

## Beware of bihemispheric stroke after Omicron variant infection in the elderly

SARS-CoV-2 infection can cause thrombosis in infected individuals.<sup>[1]</sup> Thromboembolic events, including ischemic stroke, are major complications of coronavirus disease 2019 (COVID-19).<sup>[2]</sup> Among strokes, bihemispheric ischemic stroke is uncommon, suggestive of an embolic source, and associated with increased death and disability.<sup>[3]</sup> In Japan, August 2022 was the seventh wave of the COVID-19 pandemic, with approximately 200,000 people infected with Omicron variants per day. During this period, we experienced elderly patients who developed bihemispheric stroke after Omicron variant infection, all with poor prognoses. A case series in clinical practice should first be considered to determine whether Omicron variants are prone to thrombosis.

### Subjects and Methods

We present a case of a patient who fully recovered from an Omicron variant infection and subsequently developed a severe stroke. Since D-dimer was high in this case, we decided to routinely measure D-dimer after the Omicron variant infection. To determine whether omicron variant infection increases D-dimer levels in the elderly, we collected D-dimer values 1 month after infection from the medical records of Omicron variant-infected patients aged 80 years or older without hypertension, diabetes, or atrial fibrillation in August and September 2022. Written consent was obtained from family members for the cases, and informed consent for D-dimer measurement was obtained in the form of opt-out through the hospital bulletin board.

### Case Presentation

A 90-year-old woman was brought to the emergency room with a cough and a high fever of 40°C and admitted after a polymerase chain reaction test proved positive for COVID-19. The patient had been independent and living alone before this hospitalization, and had no history of hypertension, diabetes, hyperlipidemia, or heart disease. Chest X-ray showed no pneumonia, and blood tests were almost within standard limits. The diagnosis of upper respiratory tract infection caused by COVID-19 was made, and the patient was treated with 5 days of antiviral therapy (1.6 g/day of molnupiravir) and intravenous infusion for anorexia and recovered well in 10 days. Two weeks later, however, she suddenly became unconscious and was again brought to the emergency room. Her level of consciousness was comatose and her blood pressure

was 90/70 mmHg, showing a decreasing trend. Blood tests showed a mild increase in white blood cells and a high D-dimer of 16.2 µg/ml. Her computed tomography scan of the head showed an extensive ischemic stroke in the brainstem and bilateral cerebellum [Figure 1], which unfortunately did not respond to life-saving treatment. During COVID-19 treatment, the electrocardiogram (ECG) was in sinus rhythm and no atrial fibrillation was observed. Therefore, after COVID-19 treatment, no further examination or treatment was performed because the patient was independent in activities of daily living and had no symptoms that would raise suspicion of heart failure, arrhythmia, or thrombosis. A limitation of this case was that blood data, ECG, and carotid echocardiogram were not performed immediately before the onset of stroke. Another limitation of this case is that magnetic resonance imaging and magnetic resonance angiography could not be performed because of the rapid deterioration of the patient's general condition at the onset of stroke. Despite these limitations, the abnormally high D-dimer at the onset of stroke, with no apparent cause, suggests that the Omicron variant infection caused the coagulation abnormality that led to the infarction.

### D-dimer Values after Omicron Variant Infection

Twenty patients over the age of 80 years who were infected with the omicron variant, and had no risk



**Figure 1:** Head computed tomography image of the patient head CT scan of the patient indicated low-density area beginning to appear in the brainstem and bilateral cerebellum (indicated by white arrows). CT: Computed tomography

factors for thrombosis were included in the analysis. Seven were men and 13 were women, with a mean age of 83.2 years. One month after the Omicron variant infection, 18 of the 20 patients had normal D-dimer levels of 1.0 µg/ml or less, but 2 had abnormally high levels of 5.5 µg/ml and 16.4 µg/ml. These two patients had no subjective symptoms. The D-dimer positivity rate at 1 month after the Omicron variant infection was 10%. These two patients with asymptotically high D-dimer levels after Omicron variant infection were prescribed anticoagulants to prevent stroke. Of the 20 eligible subjects, 17 were treated with antivirals at an early stage, and 2 subjects with high D-dimer levels were also treated with antivirals at an early stage.

## Discussion

There is emerging evidence that COVID-19 infection can trigger thrombosis because of a hypercoagulable state, including large-vessel occlusion ischemic strokes. Kurian *et al.* showed that COVID-19 infection increases the risk of inducing bihemispheric ischemic stroke. They reported in detail 5 cases of bihemispheric ischemic stroke associated with COVID-19 infection; the patients were under 70 years of age, had elevated D-dimer, ferritin, and interleukin-6, and showed severe viral inflammation and hypercoagulability.<sup>[4]</sup> We also reported a case of cerebral infarction in the insular cortex after the COVID-19 conventional strain pneumonia.<sup>[5]</sup> In a multivariate analysis controlling for race and ethnicity, COVID-19 infection is significantly and independently associated with large vessel occlusive stroke, with an odds ratio of 2.4.<sup>[6]</sup> All of these reports are mainly from conventional strains and are cases of high inflammation, such as pneumonia. However, the Omicron variant, which is currently exploding in Japan, is primarily an upper respiratory tract infection, with a decreased incidence of pneumonia and cytokine storms. Despite the mild respiratory symptoms, stroke occurs with a certain frequency in the elderly. Even if the Omicron variant reduced pathogenicity to the respiratory system, it may not alter the properties affecting the coagulation system causing thrombotic disease. In general, early antiviral therapy against COVID-19 is effective in reducing viral replication and preventing complications such as thrombus formation in elderly populations.<sup>[7]</sup> Our case was treated with antivirals early in the infection but developed a severe stroke. The use of antiviral agents does not necessarily prevent cerebral infarction. In the present study, approximately 10% of patients had

asymptomatic hypercoagulability after the Omicron variant infection, suggesting that endothelial cell inflammation may persist.

## Conclusion

Although the omicron variant is less pathogenic to the respiratory system, hypercoagulability may occur in the elderly, as with previous strains. Therefore, the elderly should be aware of serious thrombotic complications, especially large vessel occlusive stroke including bihemispheric stroke, and patients with elevated D-dimer after Omicron variant infection should be given appropriate anticoagulation for a period of time. Further case series and case-control studies are needed to prove a causal relationship between thromboembolism and Omicron variants.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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