10

COVID-19 and Stroke: A Neurological Perspective

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Abstract: The risk factors for stroke increase with age. During the pandemic, the novel coronavirus disease (COVID-19) has become another risk factor for stroke. Although in its infancy, emerging data suggest that COVID-19 not only increases the risk of stroke, especially in the elderly, but also its severity. Thromboembolic events leading to a hypercoagulative state appear to be the leading mechanism. This chapter provides an overview of our current knowledge of COVID-19 being a risk factor for stroke. The epidemiology, risk factors, pathology, and mechanisms of COVID-19-mediated stroke are discussed from a neurological perspective.

Keywords: cerebrovascular diseases; COVID-19; pandemic; stroke; thrombosis

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INTRODUCTION

The novel coronavirus disease (SARS CoV-2 or COVID-19) has affected over 110 million people worldwide and resulted in more than 2 million deaths as of February 2021. While the primary clinical features of COVID-19 infection are pulmonary, along with general symptoms such as weakness, fever, cough and dyspnea, neurological signs and symptoms have also been reported, prompting the importance of neurological evaluation of COVID-19 patients (1–7). Neurological diseases account for 10.2% of global loss in health, cause 16.8% of global deaths, and 9.4 million people in the world lose their lives every year because of neurologic diseases (8). The COVID-19 pandemic is an additional ongoing threat for this widespread and important group of diseases (7, 9–12). While the field is rapidly emerging, this chapter summarizes our current knowledge on the role of COVID-19 in stroke from a neurological perspective.

THE EFFECTS OF COVID-19 ON STROKE EPIDEMIOLOGY

It has been reported that bacterial and viral infections can trigger acute ischemic stroke, probably through the prothrombotic effect of the inflammatory response (13–15). COVID-19 increases the risk of acute ischemic stroke. Li et al. reported that, of the 219 patients with COVID-19, 10 (4.6%) developed acute ischemic stroke and 1 (0.5%) had an intracerebral hemorrhage (16). These findings were supported by the report of Kverland et al. who showed that elderly patients are at high risk of developing stroke and cerebrovascular complications (17).

The European Academy of Neurology (EAN) core COVID-19 Task Force initiated a survey on neurological symptoms observed in patients with COVID-19 infection (18). The survey was mainly completed by neurologists. By 27 April 2020, data were collected from 2343 responders (out of 4199), of whom 82.0% were neurologists, mostly from Europe. According to the survey data, the most common findings were headache (61.9%), myalgia (50.4%), anosmia (49.2%), ageusia (39.8%), impaired consciousness (29.3%), psychomotor agitation (26.7%), day-time sleepiness (24.3%), encephalopathy (21.3%) and cerebrovascular events (21%). Less frequent neurological findings were dysphagia (11.2%), sleep disorders other than hypersomnia (10.7%), peripheral nerve damage (8.5%), seizures (8.1%), ataxia (7.4%), meningeal signs (5.7%), movement disorders (5.2%), and visual abnormalities (5.1%). As can be seen, cerebrovascular disorders were one of the most common findings in COVID-19 patients. (18). Qureshi et al. reported that about 4.9% of COVID-19 patients had an acute ischemic stroke during initial hospitalization (19, 20). When compared with COVID-19-negative patients, there was a two-fold increase in death, or discharge to a destination other than home, in COVID-19-positive patients (19). In a systematic review, Fraiman et al. (21) reported that, of the 275 patients with cerebrovascular events, 226 had an ischemic stroke, 35 had a hemorrhagic stroke, and 14 cases were with cerebral venous sinus thrombosis (CVST). In the prospective study of Karadas et al., the frequency of cerebrovascular diseases was 3.8% (22). Age was reported as an important risk factor for stroke and COVID-19. Most patients were significantly older with cardiovascular risk factors, including hypertension, diabetes and a

medical history of cerebrovascular disease (17, 20, 21). Other risk factors included smoking, alcohol consumption and chronic kidney disease (17, 21).

MECHANISMS OF COVID-19-MEDIATED CEREBROVASCULAR COMPLICATIONS

The detection of neurologic symptoms in COVID-19 patients can be improved through awareness. It is possible that some findings in these patients who are isolated, and whose examination conditions are difficult, will be overlooked. The most common patient-reported symptoms are headache, nausea, and vomiting. Also, vertigo, sleep disorders, visual disturbances, myalgia, seizures, and changes in consciousness have been reported. Olfactory and taste disorders are the most common early neurologic findings (23, 24).

COVID-19-mediated neurological symptoms are thought to occur through various mechanisms. These mechanisms can be summarized as follows: (i) invasion of the virus into the neurologic system by a neurotropic effect; (ii) the inflammatory response initiated by the virus causing secondary damage in neurologic systems; (iii) the effects on the respiratory and cardiac systems causing hypoxemia in the brain; and (iv) the viral and inflammatory effects on coagulation parameters, for example, increased fibrin D-dimer levels, erythrocyte sedimentation rate, lactic acid dehydrogenase, and lymphopenia, leading to cerebrovascular disease (7, 25–27).

SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) in brain endothelial and smooth muscle cells. Angiotensin II is pro-inflammatory, induces vasoconstriction, and promotes organ damage. Depletion of ACE2 by SARS-CoV-2 may enhance the activity of the ACE1/angiotensin II axis and promote tissue injury, predisposing to stroke (18, 21, 27, 28). Stroke has been shown to occur at a higher rate in patients with COVID-19 compared with patients with influenza (14). Evidence suggests that infected patients may develop significant coagulopathy which leads to thromboembolic complications like stroke, peripheral artery thrombosis, deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, and venous sinus thrombosis (29, 30). Histopathologic analysis of the ischemic brain of a COVID-19 patient revealed hypoxic neurons, significant edema from the underlying ischemic insult, fibrin thrombi in small vessels, and fibroid necrosis of the vascular wall without any signs of vasculature inflammation (31). The authors suggested that the cerebrovascular thromboembolic events in COVID-19 infection may be related to acquired hypercoagulability and coagulation cascade activation due to the release of inflammatory markers and cytokines, rather than virus-induced vasculitis. Microthrombi within the vessels were more consistent with a systemic inflammatory response-mediated mechanism, probably related to elevated serum inflammatory markers such as D-dimer and fibrinogen (31, 32).

Venous thromboembolism is also higher in patients with COVID-19, especially in those who were severely affected and needed intensive care (33) (Table 1). Brain biopsy was generally negative for the presence of SARS-CoV-2 RNA (RT-PCR assay) (31). Laboratory findings showed a hypercoagulable state as evidenced by elevated C-reactive protein, fibrinogen, D-dimer and ferritin

TABLE 1 **Registries, Observational Studies and Case Series of Cerebrovascular Disease (CVD) Manifestations with COVID-19 (9, 16, 18, 19, 21, 22, 27, 33)**

Authors	Publication Type	Sample size	Cerebrovascular Disease
Fraiman et al. (21).	Systematic review	275	226 AIS, 35 HS, 14 CVST
Karadas Ö, et al. (22)	Prospective, observational study	239	7 AIS, 2 ICH
Klok FA et al. (33) 0	Retrospective, observational study	184	3 AIS
Li et al. (16)	Retrospective, observational study	219	10 AIS, 1 ICH
Mao et al. (9)	Retrospective, observational study	214	4 AIS, 1 ICH
Morassi et al. (27)	Case series	6	6 AIS, 2 ICH
Moro E et al. (18)	Survey 2343 respondent		%21 CVO
Quereshi et al. (19)	retrospective cohort study	103	AIS

AIS, acute ischemic stroke; HS, hemorrhagic stroke; CVT, cerebral sinus thrombosis.

levels (17, 31). Other findings included leukocytosis, leucopenia, thrombocytopenia, thrombocytosis, and elevated lactate dehydrogenase (18).

Radiological features of patients with COVID-19 revealed findings typical of stroke. Computed tomography (CT) of the head showed areas of infarction of the involved arterial region. CT angiogram (CTA) of the head and neck showed thrombus, suggesting large vessel occlusion, and focal narrowing of the vessel, but did not demonstrate evidence of vessel dissection or atherosclerotic plaques (31). CT, CTA, MRI (magnetic resonance imaging) and MRA (magnetic resonance angiography) revealed supratentorial lobar intracerebral hemorrhage (ICH), deep supratentorial ICH, cerebellar and truncal ICH, extensive supra- and infratentorial ICH in addition to venous infarction with hemorrhagic transformation (64.29%). Involvement of the transverse sinus, straight sinus, sigmoid sinus, superior sagittal sinus and the vein of Galen were seen (18, 21).

Previous stroke history has been reported not only as a risk factor for COVID-19 but also for more severe forms of the diseases and poorer prognosis (21, 34). In-hospital mortality was significantly high in patients with acute ischemic stroke during the pandemic period (8.1% versus 7.6%, $P = 0.006$) (33). Registries, observational studies and case series of cerebrovascular disease (CVD) manifestations with COVID-19 are shown in Table 1 (9, 16, 18, 19, 21, 22, 27, 33).

STROKE CARE DURING COVID-19

Since the beginning of the COVID-19 pandemic, there have been lockdowns and efforts to increase awareness of social distancing and hygiene measures.

Lockdown periods could cause hesitation among patients to admit themselves to hospitals for routine care of chronic diseases, or for acute health care such as stroke, which is a time-dependent condition (34). Richter et al. conducted a nationwide study using the administrative databases of all hospitalized patients diagnosed with acute ischemic stroke (AIS), transient ischemic attack, or intracerebral hemorrhage, including 1463 hospitals in Germany (35). To evaluate the effects of the pandemic on stroke admissions, they compared case numbers and treatment characteristics of pre-pandemic and pandemic periods. There was a significant decline in hospitalization for AIS (–17.4%), transient ischemic attack (–22.9%), and intracerebral hemorrhage (–15.8%) during the pandemic. Interventional procedures continued for the patients who were admitted. IVT rates in patients with AIS were not different but mechanical thrombectomy rates were found to be significantly higher during the pandemic. Patients with AIS continued to receive acute recanalization treatment (35). Schlachetzki et al. analyzed data related to ischemic stroke from 12 hospitals; intravenous (IV) thrombolytic treatment, endovascular treatments (EVT), and related consultations using the telestroke (stroke telemedicine) TEMPiS "working diagnosis" were analyzed (36). They performed the analysis prior to, within, and after easing of lockdown. They concluded that the decrease in emergency admissions for stroke during the pandemic was largely attributed to patients not seeking medical attention and a lack of stroke awareness (36). There are further reports showing a similar trend of time-dependent declines in hospitalization for stroke during the pandemic and nationwide lockdowns (37–46). Reduced social contact, fear of potential in-hospital COVID-19 infection, disrupted functioning of stroke centers, active emergency services, and lack of family members or bystanders are some of the additional reasons for reduced hospitalization for stroke during the pandemic (47). This requires due attention because patients may be putting themselves at risk during the pandemic. Acute stroke therapies are time-sensitive, and therefore decreased healthcare access may lead to more disabling or fatal strokes or more severe non-neurological complications related to stroke.

CONCLUSION

Current evidence shows that COVID-19 predisposes patients to various cerebrovascular and neurological complications including stroke. The SARS-CoV-2 virus promotes a hypercoagulative state through various mechanisms, but further studies are required to better understand the mechanisms and treatment of COVID-19-mediated stroke. While it is unpredictable how long the current situation will last, there have been unprecedented changes in service delivery, education, research, dissemination of existing methods, and organization and meetings. There has already been an enormous sharing of expertise throughout the world to help implement best practices, which is a major achievement.

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