

Stroke During COVID-19 Pandemic

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Coronavirus disease 2019 (COVID-19) pandemic has affected the whole world and is still a major threat to humanity. Knowledge about the frequency of stroke, which is still a leading cause of morbidity and mortality, during this pandemic, its associations with COVID-19 and its clinical course in infected people are gradually increasing.

The frequency of stroke in the pandemic era can be evaluated in two different perspectives; for the general population and in cases diagnosed with COVID-19. The frequency of stroke is reported between 2.8% and 5.4% among confirmed and hospitalized COVID-19 cases. (1-2). In another study evaluating the patients in intensive care unit (ICU), the frequency of ischemic stroke was found to be 1.6% (3). Most of the reported cases are diagnosed with ischemic stroke (4). However, the studies mentioned above have a retrospective design and a small sample size. Other concerns include the lack of detailed clinical and neuroradiological features and a higher rate of stroke in COVID-19 cases with moderate and severe clinical course. Initial observations indicate that the presence of ischemic or hemorrhagic stroke is associated with poor prognosis in COVID-19 infection (1). This might partially be explained by the higher prevalence of stroke risk factors in these patients such as hypertension and diabetes, which are also indicative of poor outcome in COVID-19 infection.

On the contrary, most of the clinicians observed a decrease in the number of stroke admissions to the emergency departments (ED). In a report from Italy, which experienced the most devastating effects of the COVID-19 pandemic, only 6 patients with acute stroke had admitted to the ED between 21 February and 25 March 2020 and only one patient with large vessel occlusion was recorded. They also reported that the average monthly number of 5 years for acute stroke was 51 and large vessel occlusion ratio was found to be %21 before the pandemic (5). The discrepancy between these numbers is striking. To reduce COVID-19 infection transmission rate, people were asked not to visit the ED unless it was truly necessary. Patients with minor stroke presentations might have been reluctant to go to the ED during the pandemic. These precautions may partly explain the reductions in stroke acute admission. However, the paucity of stroke admissions can't solely be explained by this socio-demographic reasoning, since patient with major strokes and severe clinical presentations would still have to admit to the EDs.

Recently, Oxley et al. shared their concerning observations about an increase in the number of young ischemic stroke cases presenting with severe ischemic stroke in New York City, the epicenter of the pandemic in the USA. While the number of patients admitted with stroke due to major vascular occlusion under the age of 50 was 0.73 in the 2 weeks before the pandemic, five patients applied to the EDs during the period of 23 March - 7 April 2020 (6). All of them also tested positive for COVID-19 and only 3 of them had a history of well-known risk factors for stroke such as hypertension, diabetes or hyperlipidemia. The National Health Institute Stroke Scores (NIHSS) on admission varied between 13 and 23 and mean time from onset to admission was 12.3 hours (2-28 hours). The patient admitted to the hospital on the 28th hour of symptoms reported that her delay in admission was caused by concerns about getting infected. Unfortunately, she had missed the opportunity of receiving acute stroke therapy. Among these patients, only one patient improved after thrombectomy, and this patient had to be transferred to the intensive care unit (ICU) due to COVID-19 related multiple organ failure. These delayed admissions to stroke centers may affect acute stroke therapy adversely during the pandemic (6).

There might be several explanations for underlying pathophysiological mechanisms leading to stroke in the course of COVID-19 infection. The uncontrolled cytokine storm in severe COVID-19 presentations leads to multi-organ failure. Pathological destructive mechanism operating through the endothelial system leads to the activation of the microthrombotic pathway and may result in stroke. Levels of serum markers of inflammation and thrombosis such as d-dimer, fibrinogen, CRP, tumor necrosis factor-alpha (TNF-a), interleukin 2 (IL-2) receptor and interleukin 6 (IL-6) are increased in COVID-19 patients. It has been proposed that increased IL-6 levels are associated with increased infarct volume and poor outcome in patients with stroke (7). Another study showed that IL-6 has a role in promoting post-stroke angiogenesis (8).

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Viral inclusion particles were detected in endothelial cells in postmortem examinations of infected patients. Direct endothelial damage and endothelial inflammation may cause ischemic events (9). In sepsis, excessive complement activation generates membrane attack complexes which lead to endotheliopathy. Chang (2019) proposed the “two-activation theory of the endothelium” (10). Inflammatory pathway activation may trigger release of cytokines (IL-1, IL-6, TNF- α , etc.) and lead to systemic inflammatory response syndrome (SIRS). The microthrombotic pathway activates platelets and triggers exocytosis of unusually large von Willebrand factors (ULVWF). The platelet-ULVWF complexes form microthrombi in targeted tissues. As a result, endothelial injury associated with microthrombotic disease may lead to multiple organ failure and thrombotic thrombocytopenic purpura (TTP) in this clinical setting. Cytokine storm and prothrombotic activation in the course of COVID-19 may cause widespread microthrombi formation resulting in increased d-dimer levels in patients (11). Furthermore, acute myocarditis and heart failure may be a risk factor for cardioembolic strokes in patients with COVID-19 (12). Hypoxia related acute respiratory distress may alter cerebral autoregulation and may cause intracerebral hemorrhage, cerebral vasodilation, and edema (13). Increased levels of D Dimer, ferritin, lactic acid dehydrogenase, and IL-6 together with lymphopenia can be indicators of cytokine storm in severe COVID-19 infection (14). Inflammasome related inflammation, type I interferon response, and NF κ B also may contribute to hyperinflammatory response (15). Upon these findings decreased fibrinogen and thrombocytopenia may lead to coagulopathy. Moreover, thrombocytopenia and anticoagulants used for preventing thrombosis increase the risk of intracerebral hemorrhage and may be deleterious for the already very sick patient.

In conclusion, there are still too many unknown factors about stroke from the perspective of the COVID-19 pandemic. In this short period of time, we may infer that COVID-19 seems to have different clinical features in comparison to the features of other well known viral pneumonia. Our knowledge in this era will increase with careful monitoring and recording of new cases. This will help to understand the underlying pathophysiological mechanisms and prompt clinicians to navigate new preventive and therapeutic approaches in the stroke management of COVID-19 pandemic in a timely fashion.

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