SARS-CoV-2 and Acute Cerebrovascular Events

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Since the coronavirus disease 2019 (COVID-19) pandemic, due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, accumulating evidence indicates that SARS-CoV-2 infection may be associated with various neurological manifestations, including acute cerebrovascular events (i.e., stroke and cerebral venous thrombosis). These events can occur prior to, during and even after the onset of COVID-19's general symptoms. Although the mechanisms underlying the cerebrovascular complications in patients with COVID-19 are yet to be fully elucidated, the hypercoagulability state, inflammation and altered angiotensin-converting enzyme 2 (ACE-2) signaling in association with SARS-CoV-2 may play key roles. ACE-2 plays a critical role in preserving heart and brain homeostasis. As the number of published COVID-19 cases with cerebrovascular events is growing, prospective studies would help gather more valuable insights into the pathophysiology of cerebrovascular events, effective therapies, and the factors predicting poor functional outcomes related to such events in COVID-19 patients.

Keywords: coronavirus disease 2019 (COVID-19) ; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ; stroke ; cerebral venous thrombosis ; hypercoagulability ; angiotensin-converting enzyme 2 (ACE-2)

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the first one of the recorded pandemics that has caused a global burden on society and health care professionals. As of the date of writing this article, on June 07, 2021, over 173.41 million cases have been reported across 188 countries and territories, resulting in more than 3.73 million deaths, and over 2.13 billion people who have been vaccinated [1]. The clinical manifestations of this disease are broad, ranging from asymptomatic cases to those with severe symptomatic disease and a case fatality rate of 2.3% [2]. The mortality is higher in elderly individuals, patients with medical comorbidities, or those with immunocompromised conditions [3]. While the primary mode of attack of the SARS-CoV-2 is through respiratory pathways, early in the pandemic reports from Wuhan, China, revealed that patients with COVID-19 might also develop neurologic symptoms (e,g. headache, dizziness, and myalgia) [4]. Ever since, it has been found worldwide that neurological complications affecting both the central and peripheral nervous system (CNS and PNS, respectively) may occur in a considerable number of patients with COVID-19 [3][4][5][6]. Direct invasion of the nervous system by SARS-CoV-2 through olfactory nerve, retrograde axonal transport, gut-brain axis, or hematogenous spread has been suggested [6][7][8][9]. Critically ill COVID-19 patients admitted to intensive care unit (ICU) may have additional risk factors for the nervous system involvement, which include deep sedation and prolonged mechanical ventilation related to severe prolonged hypoxemia, immobility and critical illness myopathy or neuropathy related to prolonged hospitalization, social isolation, and delirium [10]. A correlation between SARS-CoV-2 related acute lung injury and brain hypoxia has been recently described, which may play an important role in neurological dysfunction following SARS-CoV-2 infection [11][12].

Recent investigations have also indicated that some patients with COVID-19 may present with acute cerebrovascular events such as stroke [13][14] and cerebral venous thrombosis [15][16]. Although the mechanisms underlying such complications remain to be fully elucidated, hypercoagulability state, hyper-inflammation, and cytokine storm, as well as cerebral endothelial dysfunction may play crucial roles [17][18][19][20]. We discuss the possible mechanisms underlying the acute cerebrovascular events related to SARS-CoV-2 infection and also review the current epidemiological studies and case reports of neurovascular complications in patients with COVID-19 and relevant therapeutic approaches that have been considered worldwide.

2. Hypercoagulability related to SARS-CoV-2

One of the important findings related to the SARS-CoV-2 infection is a widespread observation of hypercoagulable state indicated by elevated D-dimer level, prolongation of prothrombin time (PT), activated partial thromboplastin time (aPTT), and abnormal platelet counts [18][21]. Both thrombocytopenia and elevated D-dimer can be justified by the disproportionate

activation of the coagulation cascade and use of its substrates; however, the pathophysiology of SARS-CoV-2 related coagulopathy is still debatable.

While pneumonia itself can cause inflammation and a hypercoagulable state, cytokine release syndrome (CRS)- and macrophage activation like syndrome (MAL)-like phenomenon are also likely to play important roles [17][18][19][21]. When endothelial cells are damaged, generally sub-endothelial cells, which are chromogenic, are exposed. The sub-endothelial cells contain Von Willebrand factor (VWF) and other thrombophilic proteins. Activated endothelial cells along with VWF will cause platelet aggregation and platelet plug formation as the primary homeostasis response. Secondarily, the coagulation cascade is activated and involves both extrinsic and intrinsic pathways followed by a common pathway [22]. When coagulopathy results from hyper inflammation and not an endothelial cell injury, the activated cascade would be an extrinsic pathway by activation of tissue factor or CD142 [23]. Tissue factor is expressed on mononuclear cells in response to interleukin (IL)-6 and other inflammatory cytokines and will activate the extrinsic pathway [24]. Also, inflammatory cytokines impose an inhibitory effect on anticoagulation regulators like tissue factor pathway inhibitors and ADPase [25][26]. Viral infection pro-coagulopathy seems to be both dependent on endothelial cells as well as innate immunity by hyper-activation of toll-like receptors (TLRs) along the surface of monocytes, macrophages, dendritic cells, and fibroblasts. Another possible contributor to this hypercoagulable phenomenon is the formation of acute reactive oxygen species and oxidized phospholipids due to acute lung injury, which seems to initiate Toll-like receptor 4 (TLR4)−TRIF (TIR-domain-containing adapter-inducing interferon-β)−TRAF6 (TNF receptor-associated factor 6)−NF-κB (nuclear factor κ-light-chain-enhancer of activated B cells) pathway [27][28]. The downstream pathway for both hyperactivation of TLRs in response to viral infection as well as acute lung injury involves NF-κB activation. As a result of NF-κB activation, there will be more IL-6 and TNF-α, which are also bi-product of CRS and MAL reactions [19][29]. Coagulopathy was previously observed in infection with other Coronaviridae viruses including SARS and Middle East respiratory syndrome (MERS) [27][30]. It is also suggested that COVID-19 may induce antiphospholipid antibodies, but usually, these antibodies are transient and found not to be pathogenic [31].

Although there are some prospective studies currently looking at the incidence of thrombotic events, early studies have already confirmed increased frequency of intravascular thrombosis leading to pulmonary embolism, myocardial infarction, ischemic strokes, and even cerebral venous sinus thrombosis. A thrombotic event was sometimes reported as the first presentation of COVID-19 infection [18][32][33]. However, whether prophylactic anticoagulation for severe SARS-CoV-2 infection is beneficial still has to be considered, according to common concurrent thrombocytopenia [17][21].

3. SARS-CoV-2 and angiotensin-converting enzyme 2

SARS-CoV-2 has spike (S) glycoproteins on its outer envelope, which have a strong affinity toward the human angiotensin-converting enzyme 2 (ACE-2) as the host cell receptor [34][35]. The binding of SARS-CoV-2 to ACE-2 is a crucial element for viral infectivity and multi-organ damage. ACE-2 is expressed in various human tissues such as CNS (glial cells and neurons), skeletal muscle, gastrointestinal tract, and endothelial cells [35]. In the cerebral vasculature, endothelial ACE-2, as part of the renin-angiotensin system (RAS), plays an important role in the modulation of cerebral blood flow. Key components of RAS are angiotensinogen, renin, angiotensin I (Ang I), angiotensin II (Ang II), ACE, ACE-2, Ang type-1 receptor (AT1R), Ang type-2 receptor (AT2R), and Mas receptor. Classically, Ang II that is produced from Ang I by ACE activity, mediates vasoconstriction, neuroinflammation, and oxidative stress through activation of AT1R and AT2R. Alternatively, Ang II can be converted to Ang-(1-7) by ACE-2 activity, which in turn activates the Mas receptor, mediating vasodilation, anti-inflammatory, and antioxidant responses [36].

Overactivation of ACE/Ang II/AT1R/AT2R or dysfunction of ACE-2/Ang (1-7)-Mas receptor axis may contribute to the pathogenesis of acute ischemic stroke via increased vasoconstriction, oxidative stress, and vascular inflammation (i.e., vasculitis) [36]. In SARS-CoV-2 infection, binding to ACE-2 may downregulate ACE-2 [37], leading to excess ACE-mediated Ang II production and less ACE-2-mediated Ang-(1-7) production [20]. This SARS-CoV-2-induced imbalance between classical and alternative RAS axis ultimately promotes ischemia via increased cerebral vasoconstriction, hyper-inflammation, and oxidative stress [20]. Ang Ⅱ promotes thrombosis by increasing the release and secretion of plasminogen activator inhibitor type 1 (PAI-1) and enhances tissue factor (TF) expression [38]. In contrast, activation of the angiotensin-converting enzyme (ACE)2/angiotensin-(1-7)/Mas receptor, would cause antithrombotic activity [39]. SARS-CoV-2 decreases activation of ACE2, the result is an imbalance between classical and alternative RAS axis ultimately promotes ischemia via increased cerebral vasoconstriction, hyper-inflammation, oxidative stress, and thrombogenesis [20]. These data raise the possibility that recombinant human ACE-2 might be beneficial in preventing ischemic stroke in COVID-19 patients with known stroke risk factors.

4. Acute cerebrovascular events in COVID-19

Prior articles indicate that viral respiratory infections are independent risk factors for both ischemic and hemorrhagic strokes [40]. Acute cerebrovascular events have been reported as one of the neurological complications that can occur in COVID-19 patients [41][42]; there is overall a propensity towards occlusion of (i) large vessels (e.g. internal carotid, middle cerebral [M1 and M2 segments], or basilar arteries); (ii) multi-territory vessels; or (iii) uncommon vessels (e.g. pericallosal artery [43]) [44]. On the other hand, intracerebral hemorrhage, cerebral venous thrombosis, and small-vessel brain disease develop less frequently in COVID-19 patients [44]. Several cases with atypical neurovascular presentations have also been reported, including bilateral carotid artery dissection [45], posterior reversible encephalopathy syndrome (PRES) [46], and vasculitis [47][48]. The pathophysiology, still unclear, is possibly related to direct damage of the vessel mediated by the virus once it invades the CNS [49], or it could be related to the development of underlying coagulopathy and thromboembolisms as we discussed earlier [33][50][51]. Another suggested mechanism is cardioembolic from direct damage of the myocardial cells, as evidenced by cardiac dysfunction and arrhythmias in these patients [52]. Accordingly, myocardial cells express ACE-2 receptors abundantly, then vulnerable to SARS-CoV-2 infection [35].

In a retrospective study that included 214 patients with confirmed COVID-19 infection, about 6% presented with acute cerebrovascular events, mainly ischemic strokes. Stroke symptoms tend to appear later during the hospitalization, with a median of 10 days after the onset of symptoms, and this was also confirmed by a larger retrospective study [53]. These patients seem to have a more severe infection with higher levels of inflammatory markers and higher D-dimer levels, older age, more comorbidities (hypertension in particular), and fewer typical symptoms associated with COVID-19 [54]. Indeed, for many COVID-19 patients presenting with acute strokes or other neurological manifestations, the diagnosis of infection is made after the hospital admission. Current recommendations from the American Heart Association (AHA) and American Stroke Association (ASA) include the use of personal protective equipment (PPE) for all the stroke teams at the time of stroke code activation since many stroke patients are unable to provide history and information for appropriate COVID-19 screening. It is indeed suggested to treat every code stroke patient as potentially affected by the infection in order to avoid any delay in trying to understand the infection status, following the same treating guidelines available for non-COVID-19 patients [55][56]. A dedicated track for triage and management of suspected or proven COVID-19 patients with stroke-like symptoms was also suggested and implemented in Italy with a mobile CT scan unit [57]. Patients eligible for neurointerventional procedures should be treated accordingly with the minimum number of staff in the angio suite and restricted access for essential staff, only ensuring quality control of negative pressure environment and following appropriate precaution protocols [58][59]. After appropriate treatment, stroke patients should be admitted to dedicated ward or ICU units where possible, and stroke teams should guide staff familiar with managing acute ischemic or hemorrhaging stroke patients [56].

4.1. Ischemic stroke

Acute ischemic stroke appears to be the most common form of stroke seen in patients with COVID-19. The initial retrospective case reports from Wuhan in China reported 6 cases (2.34%) of stroke among 214 patients analyzed, five of which were ischemic in nature [54]. Another study from Italy reported nine ischemic strokes (2.5%) among a cohort of 388 patients [51]. Different incidence rates were reported in two large studies. The first is a recent case series of 1419 patients with the diagnosis of COVID-19 admitted in a hospital in Madrid, Spain, reported a total of 14 patients with the systemic arterial thrombotic event (1% incident), of which eight presented with the cerebrovascular event (six with acute ischemic stroke and two with transient ischemic attack) [53]. A similar incidence (0.9%) was reported in the second large retrospective study of 3556 COVID-19 positive patients, of which 32 were diagnosed with ischemic stroke, 65.6% defined as cryptogenic subtype, and 34.4% as an embolic stroke of undetermined source [60]. There is a possibility that the total numbers are underestimated since patients with small acute strokes may present without apparent focal neurological symptoms and may be undiagnosed. Indeed, a case series from France documented three encephalopathic patients, with no signs suggestive of ischemic stroke, whose diagnosis was made after undergoing MRI to better address the cause of their encephalopathy [61]. Also, the difference in the incidence rates could be explained by the different patient populations and larger cohorts. Another case series Houston (Texas, USA) reported a total of 12 patients with COVID-19 who developed stroke, among which 10 cases had an ischemic stroke (including one patient with hemorrhagic transformation), and 2 had intracerebral hemorrhage [62]. Inflammatory markers (e.g., D-dimer and IL-6) were elevated in a majority of these cases [62]. The etiology was an embolic stroke of undetermined source (ESUS, 6 cases), cardioembolic (2), carotid dissection (1), hypertension-related hemorrhage (1), rupture of mycotic aneurysm related to infectious endocarditis (1), and unknown (1 case due to limited workup) [62].

Stroke patients with COVID-19 infection usually present with higher National Institutes of Health Stroke Scale (NIHSS) score at admission [60][63], more severe disease course, immunocompromised, and with different comorbidities and cardiovascular risk factors [53][54]. The age range is reported to be usually over 50 years old. However, more recently, a

case series from New York City showed 5 COVID-19 patients younger than 50 affected by a large vessel ischemic stroke presented in the emergency department within a two-week period higher than usual. Two of the five patients were previously healthy; one, had hypertension and hyperlipidemia, another had undiagnosed diabetes, and the last reported patient had a history of prior mild stroke and diabetes [64]. Data from a larger patient cohort from New York City reported stroke in COVID-19 positive patients, mainly in men (71.9%), white (70%), with an average age of 62.5-year-old versus 70-year-old in the COVID-19−negative stroke patients. Moreover, patients with COVID-19 and ischemic stroke appeared to have higher mortality than controls [60].

A large multicenter study reported stroke characteristics in 432 COVID-19 patients admitted to 71 centers from 17 countries. They observed a considerably higher rate of large vessel occlusions, a much lower rate of small vessel occlusion and lacunar infarction, and a considerable number of young strokes when compared with the population studies before the pandemic [63]. More data and studies on the incidence of stroke in young COVID-19 patients are needed.

A large international multicenter study on 17,799 COVID-19 hospitalized patients reported 156 stroke episodes, 123 (79%) of whom presented with acute ischemic stroke 27 (17%) had intracranial hemorrhage, and 6 (4%) presented with cerebral venous sinus thrombosis. The mean age for ischemic stroke among hospitalized COVID-19 was 68.6 years [65]. Another multicenter prospective cohort study that included 150 patients with COVID-19 related ARDS showed 64 thrombotic complications, 2 of which were acute ischemic stroke despite anticoagulation [66].

Given the hypercoagulable state related to the infection, as a possible cause of ischemic stroke, prophylactic anticoagulation with low molecular weight heparin (LMWH) may be recommended for patients with severe COVID-19, according to the International Society of Thrombosis and Hemostasis (ISTH) [67]. The American Society of Hematology (ASH) guideline panel recently suggested “using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with coronavirus disease 2019 (COVID-19)–related critical illness who do not have suspected or confirmed venous thromboembolism (VTE) (conditional recommendation based on very low certainty in the evidence about effects)” [68].

Higher mortality rates were observed in association with elevated PT and D-dimer levels and decreased platelet counts and fibrinogen at day 10 and 14 from the onset of symptoms [67]. Monitoring these parameters can help determine the prognosis and the selection of patients that require admission and aggressive treatments. Interestingly, in a retrospective study that included 449 patients with severe COVID-19 infection and elevated D-dimer, the use of LMWH was associated with lower mortality [69]. However, data on the efficacy of LMWH in preventing venous and arterial thromboembolic complications are conflicting [51][66]. In a case report of 6 patients presented with acute ischemic stroke and confirmed COVID-19 infection with associated elevated D-dimers level (≥ 1000 μg/L), two patients had ischemic stroke despite therapeutic anticoagulation [13]. Data from the same study showed that the primary mechanism underlying the ischemic stroke was large-vessel occlusion, and stroke usually occurred later in the course of the disease, between days 8 and 24 from the onset of symptoms. Further investigations are warranted to establish the actual need for therapeutic anticoagulation in patients with COVID-19 to reduce the risk of ischemic stroke.

PROTECT COVID (A Randomized Clinical Trial of Anticoagulation Strategies in COVID-19) is ongoing to compare the effectiveness of therapeutic versus prophylactic anticoagulation in patients with COVID-19 infection and mild to moderate elevation in D-dimer level greater than 500 ng/mL (clinical trial identifier: NCT04359277) [60]. Other randomized trials are also ongoing to investigate the anticoagulation benefits in patients with COVID-19 (NCT04362085, NCT04345848, NCT04406389, NCT04528888).

Despite the lack of defined data on the prognosis of stroke-related to COVID-19 infection, the overall outcome appears to be poor since the majority of stroke patients are older and presenting with severe infection and more comorbidities [53][60][70][71][72]. Nonetheless, mechanical thrombectomy for emergent large vessel occlusion could be justified since it can improve the outcome and should be offered to all the potential candidates notwithstanding the infectious status [59].

4.2. Hemorrhagic stroke

A small number of stroke patients with COVID-19 infection present with cerebral hemorrhage. The initial retrospective case series of 214 patients from Wuhan in China [54] reported only one case of hemorrhagic stroke. Similarly, another retrospective case series again from Wuhan reported one hemorrhagic stroke within 13 patients presented with acute cerebrovascular events [72]. Additional 5 case reports of hemorrhagic stroke have been published [8][54][55][56]. A ruptured aneurysm in the pericallosal region [73] or posterior-inferior cerebellar artery (PICA) [14] was found in two cases. A hypothesis about the underlying pathophysiologic mechanism of cerebral hemorrhage is the reduced expression and function of ACE-2 in SARS-CoV-2 infected cells. ACE-2 is expressed in vascular endothelial cells, and its signaling is involved in regulating cerebral blood flow and reducing the body blood pressure. In the case of COVID-19 infection, the

signaling is altered with subsequent hypertension and predisposition to developing hemorrhagic stroke from arterial wall rupture [43]. Another possible mechanism is the underlying coagulopathy induced by the infection with thrombocytopenia [71]. Future observations may better clarify the incidence and clinical and laboratory characteristics of COVID-19 patients presenting with hemorrhagic strokes.

4.3. Cerebral venous thrombosis

Cerebral venous thrombosis has been reported in several studies. In a multinational retrospective study, all cases of cerebral venous sinus thrombosis (CVST) with COVID-19 infection were collected from the start of the pandemic to the end of June 2020. They reported 13 post-COVID-19 CVST patients and compared their characteristics with the CVST data obtained before the COVID-19 pandemic from the same centers. They concluded that compared to non-COVID -19 infected CVST patients, patients with the infection tended to be older, had fewer CVST risk factors, and worse outcomes [74].

Several smaller studies reported CVST in 7 adults (age range between 32 and 62 years, 62.5% female) and one pediatric (a 13 years old male) patient with COVID-19 [16][32][75][76][77]. Headache was a presenting symptom in 6 (85.7%) cases, variably accompanied by different focal neurological deficits, confusion, and impaired consciousness [16][32][76][77]. Although in 3 patients, the treatment and outcome were not reported [16][77], the condition was fatal in 3 out of 5 cases (60%) within a few days of onset despite anticoagulation and supportive therapy. Notably, in some cases, neurological symptoms occurred about two weeks after the onset of general symptoms (i.e., fever, cough, or dyspnea) of COVID-19 [16][77]. Therefore, the possibility of this potentially life-threatening condition should not be overlooked even when patients present several days to weeks after the onset of COVID-19. A more recent multicenter 3-month cohort study of 13,500 consecutive patients with COVID-19 in New York City has found the imaging-proved cerebral venous thrombosis incidence of 8.8 per 10,000 cases, which is higher than expected (i.e. 5 per million annually) [78]. In this study, despite the standard management [79] consisting of anticoagulation, endovascular thrombectomy, and surgical hematoma evacuation, the mortality rate was 25% [78].

Overall, various degrees of elevated acute phase reactants (e.g., CRP and ferritin), hypercoagulability factors (e.g., D-dimer and aPTT), and abnormal platelet counts were found in these cases [16][32][76][77], suggesting a possible association with hypercoagulability state in the setting of SARS-CoV-2 infection. It is unclear whether monitoring of these markers has any value for predicting the onset or severity of cerebral venous thrombosis in these cases. This needs further detailed information on COVID-19 patients with such complications.

5. Therapeutic approaches

Administering tissue plasminogen activator (tPA) in patients with COVID-19 and stroke is one of the therapeutic options. The role of other anticoagulants such as low molecular weight heparin (LMWH) or full-dose heparin is uncertain. There is some data that LMWH may be useful in sepsis-induced coagulopathy [69]. Although aspirin therapy in COVID-19 patients with ischemic stroke (especially in those who cannot take anticoagulants due to risk of hemorrhagic transformation [80] or other medical limitations) can be considered as a secondary preventive approach, this medication is not indicated in patients with disseminated intravascular coagulation, high risk of bleeding, or thrombocytopenia [81][82].

One reasonable treatment for COVID-19 patients is human recombinant soluble ACE-2 (hrsACE-2). There are two mechanisms of action for it: (1) Preventing the SARS S protein from binding to lung and endothelial endogenous ACE-2; therefore, reduces infection of host cells; (2) Inhibiting the ACE-2 depletion by the SARS-CoV-2 virus. Considering ACE-2 is exhibited by brain endothelium and neurons, it is probable that depletion of ACE-2 by virus damages the endothelial function and leads to acute stroke. Along with other known treatments, medications that affect RAS system such as angiotensin (1-7) may be appropriate therapies for COVID-19. Angiotensin role is currently under evaluation in clinical trials (NCT04332666). In addition, AT1 receptor blockers (ARBs), like losartan, could be preclusive in stroke [83]. On the other hand, other study has shown that early intravenous thrombolysis and immediate mechanical thrombectomy had poor outcomes in patients with acute ischemic stroke due to large vessel occlusion with COVID-19 [93]. Overall, more well-designed, randomized, controlled trials are needed to provide an evidence-based approach for prevention or treatment of acute cerebrovascular events in patients with COVID-19 [84].

6. Conclusion

A growing body of evidence indicates that acute cerebrovascular events, including both ischemic and hemorrhagic strokes and cerebral venous thrombosis, may occur in patients with COVID-19. The underlying mechanisms of such events are still not completely understood. Still, they may include hypercoagulability state, inflammation and cytokine storm,

endothelial dysfunction, and aberrant RAS axis due to binding of SARA-CoV-2 to endothelial ACE-2. These abnormalities ultimately cause vasoconstriction, oxidative stress, inflammation, and thrombogenesis. As these complications, especially cerebral venous thrombosis, are potentially life-threatening, physicians need to be vigilant when encountering patients with COVID-19 who have neurological symptoms such as headache, confusion, altered mental status, seizure, and focal neurological deficits. Due to the small number of published cases or mainly the retrospective design of previous clinical studies, (i) the functional outcome with available therapies (e.g., LMWH) for thrombotic events and (ii) inflammatory or coagulable markers that can be efficiently used for monitoring or predicting such events in COVID-19 are still elusive, requiring large cohort of patients with such complications.

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