Stroke and COVID-19 Pandemic: The Dilemma

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Abstract: Background: While the COVID-19 pandemic affected more than thirty million people worldwide, still the true link between COVID-19 and the incidence of stroke remains to be elucidated.

Methods: Herein, we briefly discuss virology of COVID-19 and approaches for diagnosis and treatment of COVID-19 patients, as well as the mechanisms that link stroke and COVID-19.

Results: Many pathophysiologic and immunologic mechanisms have been implicated in stroke occurring among patients with COVID-19. COVID-19 pandemic has, in different ways, negative impacts on the care of stroke patients world-wide, and still, neurologists have to face many challenges to improve the care of stroke patients during such crisis.

Conclusion: Although the control of the COVID-19 is of crucial importance, at the same time, the management of stroke must not be neglected. Therefore, preserving care for critical conditions such as stroke, and providing strategies to ensure this continues, have a priority even during the crisis. Till vaccine is available for COVID-19, strategies for rapid diagnosis and those for treating patients with that disease are evolving. Further studies are warranted.

Keywords: COVID-19, stroke, pathophysiology, outcomes, stroke and COVID, SARS-CoV, COVID virology.

1. INTRODUCTION

The coronavirus infection COVID-19 first presented as an outbreak of a typical pneumonia in Wuhan, China, on December 12, 2019. Since then, it has spread globally to infect over 30 million people. The true link between COVID-19 and incidence of stroke remains to be elucidated. Many pathophysiologic and immunologic mechanisms have been implicated in stroke occurring among patients with COVID-19. In this review, we will discuss the virology of COVID-19, approaches for diagnosis and treatment of COVID-19 patients, as well as the mechanisms that link stroke and COVID-19.

2. MATERIALS AND METHODS

2.1. COVID-19 Virology

SARS-CoV-2, the virus causing COVID-19, is a novel beta coronavirus (large RNA virus) that shares 80% sequence homology with the earlier SARS-CoV virus that caused the SARS outbreak in 2003 [1]. However, SARS-CoV-2 has evolved several features that make it more efficient than SARS-CoV. The most critical receptor binding domain of SARS-CoV-2 preserved the overall configuration of the SARS-CoV binding domain, including 8 of the 14 residues being completely identical [2]. However, the 3D structure of the SARS-CoV-2 binding site shows that it is more compact, has improved binding stability, and potentially enhanced ACE-2 receptor binding affinity [2]. Another important difference is that SARS-CoV-2 contains a polybasic (furin) cleavage site inserted at the boundary of the S1/S2 subunits of the spike S-protein [3, 4]. This furin binding site is a feature shared by several recent highly pathogenic, viruses including avian influenza, and can enhance the virus’s ability to internalize into cells. ACE-2 has been confirmed recently as the SARS-CoV-2 internalization receptor causing COVID-19 [4], in concert with the host’s TMPRSS2 membrane protease that primes the spike S protein of the virus to facilitate its cell entry [5]. ACE-2 is the same functional receptor of the earlier SARS-CoV-1, however, the presence of TMPRSS2 significantly enhances viral infectivity [6].

2.2. Diagnostic Approaches for COVID-19

SARS-CoV-2 infection can generate a diverse range of responses in patients, ranging from completely asymptom-
ic virus shedding to a severe inflammatory response, including cytokine storm-like outcomes that are accompanied by high mortality [7]. Our current knowledge is that 81% of infected individuals have mild disease, 14% have severe symptoms requiring hospitalization, while 5% become critically ill, requiring mechanical ventilation. These differences in response could be attributed to the degree of viral load, host immune response, age of the patient, and presence of co-morbidities.

Similar to other infectious diseases, appropriate specimen collection is the key step in the laboratory diagnosis of COVID-19. Acceptable specimens include upper respiratory tract, lower respiratory tract, stool, whole blood, and serum specimens, yet the respiratory secretions are the most frequently sample for diagnosis [8]. SARS-CoV-2 has been detected in nasopharyngeal, oropharyngeal and throat swabs, sputum, bronchoalveolar lavage fluid (BALF), whole blood, serum, stool, urine, saliva, and rectal and conjunctival swabs [9, 10].

Currently, the virus has not been detected in cerebrospinal fluid, pericardial effusion, peritoneal effusion, posterior fornix, joint fluid, peritoneal exudate, semen, and female reproductive tract secretions [8-10].

2.3. Incidence of Stroke at the Time of COVID-19 Pandemic: Increased or Decreased?

Despite the world-wide spread of COVID-19, the true relationship between it and the incidence of stroke remains to be elucidated. It has been suggested that COVID-19 infection may cause stroke, by itself. In an interesting study from Wuhan, China, 36.4% of COVID-19 patients had neurological symptoms, which were more encountered in patients with severe disease [11]. Among those neurological disorders, stroke complicated COVID-19 infection in 5.9% of patients. Characteristically, patients with stroke were older, had more severe pneumonia, and more cardiovascular co-morbidities [11]. Potential mechanisms by which COVID-19 might increase the risk of stroke have been identified.

Stroke mechanisms may include hypercoagulability status due to critical illness and cardio-embolism from SARS-CoV-2-related cardiac injury. As the obligate receptor for the virus, human angiotensin-converting enzyme (ACE-2) is expressed in epithelial cells throughout the body, including in the central nervous system (CNS), this raises the probability of a direct role in viral infection [12, 13]. On the other hand, at the time of the COVID-19 pandemic, there was an apparent reduction in the numbers of stroke cases in many parts of the world. Reports pulled out from multiple countries showed a sharp reduction in the number of stroke-related admissions [12]. Many explanations were considered. It may be due to a reduction in admissions of patients with milder stroke; some patients have fears of infection if they are referred to hospital during times of lockdown and social distancing. In a recent report from Italy, other mechanisms were claimed [14]. First, it could be related to the controversial role IL-6 plays in stroke. While in COVID-19 affected patients, high levels of serum markers for thrombosis and inflammation have been reported, as well as increased levels of inflammatory cytokines (interleukin [IL]-2R, IL-6, and tumor necrosis factor-α) [15]. Indeed, there were controversial reports where high IL-6 levels have been reported to have a negative effect on brain infarct volume and long-term outcome [14]. On the contrary, there was evidence that IL-6 has a protective effect and helps in the improvement of post-stroke angiogenesis in ischemic stroke [14, 15].

Second, a possible explanation is related to the observation that most COVID-19 patients have thrombocytopenia [16]. Could the decreased platelet levels be related to the reduction of large vessel occlusion (LVO) strokes, remains a question. Third, the burden of chronic persistent infections rather than one single current infectious disease, seems to be associated with risk for stroke [14]. Another explanation came from Markus and Brainin [12]. As pollution is associated with an increased risk of cardiovascular disease and stroke, the striking reduction in pollution observed in multiple countries during the pandemic secondary to lockdown, could have a potentially protective effect against stroke [12].

2.4. Is Stroke a Risk Factor for COVID-19, or is COVID-19 a Risk Factor for Stroke?

From our experience in patients with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS), the presence of cerebrovascular disease (CVD) in those patients was associated with worse outcomes. Whether CVD predicts outcomes of patients with COVID-19 is still unknown. A pooled analysis has showed ~2.5-fold increase in odds of severe COVID-19 in patients with a history of CVD, but there was no association with mortality [17]. On the other hand, in patients with stroke, the presence of COVID-19 infection itself could be a potential factor in the genesis or worsening of stroke. The virus causing COVID-19 can enter the CNS through two distinct pathways: retrograde neuronal diffusion or hematogenous diffusion. The spread of COVID-19 through the cribriform plaque of the ethmoid bone can lead to brain involvement. This brain involvement might remind us of similar recently emerged viral infections [18, 19]. This could happen during an initial or subsequent infection phase. The presence of ACE-2 receptors on both capillary and neuronal endothelial cells could be responsible for the subsequent spread and damage to the cerebral nervous system, characteristically without substantial inflammation [12, 13].

Representing a sevenfold increase in what would normally be expected, Oxley et al. [20], reported five cases of large vessel stroke over a 2-week period in COVID-19 patients under age 50 years. Remarkably, all cases had either no or mild, COVID-19 symptoms.

2.5. Impacts of the COVID-19 Pandemic on Care of Stroke Patients & Challenges to the Neurologist

The COVID-19 pandemic has both direct and indirect major implications for stroke care. While a minority of countries did manage to maintain a full range of acute stroke ser-
vices, most have experienced significant service reorganization. The later faced two problems. First, reallocation of neurology and stroke beds, including Intensive Care Unit (ICU) facilities to COVID-19 patients which necessitated moving of stroke units to less optimal accommodation. Second, the crisis needed redeployment of stroke physicians, nurses and other stroke healthcare-related workers to look after COVID-19 patients [12]. At the best services, intravenous thrombolysis is under threat because of pressures and delays imposed by managing potentially infected patients. This has resulted in the increased door to needle times and missing the therapeutic window for the worst stroke patients. Adding to this dilemma, there were delays in hospital admission or referrals, or patients preferring not to enter the hospital at all. The potential impact on developing countries was worse. Many have not only much less developed stroke care, but also less developed acute medical services to manage the COVID-19 pandemic, including the major challenge of shortage of ventilators in the intensive care units [12].

2.6. Potential Solutions

Best practice guidelines had to offer guidelines on how to manage stroke in the context of the current pandemic, while safeguarding health care workers. Telemedicine was found to offer many opportunities during the current crisis. Stroke has led the way in telemedicine for acute assessment for thrombolysis, which continues to be a central part of stroke care, particularly in rural settings. Utilizing telemedicine had avoided the use of needed Personal Protective Equipment (PPE), allowed a reasonable stroke evaluation, and reduced the risk of exposure for the stroke-managing team [12, 14, 20].

2.7. Possible Strategies to Control COVID-19

It is thought that the most important public health solution for control of COVID-19 is an effective vaccine for the broad population remaining at risk. Until a vaccine is developed, the best defense is avoiding infection altogether through frequent, thorough hand washing and social distancing.

On the other hand, various therapeutic strategies have been adopted to control viral infection. Viral attachment can be inhibited by either blocking the viral binding sites or host receptors. Viruses can be inhibited at various stages of their infection [21]. Some of the strategies directly inhibit viral replication by targeting DNA/RNA polymerase, post-translation modification of viral proteins, or viral assembly [21]. Interestingly, phytochemicals have several mechanisms that can inhibit viral replication. For instance, epigallocatechin gallate (EGCG) inactivates the host enzyme or viral enzyme, which promotes the growth of the virus, such as RNA polymerase, protease, and reverse transcriptase [22]. Another mechanism adopted by flavonoids is to inhibit phosphorylation of the protein, which restricts the replication of HIV [22]. The inhibition of various viruses, such as influenza virus, HIV, and herpes simplex virus (HSV), was achieved at the stage of viral RNA synthesis [23]. Phytochemicals might have similar actions for SARS-CoV-2 [23].

Vaccines represent a great hope to manage COVID-19. However, typically they require years of research and testing before reaching the clinic, but scientists are racing to produce a safe and effective coronavirus vaccine by 2021. Currently, researchers are testing 40 vaccines in clinical trials on humans, and at least 92 preclinical vaccines are under active investigation in animals. Immunoinformatics and structural vaccinology strategies could have an important potential for developing a vaccine against SARS-CoV-2 [24]. Recently, the first multiepitope vaccine construct using the 3CL hydrolase protein of SARS-CoV-2 was achieved. The design of the multiepitope vaccine was built using helper T-cell and cytotoxic T-cell epitopes from the 3CL hydrolase protein along with an adjuvant to enhance immune response; these are joined to each other by short peptide linkers. The vaccine also carries potential B-cell linear epitope regions, B-cell discontinuous epitopes, and interferon-γ-inducing epitopes. Epitopes of the constructed multiepitope vaccine were found to be antigenic, nonallergic, nontoxic, and covering large human populations world-wide [24].

CONCLUSION

Although the control of the COVID-19 is of crucial importance, at the same time, the management of stroke must not be neglected. Therefore, preserving care for critical conditions such as stroke, and providing strategies to ensure this continues, have a priority even during the COVID-19 crisis. Till vaccine is available for COVID-19, strategies for rapid diagnosis and those for treating patients with that disease are evolving. Further studies are warranted.

AUTHORS’ CONTRIBUTIONS

All authors have read and approved the manuscript. S.M.: Conceptualization, design, Data acquisition, Data analysis Manuscript editing, and Manuscript review. S.A.: Conceptualization, Data acquisition, Data analysis view. O.A.: Conceptualization, Data acquisition, Data analysis view. N.A.: Conceptualization, design. A.A.: Conceptualization, design

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