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Care for Patients with Stroke During the COVID-19 Pandemic: Physical Therapy and Rehabilitation Suggestions for Preventing Secondary Stroke

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Infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the development of the novel 2019 coronavirus disease (COVID-19) and associated clinical symptoms, which typically presents as an upper respiratory syndrome such as pneumonia. Growing evidence indicates an increased prevalence of neurological involvement (e.g., in the form of stroke) during virus infection. COVID-19 has been suggested to be more than a lung infection because it affects the vasculature of the lungs and other organs and increases the risk of thrombosis. Patients with stroke are vulnerable to secondary events as a result not only of their poor vascular condition but also of their lack of access to rehabilitation resources. Herein, we review current knowledge regarding the pathophysiology of COVID-19, its possible association with neurological involvement, and current drug therapies. Suggestions are also offered regarding the potential for current neurorehabilitation therapies to be taught and practiced at home.

Key Words: COVID-19—Patients with stroke—Coagulopathy—Physical therapy—Rehabilitation

Introduction

The outbreak of the novel coronavirus disease (COVID-19) in 2019 has had a tremendous impact on public health. The number of infected patients is continually increasing, and the total number of deaths has exceeded 250000 people as of March 2020. Reports on clinical symptoms have provided increasing evidence of neurological deficits, including cardiovascular events and the formation of peripheral nerve lesions.[1] Recent observations have also revealed a growing number of thrombotic events resulting in stroke among young adults, some of whom have been asymptomatic or have only had mild symptoms of COVID-19.[2]

Although no recent data have definitively indicated whether the rate of infection with COVID-19 has been higher among patients with stroke, comorbidities such as hypertension, diabetes, and cardiovascular disease have been reported to be closely related to increased infection rates among patients with stroke.[3,4] Secondary stroke risk may be increased not only because of the thrombotic properties of COVID-19 but also because of physical inactivity resulting from isolation or restricted access to hospital facilities and therapy among these patients.

This review discusses the relationship of COVID-19 to the neurological aspects of pathophysiology and immune

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responses. To address the current concerns regarding a lack of access to drug therapy, some neurorehabilitation techniques can potentially be taught and practiced at home.

Pathophysiology and immune response

Coronaviruses are enveloped positive strand RNA viruses with the largest known RNA genome.[5,6] The RNA genome of coronaviruses is highly variable and subject to recombination, which is a typical feature of RNA viruses. This feature enables them to quickly spread among humans and animals, sometimes leading to life-threatening conditions. However, some highly contagious and pathogenic strains are occasionally produced from recombination within intermediate hosts. The corona-like appearance with club-shaped spikes is the main feature of the virus. The nucleocapsids are helically symmetrical and are packed by the envelope of the virion.[6–8] Among the functions of the structural proteins, the envelope has a crucial role in virus pathogenicity through the promotion of viral assembly and release.[9]

The pathogenic lesions of coronavirus infection arise mainly from immunopathological events that result in fatal pneumonia.[9] Pathogen-associated molecular patterns comprising viral RNA form during viral replication and trigger immune recognition.[10] This results in the expression of type I interferon and proinflammatory cytokines for protection against infection by the virus, which constitutes the early stage of defense against the virus.[11]

In some severe cases, the cytokine storm induced by interleukin 6 (IL-6) causes massive tissue damage, characterized by fever and multiple organ dysfunction.[10,12] In addition, higher plasma levels of interleukin 2, interleukin 7, interleukin 10, GSCF, IP10, MCP1, MIP1A, and TNFα are observed in patients requiring admission to the intensive care unit.[13]

Recent observations suggest that microvascular thrombolic processes may play a prominent role in respiratory failure induced by COVID-19.[14,15] Venous thrombosis is indicated by the strong association among disease progression embolus, D-dimer levels, and chest computed tomography features.[16] This infection-associated coagulopathy suggests that COVID-19 may be a thromboinflammatory process that initially affects lung perfusion and subsequently affects all organs of the body.[17]

Role of Renin Angiontensin System and Angiotensin-Converting Enzyme 2 in the Neurological Effects of Covid-19

The renin-angiotensin system(RAS) in brain and peripheral organ played a fundamental role in regulating the electrolyte homeostatsis and cardiovascular control.[18] The classic axis with ACE(angiotensin), Angiotensin II (Ang II) and angiotensin type-1receptor(ATIR) had the vasoconstrictor effect and overactivation this axis severs as an important role in acute ischemic stroke.[19,20] In contrary, activation of the alternative axis included ACE2, Ang(1−7) and MAS receptor(MAS) results in vasodilation, anti-inflammation and angiogenesis response that may have protective effects against stroke.[20]

ACE2 serves as the main receptor for the entry of the severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) virus into human cells although COVID-19 was proposed associated with multiple receptors such as CD147 and salic acid [21–23]. The ACE2−angiotensin pathway plays a neuroprotective role in patients with stroke.[24] ACE2 is widely expressed in the cells of the central nervous system (CNS), and its expression has been shown to increase following stroke.[25] Another study using samples from human patients with stroke revealed that ACE2 was markedly higher in patients with certain types of stroke, implying that ACE2 can be used as a diagnostic marker.[26] Accordingly, ACE2 may serve as a link between SARS-CoV-2 infection and neurological effects in patients with stroke. A recent review examined whether an ACE inhibitor could reduce virus infection susceptibility by inhibiting this viral entry pathway.[27] One multinational study of 8910 inpatients infected with COVID-19 worldwide was conducted and could not confirm the harmful association of ACE inhibitors or angiotensin-receptor blockers with COVID-19 mortality.[4]

Possible Mechanism Underlying the Involvement of COVID-19 in the Development of Vascular Problems

Although the neurological effects in patients who have had a stroke directly induced by COVID-19 have not been reported, several indications have been made in recent studies. A case series study conducted early in a Wuhan hospital indicated that patients with more severe diseases developed neurological manifestations, including acute cerebrovascular accident (5.7%) and impaired consciousness (14.8%).[1] The proposed mechanism was anterograde and retrograde virus infection of the CNS system through the hematogenous or retrograde route.[1] Patients with COVID-19 and CNS involvement were observed to have lower lymphocyte and elevated D-dimer levels, indicating possible links with infection and neurological involvement.[1]

The coagulopathy of COVID-19 was initially reported through observation of the increased incidence of pulmonary embolism in highly symptomatic ill patients.[28] A link between thromboembolic events and influenza-associated pneumonia has been identified.[29] An increased procoagulant profile such as D-dimer level and fibrin degradation products was observed in patients with COVID-ARDS, and this coagulathy can be reversed after thromboprophylaxis prescription[30,31] Moreover, disseminated intravascular coagulopathy (DIC) characterized by severe thrombocytopenia and low platelet count due to the comsumption of coagulation factors was also found in severe COVID-19 patients.[32,33]

Vasculitis caused by the inflammation is considered to be an important mechanism in neurological manifestations. Previous reports on patients with SARS indicated widespread vascularity in many organs,[34] which may directly affect blood supply to the brain. Moreover, the presence of hypertension or hypotension was also considered to be a crucial factor related to the occurrence of cerebrovascular events. A study conducted in Singapore revealed that 5 of 206 patients with SARS had large vessel lesions, and 3 of them had severe episodes of hypotension.[35] Elevated blood pressure was also noted among a high proportion of critically ill patients and nonsurvivors.[1] Moreover, cardiac abnormality and arrhythmia contribute to increased stroke incidence, which may be caused by critical illnesses such as hypoxia, metabolic derangement, and systemic inflammation.[35]

An increasing number of cases of sudden loss of olfactory function have been reported. A possible mechanism was proposed to be related to central cortical neurons and the expression of olfactory receptors possessing ACE2 receptors.[13] Although damage to primary epithelial cells was considered, MRI revealed no olfactory bulb or tract abnormalities that would indicate CNS involvement.[36] Musculoskeletal injury was also reported in recent Wuhan reports. Related muscle symptoms and injury were reported to be accompanied by marked elevation in creatine kinase and lactate dehydrogenase levels.[1] This injury could be associated with ACE2 expression in the musculoskeletal system, but the ACE2 receptor cannot be detected through autopsy sampling; therefore, further studies are required.[37,38] However, a systemic immune response induced by infection may cause damage to skeletal muscle, as indicated by marked increases in proinflammatory cytokine levels in serum.[1]

Therapeutics

Current Drug Therapies for COVID-19

The lopinavir and ritonavir are HIV type I asparate protease inhibitors that have been found to be potent against SARS-CoV-2 in vitro.[39,40] In a recent randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection, the benefits of lopinavir and ritonavir treatment compared with standard care were not confirmed.[41] Remdesivir, a nucleotide analog prodrug that inhibits viral replicase, was initially developed for Ebola virus and demonstrated efficacy in reducing the virus load in MERS-CoV in nonhuman primates[42] A recent report on the application of remdsivir in patients with severe COVID-19 reported 68% clinical improvement in the need for oxygen support.[43] Although the mortality rate reached 18%, it was lower than that in a previous study that reported mortality rates of 22% and 66% (44 of 67) among patients receiving invasive mechanical ventilation.[43,44] The anti-influenza drug favipiravir (Avigan) has also demonstrated some promising effects. In a recent open-labelled randomized study, patients treated with favipiravir demonstrated quicker recovery from fever and cough but similar rates of respiratory failure compared with a control group receiving umifenovir.[45] Hydroxychloroquine and chlorquine have demonstrated the ability to inhibit SARS-CoV-2 in vitro.[46,47] Although treatment with hydroxychloroquine and azithromycin was significantly associated with decreased viral load in a small trial in France.[48] the therapeutic effect remains questionable because it failed to eliminate the virus or significantly relieve symptoms in a recent randomized controlled trial conducted in China.[49] Finally, tocilizumab, a humanized monoclonal antibody against the IL-6 receptor that was traditionally used to treat patients with rheumatoid arthritis, has also been approved for use in China.[50]

3.2. Drug Precautions for Patients With Stroke

Notably, immunomodulatory agents such as tocilizumab increase the risk of opportunistic infections.[51] Cardiac toxicity, including long QT syndrome and conduction abnormalities, is a notable effect of hydrochroquine and chroquinine application.[52,53] Tocilizumab and other IL-6 receptor antagonists may also increase CV risk by inducing unfavorable changes in lipid profiles.[54] The continued use of ACE and angiotensin-receptor blockers is still suggested because switching to another medication incurs a higher risk than that associated with infection, especially for hypertension management in patients with stroke.[55]

Neurorehabilitation Therapy Could Potentially Be Taught and Practiced at Home

Because physical therapy and rehabilitation are inaccessible resources during pandemics, neurorehabilitation often cannot be offered to patients with stroke on the same scale as it can during pandemic-free conditions, especially during the acute and subacute phases; consequently, patients may be prevented from reaching the optimal recovery phase. Studies have indicated that prolonged immobility among patients with stroke may result in significant functional decline[56] Thus, some strategies for facilitating neurorehabilitation may be applied in the absence of assistance from physical and occupational therapists. Several potential techniques can be used to stimulate neurorestoration and maintain muscle strength with minimal assistance; these are listed as follows.

Portable Transcutaneous Electrical Stimulation Device

Transcutaneous electrical stimulation (TENS) devices use different current and frequency parameters to stimulate sensory and peripheral nerves. Electrical sensory input can contribute to routine rehabilitation and improve early poststroke lower-extremity impairment

and late motor function.[57] Several studies have shown that TENS can maintain muscle strength and mass in a deconditioned state.[58,59] Such devices are safe and easy to use. In hemiplegic limbs, where the muscle groups are flaccid, proper selection of the stimulation site significantly improves the flaccid limb[57] Poststroke spasticity in lower limbs can be effectively reduced by TENS when applied for more than 30 minutes over a nerve or muscle belly in patients with chronic stroke.[59] In addition, peripheral nerve stimulation at ulnar and radial sites for 1 h has been revealed to increase corticomotor function and improve hand dexterity in patients with moderate to severe hemiparesis.[60] Thus, TENS may be utilized as a convenient tool for temporal function and muscle facilitation to maintain therapeutic effects with the provision of proper assistance. Prolonged periods of sensory stimulation, such as TENS combined with activity, can have beneficial effects for treating impaired function after stroke.

Mirror Therapy

Mirror therapy (MT) has been proven to be an effective and feasible approach for rehabilitating patients who have had a stroke.[61] MT utilizes a mirror that reflects the movement of an unaffected limb and gives the illusion of movement of the affected limb. This visual stimulus is believed to facilitate the mirror neurons involved in imitative learning through interaction with the neural motor area.[62] MT was also reported to ameliorate an imbalance in function of the cortical excitability hemisphere.[62] MT was found to confer a significant positive effect on motor function when applied for 15 to 60 min per session over the course of 2 to 8 weeks.[63] The application time is adjustable to acute, subacute, and chronic cases of stroke.[61] The mirror is normally positioned between the affected and unaffected limbs such that the movement of the healthy limb is perceived as the movement of the unaffected limb. The entire procedure is straightforward to execute through simple instruction and can be performed under minimal supervision.

Home Exercise Programs

Increasing evidence suggests that the implementation of home-based exercise is noninferior to outpatient courses.[64] Home-based locomotion training with physical therapists can achieve the target response with the same efficiency as outpatient courses among patients with stroke.[65] Mayo et al found that combined cycle and supervised walking training at home successfully improved patient's long-term walking ability.[66] Although most home-based exercise programs must be supervised by a therapist, some exercises can be performed smoothly with assistance from properly instructed family members.

Virtual Reality Exercise

The application of virtual reality (VR) is increasingly being used in stroke rehabilitation.[67] Several studies have demonstrated that VR technology can improve motor functioning.[68] VR can also be used to improve upper limb function, gait and balance, global motor function, and cognitive function in patients with stroke.[69] However, VR equipment is usually expensive and complex and may only be available in specialist hospitals. The Nintendo Wii system supplemented with a balance board and a bar enabling body movement in a VR game environment could be a viable option for use in treatment for patients with stroke. It was shown to be useful as an adjunct therapy to traditional treatment in improving dynamic balance in patients who have had a stroke.[70]

Conclusion

The COVID-19 pandemic has not only had a direct impact on people's health but also has greatly influenced public access to hospitals, which may prevent patients who have had a stroke from receiving standard rehabilitation therapy. In this review, we summarize the neurological manifestations of COVID-19 described in the accumulating reports that may lead to neurological complications in patients with stroke. The ACE2 receptor is crucial in viral transmission, but it is still not recommended that patients stop using ACE or angiotensin-receptor−blocker drugs essential for hypertension control. For the current choice in anti-COVID19 medication, we advise practitioners to be aware of the cardiovascular or infection risks associated with hydroxychloquine or immunomodulatory agents such as tocilizumab. Portable devices such as TENS devices can be easily used to maintain muscle strength and reduce spasticity at home when access to hospitals is limited. A combination of basic home exercises with VR implemented by video game consoles such as Wii may also be a feasible technique for maintaining physical balance and protecting functional deterioration.

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Disclosure of interest

The authors have no competing interests to declare.

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