ellens and Silberstein[18] reported the case of a 5-week-old patient who had COVID-19 and developed ICH. He did not have any respiratory symptoms related to his COVID-19 infection. The cerebral hemorrhage in this infant was thought to be caused by vitamin K deficiency that was exacerbated by COVID-19 infection.

Tang et al.[19] reported that nonsurvivors of COVID-19 showed significantly longer PT compared with survivors. Huang et al.[20] indicated that intensive care unit (ICU) cases showed significantly longer PT compared with non-ICU cases. Isolated prolonged PT can occur because of early and/or mild liver disease or early DIC,[21] but it is also possible that some of these patients had temporary depletion of vitamin K-dependent coagulation factors.

Our present case suggests that COVID-19 infection can cause simultaneous asymptomatic intracranial microhemorrhages and temporary depletion of vitamin K-dependent coagulation factors, which may transform the intracranial microhemorrhages into symptomatic ICH via the above-mentioned mechanisms (Fig. 4). Hence, temporary depletion of vitamin K-dependent coagulation factors resulting from COVID-19 infection may be an important risk factor for COVID-19-related ICH.

Conclusion

We propose that vitamin K levels or vitamin K-dependent coagulation factors in COVID-19 patients could predict the development of ICH and therefore should be evaluated. Furthermore, vitamin K administration as needed may improve outcomes.

Acknowledgments

None.

Abbreviations

COVID-19: coronavirus disease 2019
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
ICH: intracranial hemorrhage
DM: diabetes mellitus

PT: prothrombin time
INR: international normalized ratio
ACE2: angiotensin-converting enzyme 2
BBB: blood-brain barrier
DIC: disseminated intravascular coagulation
ICU: intensive care unit
CT: computed tomography
MRI: magnetic resonance imaging

Ethics Statement

The report was approved by the institutional review board of Kosei Hospital (No. 2021-001), and the treatment was provided according to the principles outlined in the Declaration of Helsinki. The patient provided written informed consent for this case report.

Conflicts of Interest Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Corresponding author: Narihide Shinoda, MD
Department of Neurosurgery, Kosei Hospital, 1788 Kusakabe, Doujyo-cho, Kita-ku, Kobe, Hyogo 651-1505, Japan.
e-mail: shinoda8989@yahoo.co.jp