

## COVID-19 AS A POTENTIAL RISK FACTOR FOR ISCHEMIC STROKE: A CASE REPORT

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### ABSTRACT

**Background:** Coronavirus disease 2019 (COVID-19) is a pandemic disease with a wide spectrum of symptoms. Neurological symptoms are often found in this disease. Stroke on the otherhand is a multifactorial disease that can be caused by a lot of underlying problems. Recent study suggests that patients with COVID-19 have higher proportion of ischemic stroke than patients with influenza infection.

**Case:** We report a case of a 67 years old male with a weakness on the right side that was worsened one day before admission in the hospital and shortness of breath. The patient had history of stroke before and controlled hypertension.

Head CT-scan showed a stroke infarct and Swab RT-PCR positive for SARS-CoV-2.

**Discussion:** Infection may become the risk factor of stroke. Inflammatory mediators such as TNF- $\alpha$  and CRP support the procoagulant state which leads to stroke. Infection in COVID-19 can cause an increment of inflammatory mediators, which become one of the risk factor in ischemic stroke.

**Conclusion:** COVID-19 may increase the risk of stroke due to the inflammation state that leads to a procoagulant state.

**Keywords:** COVID-19, stroke, infection

### Background

Coronavirus disease 2019 (COVID-19) is a disease caused by the novel coronavirus SARS-CoV-2, characterized by a wide spectrum of symptoms with acute respiratory distress syndrome as the majority symptom.<sup>1</sup> Even though this disease predominantly affects the respiratory tract, there is a lot of evidence that this virus can affect other systems, which include the nervous system.<sup>2</sup> Neurological symptoms can vary from mild to severe. The mildest manifestation of this disease is anosmia or ageusia, while the worst case of neurological manifestations are encephalitis, stroke, and intracranial hemorrhage.<sup>3</sup>

Stroke is a cerebrovascular condition in which a cerebral artery is occluded or ruptured, resulting in cerebral infarction or hemorrhage. It is the second leading cause of mortality globally, with 80.5 fatalities per 100,000 people. This disease also often leads to disability and death worldwide. As the world's second-biggest cause of mortality, this disease has the ability to impact aspects of life. In order to reduce the impact of this disease, current and recognized risk factors should be extensively explored.<sup>4</sup>

The risk factors of stroke are multifactorial. Many of the modifiable and hereditary risk factors linked to stroke etiology have been thoroughly investigated. Some pathogens such as bacterial (syphilis and tuberculosis), fungal (Cryptococcus and aspergillus), parasitic (neurocysticercosis), or even virus (SARS-CoV-2) may become the risk factor of stroke. However, the role of infectious pathogens in causing cerebrovascular episodes have been underrated.<sup>5,6</sup>

COVID-19 is primarily a respiratory disease. However, many reports suggest that this condition may lead to a hypercoagulability state and cause thrombotic events. The proportion of patients that have been hospitalized with COVID-19 and stroke are higher than patients with influenza infection and ischemic stroke.<sup>7</sup>

### Case Report

A 67 years old male came to the hospital with the main complaint of weakness on the right side of his body and shortness of breath. The shortness of breath was felt two days before arrival in hospital with dry cough and fever. This patient had a history of stroke in 2015 with weakness on the right side of the body. This weakness was worsened one day after shortness of breath. He also had a history of controlled hypertension and controlled diabetes. This patient took amlodipine

once daily. Physical examination showed blood pressure was 123/62 mmHg, the axillary temperature was 37,8°C, respiratory rate was 28 times per minute, and pulse rate was 88 times per minute. Glasgow coma scale was E3V5M6. This patient showed supranuclear right lingual palsy. Motor strength on the MRC scale was two on the right extremities and five on the left extremities. Sensory examination within normal limit. Laboratory examination revealed leukocytes 26.500/uL, thrombocyte 516.000/uL, Neutrophil lymphocyte ratio was 15.25, random blood glucose was 283 mg/dl, D-dimer was >10.000ng/ml, activated partial thromboplastin time (aPTT) was 22,9 seconds, prothrombin time (PT) 13,3 seconds, and C-reactive protein (CRP) 130 mg/dl. This patient also took a swab RT-PCR SARS-COV-2 test with a positive result. Upon arrival Head Computerized Tomography-scan (CT-scan) showed subacute infarction on right basal ganglia up to corona radiata (Figure 1).



**Figure 1.** Head CT-scan showed subacute ischemic cerebral infarction in left basal ganglia up to left corona radiata.

This patient was treated with enoxaparin sodium 0.6 ml twice a day, clopidogrel 75 mg once daily, citicoline 500 mg twice daily, and remdesivir 200 mg once for one day and lowered to 100 mg daily up to 10 days.

### Discussion

Respiratory infections have been known to be the risk factor of stroke even before COVID-19.<sup>8</sup> The mechanism may be inflammatory reaction that lead to the activation of the procoagulant state. There might be some pathways in activating the

procoagulant state. The monocyte activation from endotoxin can promote coagulation through thromboplastin. Cytokines such as Tumor Necrotic Factor- $\alpha$  (TNF- $\alpha$ ) may inhibit the fibrinolytic system leading to coagulation.<sup>5</sup>

Compared to the non-COVID-19 population, patients with COVID-19 had a disproportionately higher stroke rate.<sup>8</sup> SARS-CoV-2 binds to the angiotensin-converting enzyme-2 (ACE-2) receptor to enter the human cells. The ACE-2 receptor is expressed all over the human body, especially in neurons, endothelial cells, and arterial smooth cell muscle in the central nervous system, which explain many neurological manifestations in COVID-19. However, the mechanisms of stroke are still multifactorial.<sup>9</sup>

COVID-19 patients show increment in acute chemical inflammatory mediators such as TNF- $\alpha$  resulting in vascular injury and endothelial injury. TNF- $\alpha$  will bind to the TNF receptor and induce a prothrombotic event.<sup>10</sup> Coagulopathy is observed in most patient with COVID-19. The majority of patients will have a high D-dimer on examination, but their prothrombin time and activated partial thromboplastin time are normal or just slightly prolonged, which is different from disseminated intravascular coagulation (DIC).<sup>9</sup> High level of D-dimer may be a marker of systemic hypercoagulability that leads to stroke.<sup>11</sup>

There was an increment of C-reactive protein (CRP) in our patient. CRP is a marker of inflammation and a predictor of cardiovascular events. In COVID-19, CRP is often found to be increased.<sup>12</sup> This protein may also promote atherogenesis through inflammatory protein release such as reactive oxygen species (ROS), furthermore promoting adhesion of platelet to endothelial. The increment of ROS lowers nitrite oxide and endothelial dysfunction will come afterward. All of these events will cause thrombotic events.<sup>13</sup>

The high platelet count that was found in our patient is associated with COVID-19. In COVID-19, thrombocytopenia is often found. However,

thrombocytosis may also be found even though rare.<sup>12</sup> A high platelet count is a risk factor for stroke. In COVID-19, thrombocytosis is associated with the disease activity and considered to be a result of the direct action of the virus or the effect of inflammatory cytokines.<sup>13</sup>

Patients with COVID-19 and stroke must be laboratory monitored. High D-dimer in laboratory examination can be treated with low molecular weight heparin (LMWH) and can be initiated upon admission if the patient has not undergone intravenous thrombolytic therapy with the absence of hemorrhagic. Patient who receives intravenous thrombolytic therapy can get LMWH after 24 hours post thrombolytic therapy. Study from Tang et al. suggested that patient with a high D-Dimer level (6 times higher than normal baseline) benefit from taking LMWH such as enoxaparin and decrease the mortality rate.<sup>16,17</sup> The usage of a single antiplatelet in ischemic stroke with COVID-19 is not recommended. Study from Matli K et al. suggested that giving a combination of antiplatelet and anticoagulant can be more beneficial than using anticoagulant alone without the occurrence of major bleeding.<sup>18</sup>

### Conclusion

In our patient, we suggest that COVID-19 may increase the risk of stroke due to the inflammation state that leads to procoagulant state; however other risk factors such as diabetes and hypertension also have a supporting role in increasing the risk of stroke. Recent studies suggest the combination of anticoagulant and antiplatelet in treating patients with COVID-19 and ischemic stroke, even though this management strategy can be changed with emerging data.

### Conflict of Interest

None

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