



## Cerebrovascular disease in COVID-19: Is there a higher risk of stroke?

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### ABSTRACT

The presence of stroke has been observed in young adults (under fifty years of age) without cardiovascular risk factors who are suffering from COVID-19. It is speculated that there is really a significant increase, as a few cases have yet to be described, or that the infection favors his development. Cerebrovascular events are more common in older patients with stroke risk factors, such as hypertension and diabetes mellitus, and those who have elevated fibrin D-dimers. Multiple case reports and series about cerebrovascular disease (CVD) in COVID-19 has been informed. The mechanism that causes cerebral ischemia in COVID-19 remains undiscovered. However, progressively there is increasing evidence of hypercoagulability that can be or contribute to the cause. We review the current literature about CVD both epidemiology and etiology. More studies are needed to understand.

The presence of stroke is currently being observed in young (under 50 years of age) who are under the age of 50 and without cardiovascular risk factors. Oxley and colleagues recently described a case series of large-vessel strokes as an initial presentation in COVID-19 patients younger than 50 years old (Gunasekaran et al., 2020), that is, people without age or risk factors sufficient to expect a stroke. A retrospective study of data from the Covid-19 outbreak in Wuhan, China, showed that the incidence of stroke among hospitalized COVID-19 patients was approximately 5%, with the youngest patient being 55 years old (Oxley et al., 2020). There is speculation whether there is really a significant increase, as only few cases have been described, or whether the infection actually favors the development of stroke. Cerebrovascular events were more common in older patients with stroke risk factors such as hypertension and diabetes mellitus, and those who had elevated fibrin D-dimers (Mao et al., 2020) (Li et al., 2020).

Researchers at the University Hospital of Zurich noted that the SARS-CoV-2 virus or COVID-19 infects hosts through the angiotensin-converting enzyme (ACE2), expressed not only in the lungs but also in the heart, kidney, intestine and endothelial cells. And they described three cases in which they observed direct viral infection of the cells and diffuse endothelial inflammation (endothelitis) (Varga et al., 2020). COVID-19 endothelitis could explain the impaired microcirculatory function in different vascular beds and its clinical sequelae in patients with COVID-19 (Li et al., 2020; Varga et al., 2020).

Another study of 184 intensive care unit (ICU) patients with proven COVID-19 pneumonia found that 31% of them have symptomatic acute

pulmonary embolism, deep vein thrombosis, ischemic stroke, myocardial infarction, or systemic arterial embolism. Researchers speculated a problem with the coagulation system or the endothelial lining of blood vessels (Morassi et al., 2020). Coagulopathy and vascular endothelial dysfunction have been proposed as complications of COVID-19 (Zhou et al., 2020a).

Li, Y., et al.'s retrospective study 221 patients with COVID-19, 13 (5.9%) developed cerebrovascular disease after infection. Of these patients, 11 (84.6%) were diagnosed with ischemic stroke, 1 (7.7%) with cerebral venous sinus thrombosis, and 1 (7.7%) with cerebral hemorrhage. With the exception of a 32-year-old patient with cerebral venous sinus thrombosis, the patient's age ranged from 57 to 91 (Li et al., 2020). All patients showed an increased inflammatory response and a state of hypercoagulability (Li et al., 2020). These findings suggest that older adults affected by COVID-19 may be more likely to develop cerebrovascular disease (CVD) and that more attention should be given to those with risk factors for vascular disease. In the study of Yaghy et al. out of 3556 hospitalized patients diagnosed with COVID-19 infection, 32 patients (0.9%) had imaging proven ischemic stroke (Yaghy et al., 2020). It should be noted that all study participants are hospitalized patients with symptoms. Notably, only about 20% of those infected have symptoms (Wang et al., 2020; Zhou et al., 2020b); therefore, if around 1% of patients presented stroke, this corresponds to 0.2% of all those infected. In the considerably smaller sample of Li Y et al. that had 221 cases, data indicated 5% of ischemic strokes (5.9% of strokes) in symptomatic COVID-19 patients, upon admission, which corresponds to 1% of the

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total number of infected cases (Li et al., 2020). We can consequently conclude with current data that between 0.2 and 1% of those infected with COVID-19 develop ischemic strokes. Eleven of 13 (84.6%) CVD patients had severe COVID-19 infection, suggesting that severe infection may be an indicator of CVD, especially of acute ischemic stroke.

The authors conclusively consider that CVD is not uncommon in patients with COVID-19., that the patients who presented CVD were mostly older adults, and that the latter had multiple risk factors (e.g., hypertension and diabetes), more severe COVID-19 infection, and an inflammatory response that induced the state of hypercoagulable blood (Li et al., 2020).

SARS-CoV-2 penetrates the cell using as receptor the angiotensin-converting enzyme 2 (ACE2), a membrane exopeptidase mainly presents in the airway epithelium, pulmonary parenchyma, vascular endothelium, brain, kidney, heart, testicular tissue and intestine (Baig et al., 2020). The role of ACE2 is the transformation of angiotensin I into angiotensin II. These final products have vasodilatory, antifibrotic, and anti-inflammatory effects and favors natriuresis. ACE2 has been identified as the functional receptor for COVID-19 (Garabelli et al., 2008; Stewart et al., 2008; Kassiri et al., 2009; Imai et al., 2005). Autopsy results of patients with COVID-19 showed that brain tissue was hyperemic and edematous, and some degenerate neurons (Mao et al., 2020). And recent autopsy findings suggest thrombotic microangiopathy in multiple organs, especially in the lungs. With this evidence, the most plausible mechanism of early cerebrovascular accidents could be hypercoagulability leading to macro and micro thrombi formation in the vessels (Avula et al., 2020). Severe cases of COVID-19 have been shown high levels of angiotensin II, and these levels has been correlated with SARS-CoV-2 viral load and lung damage (Liu et al., 2020). This same effect has been observed during the SARS outbreak in 2003 (Li et al., 2003; Kuba et al., 2005). Moreover, large-vessel stroke was reported during the 2004 SARS-CoV-1 outbreak in Singapore (Umapathi et al., 2004).

Inflammation has been increasingly recognized as a key contributor to the pathophysiology of CVD and is involved in acute intravascular events caused by disruption of the blood supply (Iadecola and Anrather, 2011). Meanwhile, inflammatory factors in the blood (for example, interleukin and C-reactive protein) are responsible for the first molecular events triggered by coagulation abnormalities (Ding et al., 2018; Ji et al., 2014; Horvei et al., 2016).

In the study of Mao et al., 5.7% of patients developed CVD later in the course of illness in patients with severe infection (Mao et al., 2020). In Li Y et al.'s study, the incidence of stroke in COVID-19 patients was about 5%, with a median age of 71.6 years (Li et al., 2020). These patients had severe disease and a higher incidence of risk factors, such as hypertension, diabetes, coronary artery disease, and previous cerebrovascular disease (Li et al., 2020). Average time of onset of stroke after COVID-19 diagnosis was 12 days (Li et al., 2020). Elevated CRP and D-dimer indicating high inflammatory state and abnormalities with coagulation cascade might respectively contribute to strokes in patients with COVID-19 infection (Li et al., 2020).

In a study of 191 COVID-19 patients in Wuhan, China, researchers found that D-dimer levels of  $>1 \mu\text{g/L}$  were associated with an 18-fold increase in the likelihood of death before discharge (Zhou et al., 2020a). Patients with COVID-19 with an elevated serum ferritin level had a 9-fold increase in the likelihood of death before discharge (Zhou et al., 2020a). Hyperferritinemia, although nonspecific, can be a marker of an inflammatory response (Rosário et al., 2013; Kell and Pretorius, 2014). Macrophage activation syndrome (MAS), also called cytokines storm is a rare complication of Kawasaki disease (KD). Hyperferritinemia is highly specific and sensitive for detecting MAS (Han and Lee, 2020). Notably, a list of KD cases in children with COVID-19 has recently been reported (Licciardi et al., 2020). The elevation of ferritine levels has also been reported in patients with antiphospholipid syndrome and catastrophic antiphospholipid syndrome, which are both associated with arterial and venous thromboses (Nayer and Ortega, 2014). Recently antiphospholipid syndrome has been involved in the coagulopathy in patients with COVID-19 with cerebral ischemia (Zhang et al., 2020).

The mechanism causing cerebral ischemia in patients with COVID-19 it remains undiscovered, however, there is increased evidence for a hypercoagulability (Thachil et al., 2020). A recent study from the Netherlands by Klock et al. demonstrated that 31% of critically ill intensive care unit (ICU) patients develop thrombotic complications (Klok et al., 2020). Another study exploring activated partial thromboplastin time-based clot waveform analysis (CWA) in COVID-19 patients concluded that CWA parameters demonstrate hypercoagulability that precedes or coincides with severe illness (Avula et al., 2020). At the present, multiple reports of pulmonary embolism are available in the literature and it has been observed bacterial and viral infections (Grau et al., 1998). Autopsy and pathology findings are scarcely available, but recent autopsy findings have showed thrombotic microangiopathy in multiple organs, especially in the lungs Avula et al., 2020; Iadecola and Anrather, 2011; Ji et al., 2014; Zhang et al., 2020. On the other hand, pathophysiology could be causally related to the infection or hypoxia. Neuroinflammation together with prolonged hypoxia may promote neurological manifestations (Steardo et al., 2020).

In stroke associated with COVID-19, both presentation and outcome are often worse compared to other strokes. It has been reported that stroke developed mostly in patients with severe pneumonia and multi-organ failure and the outcome was poor (Morassi et al., 2020).

In addition to the mechanisms directly mediated by COVID-19, another factor at play is the delay in the presentation in the emergency services of strokes (Teo et al., 2020), since people are afraid of interacting with the health system due to the risk of being infected. . The timely and effective delivery of acute stroke care, especially reperfusion therapy for ischemic stroke, significantly improves stroke outcomes (Oxley et al., 2020; Umapathi et al., 2004).

It is still unclear whether there is an increased risk of stroke in COVID-19 patients, whether this condition is caused by the virus, or whether the incidence of stroke in young COVID-19 patients is increased. The pathophysiology of stroke in this disease appears to be due to a state of hypercoagulability. The maintained hypoxia could contribute to an increased severity of CVD. Further studies are needed for understanding neuropathogenesis of COVID-19 and the presence of stroke. It is accurately to perform high-quality and rigorous studies that are well controlled, since making forceful statements based on small case series from a few centers with no comparison groups could be controversial. Case series are useful in raising suspicion of a novel or unique association or risk factor but should be validated in methodologically sound studies.

## Declaration of competing interest

Marcos Altable and Juan Moisés de la Serna have no conflicts of interest to disclose regarding the manuscript. The authors declare that the manuscript was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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