Ischemic Brain Stroke and SARS-CoV-2/Covid 19

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Abstract

Coronavirus illness 2019 (COVID-19), a contagious infection brought on by the SARS-CoV-2 coronavirus, has been reported throughout the world. In addition to respiratory issues, a growing number of patients have been suffering ischemic strokes. The goal of this study is to examine the features of ischemic stroke following SARS-CoV-2/Covid 19 infection and to offer helpful reference resources for ensuing therapeutic care.

Keywords: Ischemic brain stroke, SARS-COV-2, Covid 19

1. Introduction

In the early phases of the COVID-19 pandemic, there has been a relatively high prevalence of thrombotic events, mainly among patients with severe COVID-19 but also among mildly symptomatic or asymptomatic patients. This seems to be the case also for stroke, even though the overall number of stroke admissions has been reduced during the pandemic, possibly because patients experiencing stroke symptoms did not seek medical attention especially when symptoms were mild, due to the fear of contracting the coronavirus. In contrast to coronary and peripheral artery disease, which are primarily caused by atherosclerosis, ischemic stroke is a heterogenous syndrome comprising multiple pathophysiological mechanisms including vascular and cardiac pathologies, many of which seem to be influenced by SARS-CoV-2 infection.

In this review, we discuss the potential pathophysiology of ischemic stroke in COVID-19 and summarize the accumulating evidence on ischemic stroke characteristics and treatment.

2. Ischemic Stroke

It is used to describe the hemiplegia and disruption of consciousness brought on by cerebral infarction and cerebral arterial obstruction based on cerebral thrombosis. The development of cerebral thrombosis is slower than that of cerebral haemorrhage and occurs more frequently in males beyond the age of 50. Aura symptoms including weakness, numbness in one leg, and dizziness are frequently more likely to happen when blood pressure is low. (McKay et al., 2004)

1.1 The Symptoms of an Ischemic Stroke

- One-sided weakness or paralysis.
- Aphasia (difficulty with or loss of speaking ability).
- Slurred or garbled speaking (dysarthria).
- Loss of muscle control on one side of your face or facial droop.
- Sudden loss — either partial or total — of one or more senses (vision, hearing, smell, taste and touch).
- Blurred or double vision (diplopia).
- Loss of coordination or clumsiness (ataxia).
- Dizziness or vertigo.
- Nausea and vomiting.
- Neck stiffness.
- Emotional instability and personality changes.
- Confusion or agitation.
- Memory loss (amnesia).
- Headaches (usually sudden and severe).
• Passing out or fainting.
• Coma.

(Paul et al., 2021)

1.2 The Causes of the Ischemic Stroke

Arteriosclerosis and hypertension are the primary contributors to it. Reduced blood pressure, sluggish blood flow, increased blood viscosity, or abnormally elevated blood coagulation and thrombosis are frequently caused by heart failure, myocardial infarction, arrhythmia, shock, syncope, water loss, postpartum haemorrhage, weariness, and lack of sleep. Leptospirosis, head trauma, polycythemia, and different viral illnesses of the brain are additional causes of cerebral thrombosis. Patients with heart conditions such rheumatic heart disease, persistent atrial fibrillation, myocardial infarction, and bacterial endocarditis may develop cerebral embolism, which can cause vegetation to slide off the embolus. Cerebral embolism can also be brought on by pulmonary or pelvic infections, venous thrombosis in the lower limbs, and certain parasite conditions. Pneumothorax, pneumoembolism for pneumoperitoneum or decompression illness, fat embolism with lengthy bone or adipose tissue injury, and cancer cells like lung cancer are some more conditions that are observed in thoracic surgery.

1.3 The Current Treatment of the Ischemic Stroke

1.3.1 Medication

The major treatments for ischemic stroke involve clearing the blockage and reestablishing blood flow to the brain. A tissue plasminogen activator is the only medication recognised as safe and effective by the US Food and Drug Administration (US FDA) (t-PA, an anticoagulant). The medication must be used within a three-hour window of stroke symptoms for optimum results (and the time window should be 4.5 hours). Unfortunately, only 3–5% of stroke victims in the US are able to reach a hospital and obtain the medication in time. As a result, relatively few individuals have actually received t-PA treatment. simultaneously to pay attention This medication cannot be used to treat hemorrhagic stroke because it increases the risk of cerebral bleeding. (Paul et al., 2021)

1.3.2 Neurointerventional Therapy

The use of a very small microcatheter is a common element of all surgical interventions using microcatheters. By creating a tiny hole in the perineum and using a microguide wire to direct the blood flow into the artery that leads to the part of the brain that is occluded. This allows for the direct application of thrombolytic medications like t-PA to the occlusive thrombus. Because of the more focused nature of this method compared to intravenous administration, the medication dose may be greatly decreased and the rescue window can be increased by around two times. Such care is typically only offered in complete stroke treatment facilities. (Xiong et al., 2022)

1.3.3 Mechanical Thrombectomy

In order to aid stroke patients with blood clots in their arteries, the MERCI thrombectomy device—the first mechanical device in the US—was designed to resemble a wine bottle opener and was introduced in 2004. This device’s use continues to be supported by microcatheter intervention technology. A tiny hole is cut in the perineum, and a microcatheter is inserted; at the neck, a smaller microcatheter is let go and directed through the artery into the brain, finally arriving at the cerebral infarction. A straight wire is extended from a tiny microcatheter into a plaque close to the infarction, where it immediately creates a bottle opener. To enable the gadget to safely remove the plaque from the brain, the coil wrap the plaque and flap the balloon at the carotid artery (remove the microcatheter together with the plaque with a syringe). (Derex & Cho, 2017)


2.1 Cytokine Storm

(Fajgenbaum & June, 2020)The binding of S proteins covering the surface of the virion to the cellular ACE2 receptor and the priming of S proteins by TMPRSS2, a host membrane serine protease, are both necessary for SARS-CoV2 to enter cells. SARS-CoV2 causes an immunological reaction after infecting respiratory epithelial cells, producing inflammatory cytokines and modest interferon (IFN) responses. Membrane-bound immune receptors and subsequent signalling pathways mediate the proinflammatory immune responses of pathogenic Th1 cells and intermediate CD14 CD16 monocytes. A cytokine storm follows from the subsequent infiltration of neutrophils and macrophages into the lung tissue. (Hu et al., 2021). SARS-CoV2 in particular has the ability to quickly activate pathogenic Th1 cells and cause them to release proinflammatory cytokines including GM-CSF and IL-6. Additional CD14CD16 inflammatory monocyte activation by GM-CSF results in significant production of IL-6, tumour necrosis factor (TNF), and other cytokines. Immune receptors that are membrane-bound, such as Fc and Toll-like receptors, may be responsible for an unbalanced inflammatory response, and inadequate IFN induction may serve as a significant cytokine production
amplifier. The extracellular nets that neutrophils create, known as neutrophil extracellular traps, may aid in the release of cytokines. IL-6 and TNF are highly expressed during the COVID-19 cytokine storm. A possible explanation for the cytokine storm brought on by the angiotensin II (AngII) pathway was put forth by Hirano and Murakami. Nuclear factor B (NF-B) is activated by SARS-CoV2 through pattern-recognition receptors. It takes up space for ACE2 on the cell surface, which leads to a decrease in ACE2 expression and an increase in AngII. The AngII-angiotensin receptor type 1 axis can activate NF-B, but it can also cause TNF and the soluble version of IL-6 (sIL-6Ra), thanks to disintegrin and metalloprotease 17. (ADAM17). To activate the signal transducer and activator of transcription 3 (STAT3) in non-immune cells, IL-6 binds to the sIL-6R through gp130. The proinflammatory cytokines and chemokines vascular endothelial growth factor, monocyte chemoattractant protein 1 (MCP1), IL-8, and IL-6 can all be produced when NF-B and STAT3 activate the IL-6 amplifier. IL-6 can connect to the membrane-bound IL-6 receptor (mIL-6R) via gp130 in addition to binding to the sIL-6R to act in cis signalling. The latter can cause cytokine storms by having pleiotropic effects on both innate and acquired immune cells. Cytokine storms might be brought on by the combined effects of SARS-poor CoV2’s acquired immune responses and unchecked inflammatory innate responses. (Hu et al., 2021)

2.2 Coagulation Dysfunction and ACE2 Transporter

Angiotensin converting enzyme II (ACE2) is recognised by SARS-CoV-2, allowing it to enter host cells(Scialo et al., 2020). SARS-CoV-2 had a better tissue affinity and infectivity than SARS-CoV because its S protein had a higher affinity with the ACE2 receptor(Beyerstedt et al., 2021) than SARS-CoV did. Angiotensin II is broken down by the SARS-CoV-2 recognition receptor ACE2 into angiotensin (1–7), which protects the vascular endothelium. This action adversely controls the activated renin-angiotensin system. Previous research has demonstrated that SARS-CoV causes endothelium damage by infecting cells, decreasing the expression of ACE2 molecules on the cell surface, activating the renin-angiotensin system, promoting vasoconstriction, and upregulating tissue factor production. A decrease in ACE2 encourages the release of inflammatory factors like CXC chemokine ligand 5, macrophage inflammatory protein 2, keratinocytes, and TNF-, resulting in the infiltration of a large number of neutrophils, which causes an excessive inflammatory response and immune damage in pneumonia models of bacterial infection. As a result, it is hypothesised that ACE2 is an important regulator of inflammatory response and coagulation dysfunction in COVID-19 patients, although additional study is required to determine the precise mechanism. (Muhanna et al., 2020)

2.3 CNS Invasion

(Nagu et al., 2020) With the cerebral blood flow, SARS-CoV-2 may spread to other target tissues and organs. The blood-brain barrier's distinct physiology prevents the virus from simply moving from the systemic circulatory system's capillaries to the brain through endothelial cells (BBB). The BBB vascularizes the central nervous system and carefully controls which chemicals can enter the brain. It is a semi-permeable barrier between blood arteries and the brain parenchyma. Endothelial cells, which make up the majority of the blood arteries, create the very tight junctions that keep chemicals and ions from seeping into the brain. A few microns distant, the neuronal termini are surrounded by astrocytes, pericytes, and brain endothelial walls. Pericytes and endothelial cells are in charge of preventing immune cells from invading. Glial cells known as astrocytes stretch protracted cellular processes around the blood vessel. By controlling blood flow and the activity of vascular smooth muscle cells, astrocytes also operate as a crucial connection between the cardiovascular and neurological systems. Immune cells, specifically perivascular macrophages, leukocytes, and microglial cells, have an impact on the BBB's functionality. These cells take part in the body's inherent defence against infections. The BBB is obviously a metabolically and physiologically active interface that makes up the neurovascular unit. (Achar & Ghosh, 2020)

A virus may traverse the BBB through three primary mechanisms: transcellular migration, paracellular migration, and the "Trojan horse" technique. In order to cross the BBB, viruses infect host endothelial cells during transcellular migration. Viral invasion of BBB endothelial cell-formed tight connections occurs during paracellular migration. A virus is absorbed by phagocytic host cells, such as neutrophils and macrophages, during the Trojan horse technique. Further research is required since SARS-CoV-2 may use one of these pathways alone or a combination of them. Axonal transport through the olfactory epithelium or dispersion into the general circulatory system and subsequent BBB crossing are two possible entry points for the CNS. The immune system is eventually activated by both mechanisms. Therefore, a crucial entrance point that may be linked to the spread of infection and disease pathogenesis is the ACE2 receptor and regulatory pathway. (Achar & Ghosh, 2020)

3. The Connection of Ischemic Brain Stroke and Covid 19

3.1 Inflammatory-Mediated Thrombosis and Hypercoagulopathy

(Tang et al., 2020) A local pulse of proinflammatory acute-response cytokines, including tumour necrosis factor (TNF) and IL-1, as well as chemotactic cytokines, including IL-8 and monocyte chemoattractant protein (MCP)-1, are produced as a result of the activation of the Inflammasome and macrophage caused by Covid 19. This increases IL-6
production over time. Inflammatory processes and the cytokine release syndrome are sustained when IL6 binds to either the membrane-bound or soluble IL6 receptor and controls the levels of IL6, MCP1, and granulocyte-macrophage colony-stimulating factor (GMCSF). Locally activated platelets have been demonstrated to cause the release of neutrophil extracellular traps (NETs) coated with tissue factor during this hyper inflammatory state. This activation of the extrinsic coagulation cascade results in the generation of thrombin, which raises the risk of thrombosis.

3.2 Cardio Embolism and COVID-19–Associated Cardiopathy

(Outkerk et al., 2020) Even in the early phases of the pandemic, studies reported several mechanisms of cardiac involvement in patients affected by SARS-CoV-2. Studies from China reported a high prevalence of increased troponin I, up to 17% among hospitalized COVID-19 patients, whereas cardiac injury was significantly associated with higher risk of cardiac arrhythmias and death.

Myocardial injury in COVID-19 patients may result from myocardial infarction, direct SARS-CoV2 injury, or indirect harm from stress and inflammatory response. In a case series of COVID-19 patients with ST-segment elevation, coronary angiography revealed no evidence of obstructive coronary disease in 33% of the patients. While this was going on, 56% of the patients had electrocardiographic abnormalities. In a similar vein, 60.7% of patients with COVID-19 and ST-elevation myocardial infarction did not require culprit revascularization, and 39.3% did not have obstructive coronary artery disease. In the general population, left ventricular (LV) dysfunction is thought to have a significant role in LV thrombi, significantly increasing the risk of stroke, particularly in the setting of anterior wall myocardial infarction. (Outkerk et al., 2020)

(Outkerk et al., 2020) Significant myocardial dysfunction may ensue from systemic inflammatory response or direct invasion of the SARS-CoV2, in addition to coronary events that may cause cardiac dysfunction. Numerous investigations found myocardial dysfunction in COVID-19 individuals with nonspecific myocarditis or Takotsubo cardiomyopathy, which has recently been linked to ischemic stroke. In a patient with COVID-19 and cardiogenic shock, viral particles were also found in the interstitial macrophages of the cardiac tissue. In contrast, 78% of COVID-19 patients who underwent cardiac magnetic resonance imaging had cardiac involvement, and 60% had ongoing inflammation with lymphocytic infiltration.

4. Intervention and Therapies of Covid 19 Induced Ischemic Brain Stroke

4.1 Traditional Antithrombotic Therapy for COVID-19 With Coagulopathy

Anticoagulant medication and thrombolytic therapy are now the standard antithrombotic therapies for COVID-19 with coagulopathy. The hypercoagulable condition of COVID-19 has been treated with heparin, an anticoagulant and anti-inflammatory medication. Tang et al. showed that heparin therapy decreased COVID-19-induced mortality. (Tang et al., 2020) Low molecular weight heparin (LMWH) has a longer half-life than heparin, is linked to less bleeding, and does not require frequent coagulation monitoring. Patients with COVID-19 should start receiving preventive LMWH as soon as they are admitted to the hospital, according to Oudkerk et al. (Outkerk et al., 2020) A high dosage of LMWH was advised for anticoagulation in COVID-19 patients admitted to the ICU because Klok et al. discovered that despite the modest dose of LMWH used to prevent systemic thrombosis, some patients with COVID-19 still had thrombotic events. It has not yet been decided how much LMWH should be utilised, and this issue is still debatable. A prior research indicated that 5.2% of participants supported a therapeutic dosage, 31.6% of participants supported an intermediate dose for moderate or severe COVID-19, and the remaining participants supported a preventive dose. During the COVID-19 epidemic, new oral anticoagulants were also advised because of their security, practicality, and potent anticoagulant effects. In addition to activating the coagulation system, SARS-CoV-2 infection also suppresses the fibrinolytic system. For COVID-19 patients with complex ARDS, tissue plasminogen activator (tPA), a thrombolytic medication for AIS, has been found to be beneficial. However, it's important to consider the bleeding risk as well. Chloroquine, a medication that has been successfully used to treat COVID-19, can also act as an antithrombotic by blocking NETs and preventing platelet aggregation. Statins may be utilised to treat thrombosis in COVID-19 patients because they can stop the virus from infecting cells and reduce the inflammatory response and coagulation activation.
Table I. (Zhang et al., 2021)

<table>
<thead>
<tr>
<th>Author/(Refs.)</th>
<th>Drug</th>
<th>No. of patients</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paranjpe et al</td>
<td>-</td>
<td>2,733</td>
<td>Compared with patients who did not receive AC, patients treated with AC had lower mortality and longer survival time.</td>
</tr>
<tr>
<td>Paranjpe et al</td>
<td>-</td>
<td>395</td>
<td>Compared with patients who only receive mechanical ventilation, patients treated with both mechanical ventilation and AC had lower mortality and longer survival time.</td>
</tr>
<tr>
<td>Tang et al</td>
<td>LMWH</td>
<td>449</td>
<td>There was a lower mortality in COVID-19 patients with D-dimer &gt;3 µg/ml treated with heparin than those who did not receive heparin.</td>
</tr>
<tr>
<td>Wang et al</td>
<td>tPA</td>
<td>3</td>
<td>P/F ratio was significantly improved in COVID-19 patients with ARDS after administration of tPA.</td>
</tr>
<tr>
<td>White et al</td>
<td>LMWH</td>
<td>69</td>
<td>Evidence of heparin resistance exists in severe COVID-19 patients, which might lead to anticoagulation treatment failure.</td>
</tr>
<tr>
<td>Arachchillage et al</td>
<td>Argatroban</td>
<td>10</td>
<td>Argatroban can be used to treat COVID-19 patients with thrombosis who have heparin resistance due to reduced antithrombin levels.</td>
</tr>
<tr>
<td>Ranucci et al</td>
<td>LMWH</td>
<td>16</td>
<td>Fibrinogen and d-dimer were significantly decreased in patients treated with low molecular weight heparin.</td>
</tr>
</tbody>
</table>

AC, systemic anticoagulation; LMWH, low molecular weight heparin; tPA, tissue plasminogen activator; P/F ratio, PaO2/FiO2 ratio; ‘-’ indicates data are not available.

4.2 Targeted Therapy Against Cytokines

Targeting cytokines in COVID-19 patients has become an unavoidable trend because of their critical involvement in causing tissue damage and a hypercoagulable condition. It has been established that IL-6 starts the inflammatory response in COVID-19 patients. The Food and Drug Administration has authorised the use of tocilizumab, sarilumab, and siltuximab as inhibitors of IL-6 and its receptor for the treatment of rheumatic and lymphoproliferative illnesses. It's significant that tocilizumab has been authorised for the treatment of COVID-19 patients with increased IL-6 levels. As IL-1, IL-6, and TNF- operate downstream of IL-17, it should get more attention. As IL-17 and its receptor inhibitors, secukinumab, ixekizumab, and brodalumab have been demonstrated to be useful in the treatment of psoriasis; however, additional research is required to determine their impact on COVID-19. (Ascierto et al., 2020) (Paniri & Akhavan-Niaki, 2020).

4.3 Therapy for the Protection of Endothelial Cells

A revolutionary strategy for treating COVID-19 now involves preventing viruses from entering cells. The presently under investigation human recombinant soluble angiotensin-converting enzyme 2 (hrsACE2) can competitively bind to viruses to prevent viruses from entering cells. (Alhenc-Gelas & Drueke, 2020) hrsACE2 has thankfully been authorised for the treatment of ARDS. Given the harm that cytokines do to endothelial cells, anti-inflammatory medication like tocilizumab may also shield these cells. Azithromycin, famotidine, and colchicine have also been shown to lessen endothelium damage. (Sardu et al., 2020)
5. Result
In addition to coronary events that may result in cardiac dysfunction, a systemic inflammatory response or a direct invasion of the SARS-CoV2 may result in significant myocardial dysfunction. Numerous studies have discovered myocardial dysfunction in COVID-19 patients with Takotsubo cardiomyopathy or nonspecific myocarditis, which has recently been associated to ischemic stroke. Viral particles were also discovered in the interstitial macrophages of the cardiac tissue in a patient who had COVID-19 and cardiogenic shock. In contrast, 60% of COVID-19 patients with continuous inflammation and lymphocytic infiltration had cardiac involvement, and 78% of those who had cardiac magnetic resonance imaging did.

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