CEREBROVASCULAR AND NEUROLOGICAL DYSFUNCTON A RESULT OF COVID-19 INFECTION IN PATIENTS WITH MIGRAINE

By
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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons)

Department of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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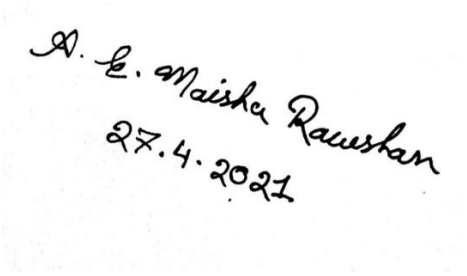

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Approval

The thesis/project titled "Cerebrovascular and Neurological Dysfunction as a Result of COVID-19 Infection in Patients with Migraine" submitted by A. E. Maisha Rawshan (16346013) of Summer, 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study does not involve any human and animal trial.

Abstract/ Executive Summary

The catastrophe resulting from the spread of the SARS-CoV-2 has affected everyone globally. It has been reported that this virus not only generates acute pulmonary and respiratory disorders but also causes cerebrovascular and neurological dysfunctions. A number of COVID-19 infected people were found to suffer from cerebral ischemia in addition to hypoxia. The probable pathway for neurological invasion of SARS-CoV-2 is through olfactory pathway, followed by interaction with the ACE2 receptors present in the brain endothelial cells. However, identifying the factors or underlying conditions that may play vital roles in causing neurological and cerebrovascular problems among the COVID-19 patients are currently crucial. Migraine is one of the most prevailing neurological disorders that has a direct relation with ischemic stroke, regulating the coagulation factors, weakening the blood brain barrier and causing neuroinflammation. Therefore, an individual with pre-existing migraine aura may be more susceptible towards COVID-19. In this review we have proposed the possible reasons of migraine to be a comorbid situation for COVID-19 patients, with regard to cerebrovascular and neurological dysfunctions.

Keywords: Migraine aura; COVID-19; ischemic stroke; cerebrovascular dysfunction; co-morbidity; neurodegenerative disease; cortical spreading depolarization.

Dedication

I want to dedicate this project to my respectable supervisor Dr. Eva Rahman Kabir, Professor and Chairperson, Department of Pharmacy, Brac University.

Acknowledgement

I would like to showcase my deepest and most sincere gratitude to my project supervisor, Dr. Eva Rahman Kabir, Professor and Chairperson, Department of Pharmacy, Brac University, whose expertise, constant guidance, sincere monitoring and motivational approaches in every sphere have inspired me to conduct this project efficiently. I sincerely express my appreciation and admiration for her patience and provided sense of direction whenever I encountered complications throughout this phase.

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List of Acronyms

CDC	Centers for Disease Control and Prevention
SAH	Subarachnoid haemorrhage
TTH	Tension-type headache
BBB	Blood brain barrier
WMH	White matter hyperintensities
ACE2	Angiotensin converting enzyme 2
TMPRSS2	Transmembrane serine protease 2
TNF	Tumor necrosis factor
EEG	Electroencephalography
CGRP	Calcitonin gene-related peptide
PACAP	Pituitary adenylate cervical nerve anatomy
PFO	Patent foramen ovale
CDS	Cortical spreading depression

1. Introduction

In 2019, the most recent type of coronavirus known as, SARS-CoV-2 was identified for causing the infectious disease, COVID-19 (Cucinotta & Vanelli, 2020). This viral infection was first discovered in Wuhan city of Hubei province in China in December 2019 as an epidemic and World Health Organization (WHO) announced this as a pandemic on March 11, 2020 (WHO, 2020). Since then, the disease has been spreading extremely fast, as of January 2021, the total number of cases are 92,747,607 worldwide, with 1,985,836 deaths and the numbers are rising. Though the pandemic started during early 2020, there are chances of another wave as predicted by experts, as such patterns have been seen in other pandemics (Arias Velásquez & Mejía Lara, 2020).

If a COVID-19 infected person sneezes or coughs, the transmission rate of the infection is higher (Ghinai et al., 2020). Although maximum individuals with this infection exhibit low to medium respiratory disturbance and can get better even without any distinctive treatments, the numerical data showing the deaths are higher particularly in terms of SARS-CoV-2, compared to other coronaviruses like SARS-CoV and MERS-CoV. Common indications of this infection are fever, coughing, breathing difficulty, pharyngitis, fatigue, and muscle aches (Cascella, Rajnik, Cuomo, Dulebohn, & Di Napoli, 2020). Several other alarming symptoms that need intensive medical treatment have been reported by the Centers for Disease Control and Prevention (CDC) include rise in pressure or continuous pain in the chest, breathing problem, fatigue, confusion and blue tint on face or lips (Centers for Disease Control and Prevention, 2020).

Even though COVID-19 commonly affects the respiratory system, current studies have found some neurological manifestations as well related to the disease, leading to headache, interrupted sleep, paraesthesia as well as stroke (Oxley et al., 2020). In addition, swelling of

brain tissue and decay of neurons of the central nervous system (CNS) as a result of viral encephalitis have also been diagnosed (Moriguchi, Harii, Goto, Harada, & Sugawara, 2020). Thus, damage of the cerebrovascular system has been found in COVID-19 infected patients.

Reports suggest that migraine is not simply a headache (Etminan, Takkouche, Isorna, & Samii, 2005; T. Kurth et al., 2005; S. Sacco et al., 2015; Simona Sacco, Ricci, & Carolei, 2012). Ischemic stroke is prevalent in migraine patients, and it has been found that cerebral ischemia may trigger migraine attacks leading to migrainous stroke or migrainous infarction. There is a potential connection between migraine and cerebrovascular disease. In recent time, large community-based case studies and cross-sectional studies have shown that migraineurs are at elevated risks of getting stroke beyond the range of a migraine attack, indicating that migraine and cerebrovascular disorder are comorbid conditions.

Migraine is a neurobiological condition that results from elevated CNS stimulation. On the scale of world's most disabling medical illnesses, migraine ranks on the top. Diagnosis of migraine is based on the intensity of the headache and its associated symptoms (Simona Sacco & Kurth, 2014). It is considered to be a contributing factor for ischemic stroke, apart from causing episodic headaches. From a latest study, it was found that each type of migraine headaches were linked to an elevated risk of stroke (relative risk meta-analysis result was 1.73; with 95% confidence interval [CI]: 1.31–2.29), where this probability was doubled in migraine patients with aura (relative risk 2.16; with 95% CI: 1.53–3.03) and even more among women under 45 years old, especially the smokers and those who takes birth control pills (Etminan et al., 2005). Others also indicated that the higher risk of stroke within younger female patients (45–54 years) is more prominent in the report (Schürks et al., 2009). However, men having migraine are also at a risk of having cerebrovascular events (T. Kurth et al., 2005). Aura in migraineurs tends to enhance the absolute risk of a cerebrovascular event as well as increase the fatality rate following a cerebrovascular event (Simona Sacco et

al., 2012). As there is positive correlation of migraine aura with cerebrovascular disease it increases the chances of stroke pathogenicity in migraine patients who are experiencing aura (Gudmundsson et al., 2010).

Multiple cerebrovascular diseases like brain venous sinus thrombosis, cerebral haemorrhage, vertebral division, and ischaemic stroke may occur with or be followed by headache. During subarachnoid haemorrhage (SAH), headaches can sometimes accompany other symptoms with time and form an important warning prior to haemorrhage. The headache is usually a demonstration of cerebral edema in ischaemic and haemorrhagic strokes, which is even more distinctive from migrainous infarction (Agostoni & Rigamonti, 2007).

A notable feature of migraine along with cerebrovascular disorder is the concept that migraine might be a potential cause of stroke and it is generally observed in young females and in patients with migraine aura. Migraine with aura may be labeled as a contributing factor for stroke (Agostoni & Rigamonti, 2007).

On the other hand, SARS-CoV-2 has been proven to cause various neurological disorders, such as encephalitis, polyneuropathy and major ischaemic stroke (L. K. Tsai, Hsieh, & Chang, 2005). Eventually, the incidence of cerebral edema and vasodilation were detected during brain autopsy of some SARS-CoV-2 patients (Y. Wu et al., 2020). In addition, monocyte and lymphocyte infiltration through the endothelium, ischemic neuron alterations and demyelination of nerve fibers were also noticed in dissections of the brain tissue of infected patients (Archie & Cucullo, 2020).

As migraine increases the vulnerability towards cerebrovascular distress along with ischemic stroke, so the increased progression of COVID-19 within such patients can result into encephalopathy. This review article aims to discuss about the comorbid roles of migraine

1.1 Neurological Disorder

Complications of the central nervous system (brain, spinal cord) and peripheral nervous system (cranial nerves, nerve roots, peripheral nerves), involuntary nervous system, mayo-neuron junction and muscles results in neurological disorders. Such disorders include epilepsy, multiple sclerosis, Alzheimer disease, dementia, stroke, migraine and headache, Parkinson's disease, brain tumors, neuro infections, trauma from head injury and neurological disorders due to starvation (Michael De Silva, Silva, & Faraci, 2016).

Neurological disorders are indeed a significant challenge on the global health. According to the Global Burden of Disease (GBD) study, the neurological disorders such as Parkinson's disease, Alzheimer disease, epilepsy, multiple sclerosis and migraine, tension-type headache (TTH), and medication-overuse headache (MOH) are responsible for 3% of the global disease load. While this is a relatively minor percentage, migraine, epilepsy, dementia and stroke account for the topmost 50 contributors of disability-adjusted life years (DALYs) (Murray et al., 2012).

One-fourth of the neurological burden is comprised of epilepsy, migraine represents one-third, whereas dementia and Parkinson's disease are within the highest 15 disorders having the most severe rise in load over the last decade. In 2010, neurological conditions accounted for 5.5% of the years of disability (YLDs), where migraine, epilepsy, and dementia were amid the uppermost 25 contributors of YLDs. In this list, migraine was found to be prevalent in neurological disorders, accounting for more than 50% of neurological YLDs and globally 2.9 % YLDs, and epilepsy constituted 1.1% of total years of disability (Murray et al., 2012).

Although migraine is relatively common, it can be a damaging neurological disorder connected with a variety of psychiatric comorbidities. The connection between neurological dysfunction and COVID-19 has been recently reported. Research has shown that COVID-19

may alter the clinical progression of any expressed neurological conditions and as a result, plays significant role in the formation of potential diseases in the long run (Gu et al., 2005).

1.2 Cerebrovascular Disorder

Cerebrovascular diseases are a diverse group of diseases separated by their distinct pathophysiological mechanisms and clinical features. The outcomes of cerebrovascular diseases are some of the world's major health problems (Mozaffarian et al., 2016). Cerebrovascular disorder is however defined in terms of both large and small vessel disorder (SVD). In this case, small vessels are present on the superficial part of the brain and inside the parenchyma, comprising smaller arteries, arterioles, capillaries and veins (Joutel & Faraci, 2014). Large and SVD look very similar, yet they have distinct features. The brain is exceptional in the allocation of vascular resistance. If small arterioles in the pial circulation or the leptomeningeal colorectal circulation are used as a basis for comparison, approximately half of the vascular resistance is in the arterioles and upstream arteries, while the other half is in the downstream circulation of the parenchyma (De Silva & Faraci, 2016). While blood brain barrier (BBB) is present in cerebral circulation, it has heterogeneous characteristics (Michael De Silva et al., 2016).

There are two types of stroke- hemorrhagic stroke and ischemic stroke. Profuse bleeding induced stroke emerges from the disruption of the brain blood vessel within the subarachnoid space which is called subarachnoid hemorrhage or brain parenchyma (intraparenchymal hemorrhage), whereas ischemic stroke is the consequence of cerebral artery blockage due to deteriorating vascular disease like atherosclerosis or lipohyalinositis. Timely detection of particular stroke types ensures more successful prognosis and treatment of cerebrovascular disease. Even though ischemic and hemorrhagic strokes are known for end-organ

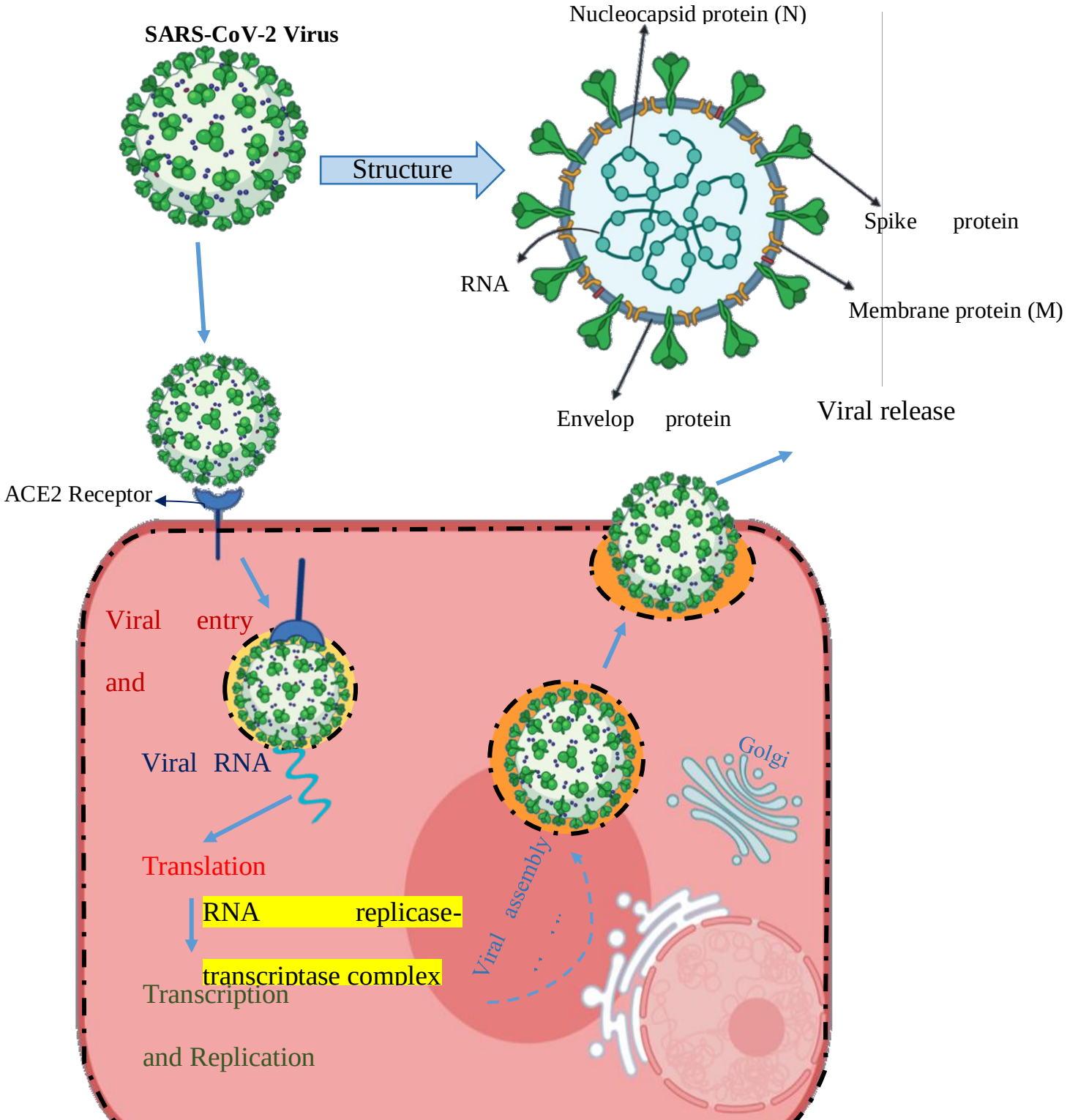
consequences, disturbances of cerebral circulation are the primary threats for hemorrhagic stroke, Alzheimer's disease, vascular dementia and other types of neurological impairment with dysfunction (Wardlaw, Smith, & Dichgans, 2013). Carotid and cerebrovascular disease mainly results in ischemic stroke, which involves both large and small vascular disease. Additionally, the stoppage of blood supply caused by blood clot in the carotid or cerebral arteries can appear as well as hemorrhagic strokes. Microvascular alterations throughout SVD lead to small areas of ischemia and microbleeds (micro haemorrhages) (Poels et al., 2012). When started, both large and small vessel disorders usually develop steadily over a long period of time. The degree of development, and hence the occurrence of large and small ischemic stroke and microbleeds are intensified across maturing and existence of vascular disease risk enhancers. Disease associated to genetics or diet can lessen or accelerate the process of development of vascular disease and brain disorders. Since arteries and arterioles together exhibit myogenic action or vasoconstriction, the degree of myogenic tone produced is dependent on the size of the vessel.

Patients having migraine demonstrated an elevated risk of vascular events, mainly in women and in patients with aura (Tobias Kurth et al., 2016; S. Sacco et al., 2015; Schürks et al., 2009). Possible underpinning pathways comprises of hyper-coagulability, platelet aggregation, endothelial dysfunction, spread of depolarization, vasospasm, cardiovascular risk factors, genetics, perplexing embolism, use of non-steroidal anti-inflammatory drugs and immobilization (Jesurum, Fuller, Murinova, Truva, & Lucas, 2012; Lee et al., 2008; Longoni & Ferrarese, 2006; Tietjen, 2009; Vanmolkot, Van Bortel, & De Hoon, 2007). Some observation-based analyses have demonstrated the rise of vascular diseases in people suffering from migraine attacks (Tzourio et al., 1995. A meta-analysis involving nine studies, which was published in 2009 revealed an escalated risk of ischemic stroke in migraine patients (pooled relative risk 1.73) (Schürks et al., 2009). This meta-analysis indicated the

prevalence of ischemic stroke solely in patients with migraine aura (relative risk 2.16) which is quite higher compared to those who are not having migraine aura (1.23, CI 0.90 to 1.69). The relative risk was climbed to a pronounced degree among women (2.08, 1.13 to 3.84) than among men (1.37, 0.89 to 2.11). Some other studies suggested an additional risk of migraine-related hemorrhagic stroke (pooled relative risk 1.48) (Simona Sacco, Ornello, Ripa, Pistoia, & Carolei, 2013).. The potential explanation for this correlation may be changes in the vessel wall migraines within the migraineurs, as well as the likelihood of arteriovenous incorrect formation that cause hemorrhagic stroke may resemble migraine headache. Neurophysiological reports have documented migraine aura to cause cortical spreading depression, which is investigated as brain sensitizing cerebral hypo-perfusion and arterial ischemia (Pietrobon & Moskowitz, 2013). As a result, migraine tends to be a systemic vascular disease as revealed by the peripheral vascular system of migraineurs and the inflexibility of artery and dysfunction in endothelium (Simona Sacco, Ripa, et al., 2013). Patients with migraine aura are more prone to stroke, both between (migraine-related stroke) and during attacks (migraine infarction) (Etminan et al., 2005). On the contrary, studies have shown that beyond aura, migraine does not intensify the hazards of stroke (Simona Sacco & Kurth, 2014). There is evidently a link between the occurrence of migraine attacks and the possibility of stroke (Etminan et al., 2005). A further critical consideration that reinforced the correlation between migraine and stroke is the subsistence of white matter abnormalities in migraine-affected patients. Populace-grounded findings suggest that migraine and particular migraine with aura, could be a significant predictor for asymptomatic (silent) brain infarcts and white matter hyperintensities (WMH) (Mark C. Kruit et al., 2004). These results generated widespread concern as WMHs facilitates the chances of suffering from stroke, dementia, and death (Debette & Markus, 2010).

1.3 COVID-19

Coronaviruses fall under the Coronavirinae subfamily, which includes four types of coronaviruses called *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus* and *Deltacoronavirus* (Cui, Li, & Shi, 2019). SARS-CoV-2 is a *Betacoronavirus* closely associated to human pathogenic coronaviruses SARS-CoV and MERS-CoV (Suliman Khan et al., 2020). SARS-CoV-2 is surrounded by an envelope and contains single stranded positive-sense RNA virus with crowns called spike protein on its surface. The diameter and the length of SARS-CoV-2 are approximately 65–125 nm and 29.9 kb respectively (Guo et al., 2020). SARS-CoV-2 structure contains 4 major proteins, named spike (S) glycoprotein, envelope (E) glycoprotein, membrane (M) glycoprotein and nucleocapsid (N) protein, and other non-structural and supplementary proteins (Figure 1). The spike (S) protein is mainly responsible for viral adhesion, fusion, entry and transmission within the host cell. This S protein is essential for the access of SARS-CoV-2 into the host cell by binding with angiotensin converting enzyme 2 (ACE2) that works as a receptor and exists in multiple organs in body (Rodriguez-Perez et al., 2020).


SARS-CoV-2 Virus
Structure
Nucleocapsid protein (N)
Spike protein
RNA
Membrane protein (M)
Envelop protein
Viral release
ACE2 Receptor
Viral entry
and
Viral RNA
Translation
RNA replicase-
transcriptase complex
Transcription
and Replication
Viral assembly
Golgi

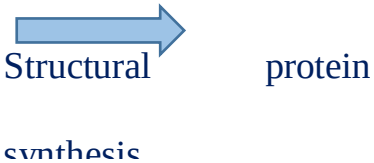


Figure 1: Structural component of SARS-CoV-2 and viral entry in the cells.

The most typical warning signs of COVID-19 are fever, sore throat, shortness of breath. As per the reports from health care staff, it has been speculated that the virus can spread into the brain and cause anosmia, hyposmia, hypogeusia and hypoxia. When SARS-CoV-2 penetrates through central nervous system, it can remain in dormant state in the tissues or can proceed to trigger neuroinflammation. The aim now is to examine infection of the olfactory bulb portion of the brain with SARS-CoV-2 and the mechanism by which it may damage the neighboring native neurons in the brain (Michalicová, Bhide, Bhide, & Kováč, 2017).

Studies showed impairment of the CNS structure and function due to viral infection consequences into major encephalitis, toxic encephalopathy and severe demyelinating lesions (Y. Wu et al., 2020). Certain viruses of neurotropic nature can cause diseases of macrophages, microglia, and astrocytes by invasive nervous tissues (Soung & Klein, 2018). Previous studies have found that respiratory infections are a noteworthy feature in the progression of acute cerebrovascular disease (Warren-Gash, Blackburn, Whitaker, McMenamin, & Hayward, 2018). In addition, influenza virus has been demonstrated to cause intensified ischemic brain damage by activating a cytokine cascade and infiltration of cytokines, raising the risk of cerebral hemorrhage induced by a tissue-type plasminogen activator (Muhammad et al., 2011).

SARS-CoV-2 has been reported to trigger numerous neurological disorders, including encephalitis, polyneuropathy and major ischemic stroke (L. K. Tsai et al., 2005). Promptly, the incidence of excess fluid accumulation into extra-cellular or intracellular cerebral space and meningeal blood vessel dilation accompanied by the existence of the SARS-CoV-2 genome in the brain were found in a number of autopsy studies of SARS cases (Y. Wu et al., 2020). In addition, monocyte and lymphocyte infiltration within the vessel wall, insufficient blood supply to the brain and nerve tissue, neuron and nerve fiber demyelination were also observed in post-mortems of the brain samples from infected patients (D. Z. Huang et al., 2003).

Another coronavirus, MERS-CoV, progresses into Middle East Respiratory Syndrome or MERS and is considered to be neuro-invasive. Various studies have shown that MERS-CoV is also able to cause various neurological abnormalities, including psychosis, seizures, ischemic stroke, disturbed consciousness, paralysis, Guillain-Barre syndrome, poisoning or contagious neuropath (Kim et al., 2017).

2. Neuropathology of COVID-19

Several neurological complications such as inability to taste and smell, encephalitis, headache, dizziness, and vomiting have been very evident among the increasing number of COVID-19 infected patients worldwide. The expression of ACE2 receptors in neurons, glial cells and endothelial tissues of blood-brain barrier does not discard the possibility of neuro incursion by the deadly virus SARS-CoV-2.

Earlier, autopsy of four SARS infected patients and four non-SARS controlled patients were performed to investigate SARS-CoV distribution in 22 different tissue-types expressing its target ACE2 receptors. The existence of SARS-CoV in the cerebrum was seen in the four fatal SARS patient samples, defining neurotropic virus behavior. SARS-CoV as well as SARS-CoV-2 both can facilitate host cell invasion via the ACE2 receptor, the existence of this virus in the CSF of some patients is alarming and indicates neuro-invasive property of the virus; nevertheless, comprehensive studies are required to determine this. Moreover, presence of this virus in blood has been documented in some cases and it is likely that the virus may propagate hematogenously and break the blood-brain barrier in response to a cytokine storm (Hirano & Murakami, 2020).

Even though the accurate path of viral entry into the CNS still stays questionable, studies show that the binding of the SARS-CoV-2 spike (S) protein to the ACE2 receptor is harmonized by transmembrane serine protease 2 (TMPRSS2) and endosomal cysteine proteases by priming the S protein (Hirano & Murakami, 2020).. However, in an experimental study where human ACE2 receptor was expressed in the transgenic mice, it was demonstrated that the SARS-CoV infected the CNS through the olfactory bulb and swiftly spread to other parts of the body via comprehensive neuronal infection (Netland, Meyerholz, Moore, Cassell, & Perlman, 2008). It is reasonable, considering the constitution of the nasal cavity and its adjacency to the forebrain, which can act as a path of viral entry (Figure 2).

Further studies have elucidated that entry of SARS-CoV to brain via the olfactory route at the onset of this disease or nasal vaccination induce inflammation and cause demyelination (Desforges et al., 2019). Hence, it is obvious that SARS-CoV viruses can enter the brain using neuronal path ways like the olfactory neuron transport system (Desforges et al., 2019). Moreover, when the virus passes the blood-brain barrier and spreads to brain tissue, it can spread via the activation of pathways with unique neurotransmitters around the cerebrum.

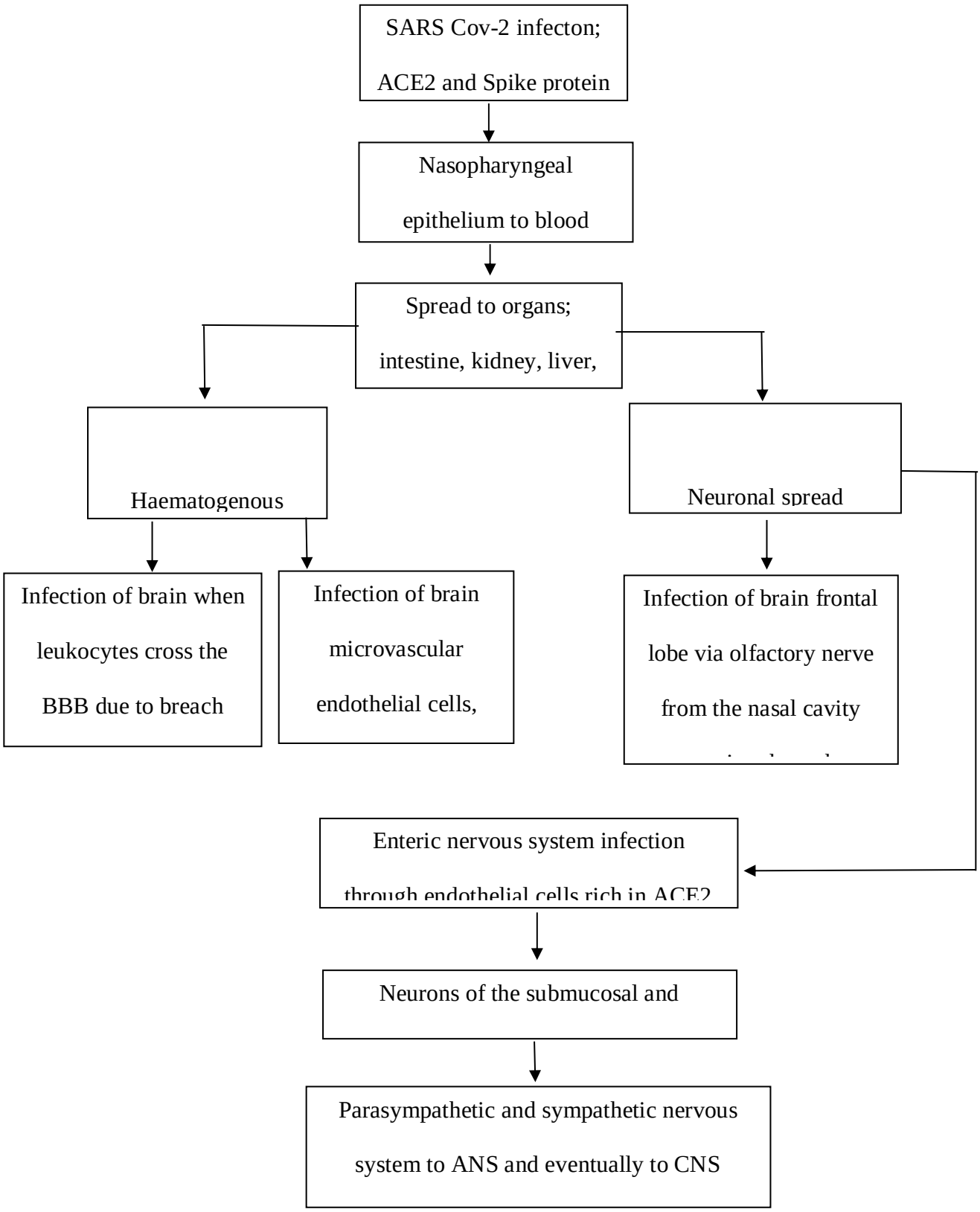


Figure 2: Schematic diagram of the possible neuro-invasiveness routes for SARS-CoV-2

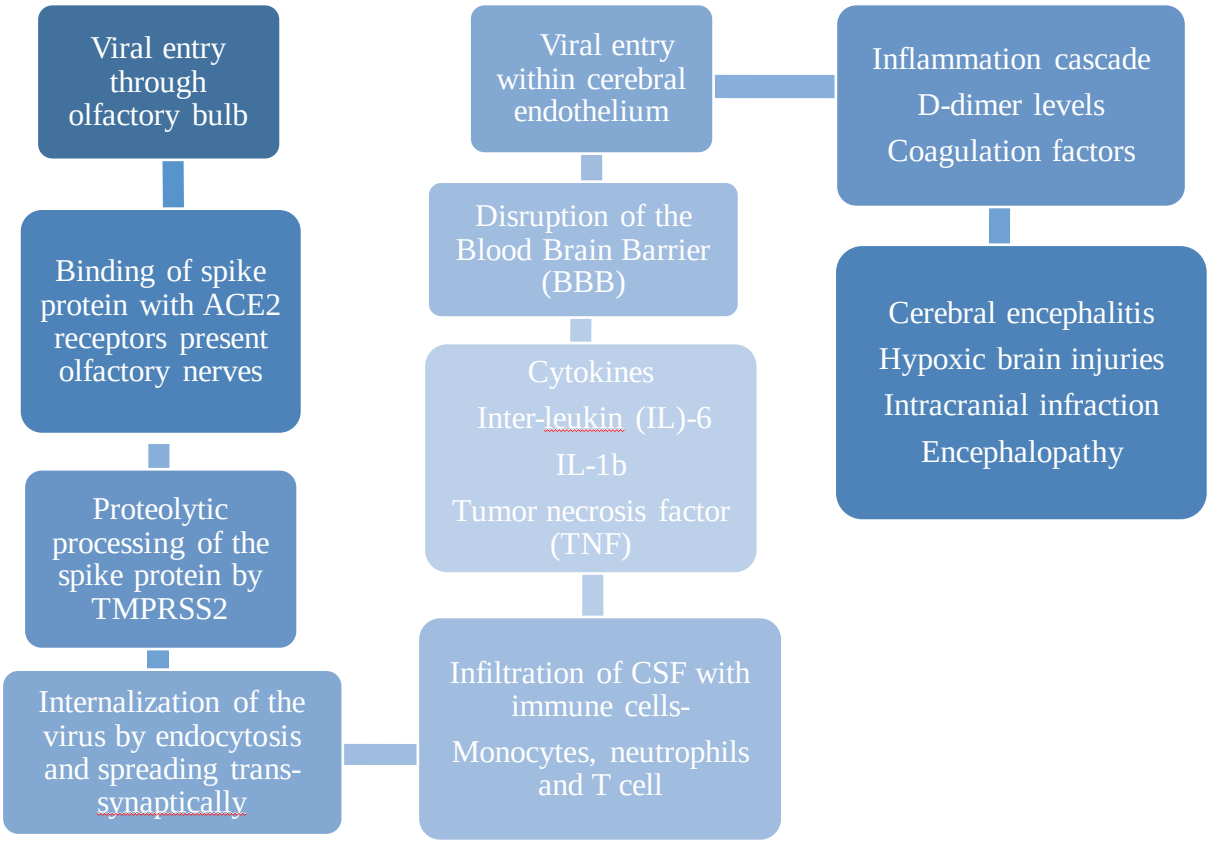


Figure 3: Neuropathology of COVID-19

The virus can also roll out via a neuron associated deteriorating mechanism where it colonizes in peripheral neurons, nevertheless eventually reaches the CNS by propagating via the distributed system of the neuronal transport machinery (Zhou, Kang, Li, & Zhao, 2020). Lately, the likelihood of neuro-invasion through the enteric pathway has also been brought into light, which indicates the influence of the virus on enteric nervous system or enter the central nervous system through abdominal vagal afferents (Esposito et al., 2020). The neuro-invasion produces debilitating effects in certain cases. A further concern is that as neurodegenerative condition often takes more than 10 years to be diagnosed, long lasting pathophysiological manifestations of SARS-CoV-2 should be perceived as a subject of major interest for researchers in this subject (Shumayila Khan & Gomes, 2020).

In addition, the spread of viruses in the lung tissue can result in decreased alveolar exchange of gases, leading to hypoxia in the CNS. A hypoxic condition triggers anaerobic metabolism of brain cells, which causes neuronal swelling, accumulation of fluid in brain, cerebral blood flow blockage, and headache due to ischemia and clotting (Abdennour, Zeghal, Dème, & Puybasset, 2012). Non-treated oxygen deprivation within the brain can cause severe cerebrovascular disease such as critical ischemic stroke in serious COVID-19 infected patients (Lin, Lu, Cao, & Li, 2020). In fact, development of toxic encephalopathy has also been documented in some of the COVID-19 patients suffering from viremia and hypoxia (Bikdeli et al., 2020). Whilst some of such patients often undergo from deadly silent hypoxia, there is a need for comprehensive review and consideration (Wilkerson, Adler, Shah, & Brown, 2020). In general, ACE2 is also responsible for regulating the inflammatory processes, while inhibiting the progression of atherosclerosis (Ferrario, Trask, & Jessup, 2005). Thus, COVID-19 raises the risk of developing atherosclerosis, which may eventually cause ischemic stroke by disrupting microcapillaries of the brain.

2.1 Cerebrovascular and neurological manifestations of COVID-19

The genetics of this deadly virus SARS-CoV-2 is 79.5% and 96% identical to SARS-CoV and bat coronavirus respectively (A. Wu et al., 2020). The SARS-CoV-2 sequence homology also appeared to be 50% similar to the MERS-CoV virus (Cataldi, Pignataro, & Taglialatela, 2020). While the fundamental signs of COVID-19 are fever, dry cough, and weakness in maximum patients, where some patients experience neurological signs with dizziness, headache, languidity, malaise, shaky walking, infarction, cerebral hemorrhage (Bikdeli et al., 2020; C. Huang et al., 2020). Additional research has provided evidences of abrupt loss of smell or taste in some patients as well (Giacomelli et al., 2020; Ryan W. Miller, 2020).

A type of longitudinal study with 214 COVID-19 infected patients showed that 36.45% of the patients had neurological problems, with severe cerebrovascular disorders, diminished wakefulness, skeletal muscle motor neuron abnormalities; 18.7% among the total infected patients having serious neurological symptoms were admitted to the intensive care unit (H. Y. Wang et al., 2020).

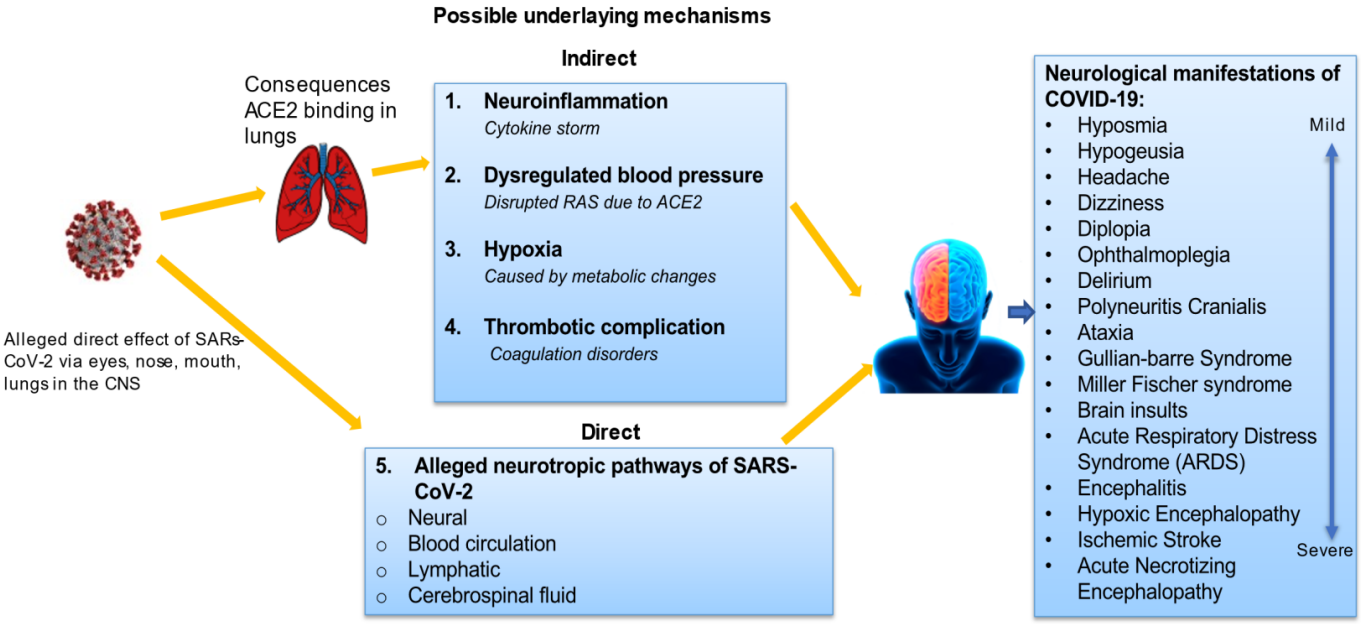


Figure 4: Cerebrovascular and Neurological Manifestation of COVID-19

.Table 1 shows multiple documentations on SARS-CoV-2 infected patients who have been reported with serious neurological and cerebrovascular dysfunction including headache, olfactory disorders, dizziness, diminished wakefulness. Perhaps the main drawback of these case reports is that an evaluation of cerebrospinal fluid (CSF) and electroencephalography

(EEG) have not been conducted to assure the existence of this lethal virus in the cerebrospinal fluid.

Table 1: Case studies on investigating neurological and cerebrovascular manifestations in COVID-19 patients

Study Type	**Time**	**Study design**	**Outcome and Symptoms**	**Reference**
Retrospective case series	13 January to 31 March	*N* = 274, admitted patients	Headache (11.31%), Dizziness (7.66%)	(T. Chen et al., 2020)
Retrospective case series	16 January 2020 to 29 February 2020	*N* = 221, admitted patients	Acute ischemic stroke (5%), CVST (0.5%), cerebral hemorrhage (0.5%)	(Y. Li et al., 2020)
Retrospective case series	16 January 2020 to 19 February 2020	*N* = 214, admitted patients	Nervous system affected (36.4%) CNS symptoms (24.8%): Headache (13.1%), dizziness (16.8%), diminished wakefulness (7.5%), acute cerebrovascular disease (2.8%), ataxia (0.5%) epilepsy (0.5%))	(Mao, Jin, et al., 2020)
Retrospective case series	1 January to 28 January, 2020	*N* = 138 admitted patients	Headache (7%), dizziness (9%)	(D. Wang et al., 2020))
Retrospective case series	1 January to 20 January, 2020	*N* = 99, admitted patients	Headache (8%), confusion (9%)	(N. Chen et al., 2020)
Cross-sectional survey	19 March, 2020	*N* = 59, admitted patients	Headache (3.4%) Taste or olfactory disorder (33.9%), Taste and olfactory disorder (18.6%)	(Giacomelli et al., 2020)
Retrospective case series	late December 2019- 26 Jan 2020	*N* = 52, admitted patients (critically ill adults)	Headache (6%)	(Yang et al., 2020)

Prospective case study	By 2 January 2020	*N* = 41, admitted patients	Headache (8%) in 38 patients	(C. Huang et al., 2020)
Case study	23 March to 7 April	*N* = 5	Large-vessel stroke (100%)	(Oxley et al., 2020)

Some other notable studies have also found that COVID-19 triggers acute stroke in patients aged between 30 to 40 years. These SARS-CoV-2 infected patients had minimal or no symptoms of the disease, however, irregular blood clotting in large arteries were identified eventually leading to severe stroke (Oxley et al., 2020).

In addition, it is evident that SARS-CoV-2 can start off a cytokine storm syndrome that can cause a variety of both infectious and non-infectious diseases, such as pancreas inflammation, acute cerebrovascular disease and several organ dysfunctions (Mehta et al., 2020). Critical patients also displayed an elevated D-dimer level and a substantial platelet depletion that could render patients comparatively more susceptible to acute cerebrovascular dysfunction. Furthermore, such patients are susceptible to different forms of bacteria, disease causing bacteria which may harm the stability of the blood-brain barrier (BBB). Ultimately, secondary infection can develop vomiting, vision loss and spasms, headaches in COVID-19 infected patients (Ripa et al., 2020).

Relying on existing case reports and literature on COVID-19 infected patients, it is clear that COVID-19 may be correlated with neurological and cerebrovascular disability, which can be lethal. Nevertheless, further research needs to be performed to validate this hypothesis.

3. COVID-19 susceptibility in cerebrovascular diseases

A quantitative meta-analysis addressing the relation within cerebrovascular disease and negative outcomes in COVID-19 infected patients (N=4448) was carried out where, (RR 2.04 [1.43.2.91], p<0.001; I2:77%). Demographic research indicated that pre-existing cerebrovascular condition was associated with fatalities (RR 2.38 [1.92.2.96], p<0.001; I2:0 %) and displayed marginal consequences for severely infected COVID-19 patients (RR 1.88 [1.00, 3.51], p = 0.05; I2:87%) (Pranata, Huang, Lim, Wahjoepramono, & July, 2020). Risk factors for cerebrovascular conditions in COVID-19 patients include lack of mobility in patients after stroke, which upsurges the chance of thrombophilia that results in thrombosis. Acute SARS-CoV-2 infection alone can cause defects in homeostasis and can lead to thrombophilia, a situation frequently experienced during systemic infection (Levi & van der Poll, 2017). New documentation of pulmonary tissue examination in critically ill COVID-19 patients has shown obstruction and micro-vascular blood clotting in pulmonary blood vessels, indicating that blockage in pulmonary artery may play a role in life-threatening conditions (Luo et al., 2020). Even worse, neither of the mentioned studies suggests somewhat operational or motor status among patients with cerebrovascular disease. Therefore, inference on this supposition cannot be confirmed or contradicted.

Additionally, evidence indicates that besides occupying pulmonary blood vessel, central nervous system can also be affected, causing major damage of the neurons (Desforges et al., 2019). Neuro invasion is one of the potential effects of COVID-19. Human coronaviruses (OC-43, 229E, MERS, and SARS) and some animal corona virus exhibit these neuro-invasive properties (Carod-Artal, 2020). The central nervous system typically exhibits very minimum levels of ACE2 or dipeptidyl peptidase 4 (DPP4), which is essential for SARS-CoV and MERS-CoV entry (Y. C. Li, Bai, & Hashikawa, 2020). Possible mechanisms for

nervedisorders following SARS-CoV-2 infection include straight invasion via blood circulation or neuronal pathways, hypoxic injury, immune system damage, and the insufficiency of major histocompatibility complex (MHC) antigens in nerve cells. SARS-CoV-2 may trigger chronic neurological problems, such as infectious toxic encephalopathy, viral encephalitis and acute cerebrovascular disease (S. T. Tsai, Lu, San, & Tsai, 2020). A study by Li et al. provided that 5% of COVID-19 infected \patients (N=221) had an acute obstruction in brain blood flow, 0.5% had blood clots in cerebral venous sinuses, and 0.5 % had uncontrolled bleeding within cerebral tissue. The prevalence was observed greater in geriatric persons having possibilities of illness (Y. C. Li et al., 2020). The researchers further stated that there was an increased inflammatory response. Additionally, hypercoagulable conditions have been identified in people who are having progressive cerebrovascular disorders. The chances of these disorders were greater in people with delayed prothrombin time (PT), international normalized ratio (INR or standard prothrombin ratio), longer thrombin time and D-dimer indicating impaired blood clotting that lead patients to thrombotic events or local coagulation of circulating blood (Bikdeli et al., 2020).

Another study mentioned 15% (95% CI, 9.3-22) and 34% (95% CI, 23-46) thrombus generation in veins were observed on day 7 and 14 respectively in COVID-19 infected patients (Middeldorp et al., 2020). A study by Oxley et al. reported 5 cases of blood flow interruption in main large artery of brain in young patients less than fifty years of age (Oxley et al., 2020). Two patients were identified aged 33 and 37 years respectively lacking the danger for stroke. Magnetic resonance imaging (MRI) and echocardiographic examination of the head and neck showed no possible origin of thrombus. Influenza can elevate the possibilities of stroke which is already shown (Warren-Gash et al., 2018). With the existence of damaged vascular system of cerebrum, these problems can be more severe..

4. Migraine and its pathophysiology

Migraine is a hereditary periodic condition, the core of which is a headache and other associated characteristics (Olesen, 2008). These attributes provide valuable insights into their pathophysiology and may be useful to devise treatments. The basic principles to be addressed are as follows:

• Genetical reasons behind migraine

• Physiological origin of the migraine aura

• Nature of headache, especially of the trigeminal vascular system

• Functions and mechanisms of peripheral branch operation of the ear relating branch of the trigeminal nerve

• Functions and mechanisms of the sensory largest nuclei or trigeminal nucleus, which is mostly related to the trigemino cervical complex including afferents coming to the upper neck, jaw and trigeminal nerve

• Brainstem and diencephalic nuclei that modulate the trigeminal pain besides sensory modalities

Migraine is a disorder of sensory operations with broad consequences of central nervous system activity, and since pain is considered as an ideal sign, a brain focused interpretation offers a basis for understanding each types of migraine headache (Hansen, Goadsby, & Charles, 2016). This is one of the most prevailing nervous system disabling disorder. It induces severe class of impairments. However, the clinical implications of migraine or headache disorders are often overlooked in most countries (Dowson et al., 2008).

The theory regarding migraine pathophysiology is making rapid progress. Enhanced understanding and identification of its clinical attributes have made migraine being perceived as a complicated fluctuating condition of the nervous system instead of merely a headache disorder. Current findings have suggested valuable developed perspectives into its gene related components, structural and functional characteristics, and pharmacological mechanisms (Charles, 2018).

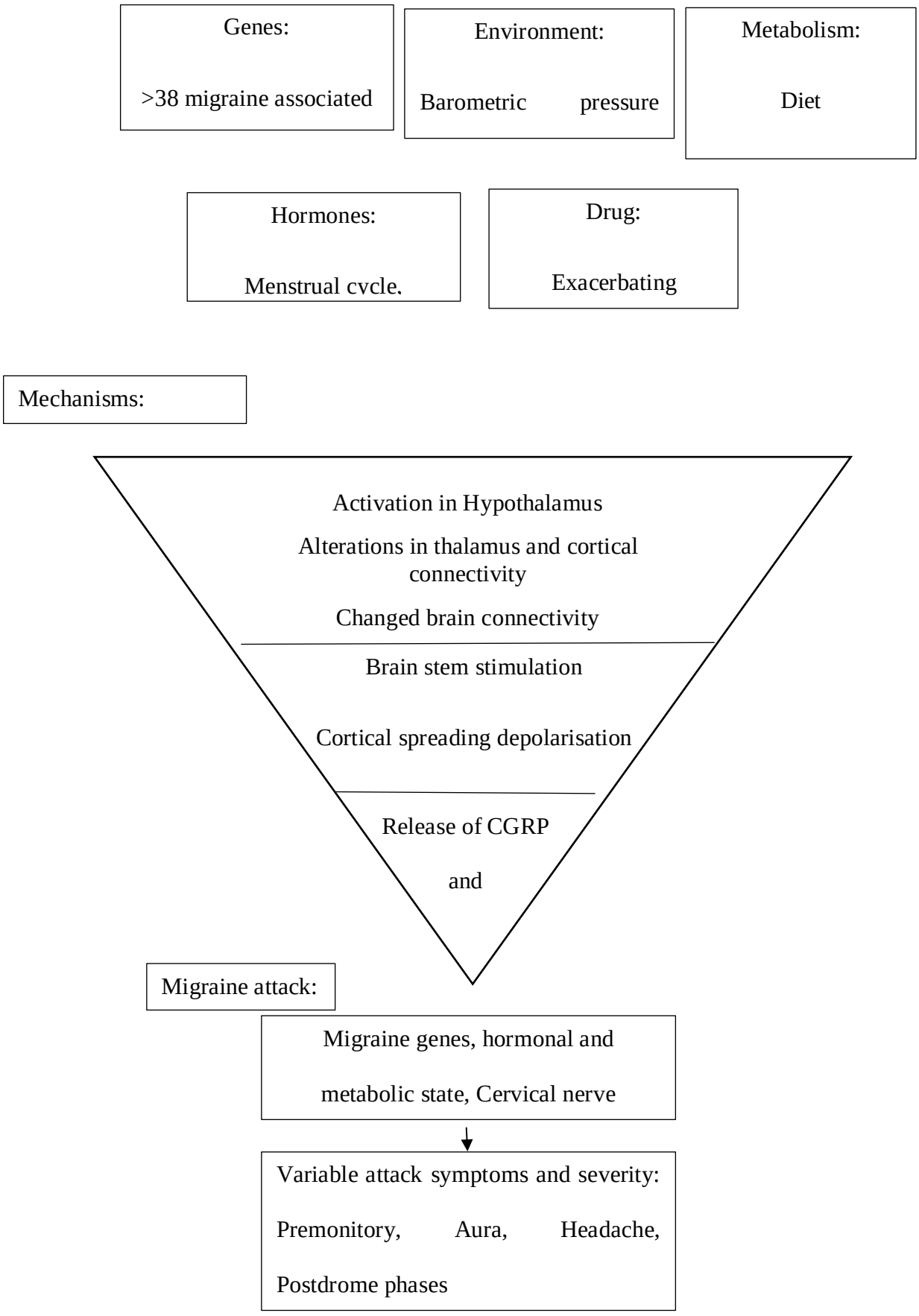


Figure 13: Causative features and mechanisms of a migraine attack

Factors influencing migraine attack and its mechanism:

A number of factors are responsible for the progression of a migraine attack which follows various mechanisms. The clinical symptoms of the migraine attack that differ in terms of genetic, physiological, and other variables e.g. calcitonin gene-related peptide (CGRP), pituitary adenylate cervical nerve anatomy (PACAP), medications and stress (Charles, 2018).

Specific symptoms and intensity of attack include:

• Premonitory, aura,headache, and post-drome

•Hypothalamic activation;

• Modification of in thalamo-cortical circuits

• Altered connectivity of the brain

• Stimulation of brainstem

• Cortical spreading depolarization

• Regulation of CGRP and PACAP Migraine genes

• Hormonal and metabolic state,

A migraine attack is generally characterized on the basis of the implication of temporal to the headache: the premonitory stage (followed by headache), the aura phase (instantly followed by or accompanied by headache), the headache phase, and the postdrome stage (after headache resolution) (Charles, 2013). While this definition of migraine attack is realistic, the phases of the attack can be superimposed and variable. Few manifestations of a migraine attack (sensory distress and pain in the neck) can be consistent during the attack, as some

(aura effects) may arrive and go. The various stages of the migraine attack provide a prospect to characterize, also differentiate the physiological alterations at the onset of a migraine attack contributing in headache progression and participating in recovery process.

Throughout the precognitive process, multiple symptoms, including yawning, frequent urination, mood changes, discomfort feelings, light sensitiveness, neck pain, and concentration problems among others (Lampl, Rudolph, Deligianni, & Mitsikostas, 2015) generally appear hours before the initial stage of headache throughout a migraine strike. Apart from some subjective symptoms, other especially sensory sensitivity can be statistically measured. For reference, deviations of quantitative sensory scale emerge hours prior to headache consistent with the frequency of subjective sensory symptoms in the premonitory phase (Charles, 2018). PET (Farooq Husain Maniyar, Sprenger, Monteith, Schankin, & Goadsby, 2014) and functional MRI (Schulte & May, 2016) reports of active migraine attacks depict alterations in the functional and hypothalamus connectivity in the hours followed by headache. These alterations in usual functioning of hypothalamus may be the reason for frequent urination, mood swings and change in appetite followed by headache. PET reports of the premonitory phase also depict that accelerated activity in the occipital cortex is induced and impulsive migraine attacks indicate changes in hypothalamic activity and communication in the hours following headache. Such variations in hypothalamic function may be responsible for frequent urination, mood changes, and changes in hunger prior to headache. Premonitory step PET experiments also indicate that amplified activation in the occipital cortex is associated with light sensitiveness (F. H. Maniyar, Sprenger, Schankin, & Goadsby, 2014) and that brainstem activation is associated with nausea (Farooq H. Maniyar, Sprenger, Schankin, & Goadsby, 2014).

The clinical relevance of the migraine aura and its possible reasons remain topics of active study. Population reports suggest that the presence of migraine with aura is linked to an

elevated risk of other co-existing diseases e.g. patent foramen ovale (Takagi & Umemoto, 2016), ischemic stroke including perioperative stroke (L. Li, Schulz, Kuker, & Rothwell, 2015), restless legs syndrome (Schürks, Winter, Berger, & Kurth, 2014), Parkinson's disease (H. I. Wang, Ho, Huang, & Pan, 2016), bipolar disorder (Saunders et al., 2014) and panic disorder (Smitherman, Kolivas, & Bailey, 2013). Besides, the other migraine symptoms, the prevalence of aura throughout migraine events is unpredictable in many other cases and the clinical characteristics of the aura itself can indeed vary significantly in a patient (Hansen et al., 2016).

While optical symptoms are predominant, auditory, speaking and olfactory symptoms are also regular (Viana et al., 2016) and may also happen in combination or separately of optical symptoms. Typical migraine causes flashing blind spots affecting about 50 percent of patients; flashing lights, scotoma without scintillation, or non-described vision distortions are also widely recorded (Charles, 2018).

4.1 Interrelationship among migraine, ischemic stroke and encephalopathy

Findings suggested that ischemic strokes might arise in migraine attacks and that migraines catalyzed by brain ischemia, previously showed a probability of having an association with both migraine and cerebrovascular disorders (Agostoni & Rigamonti, 2007). In recent years, major demographic studies found that migraineurs are at greater risk of stroke beyond the scope of an attack that contributed to a hypothesis of co-morbidity between migraine and cerebrovascular disease. As a consequence, the comorbid relationship between migraine and cerebrovascular disease can be explained through migraineurs with metabolic syndrome and the clustering of risk factors which elevates chance of cerebrovascular disease.

The risk of clinically silent infarctions, which are seen as hyperintense lesions in magnetic resonance imaging (MRI), might be enhanced by migraine also. Migraine and stroke are both expressed in people with health problems for example, the ateriopathy induced by cerebral autosomal-dominant gene with subcortical infarcts and mitochondrial myopathy, encephalopathy, lactic acidosis, also stroke-like episodes, which may contribute to common infections (Hougaard, Amin, & Ashina, 2014).

Imaging tests have found that migraine, irrespective of other coronary disease risk factors, is associated with an elevated incidence of asymptomatic infarctions, indicated as hyperintense lesions or white matter lesions on MRIs (M. C. Kruit, Van Buchem, Launer, Terwindt, & Ferrari, 2010). Thus, migraine aura can frequently increase the risk of white-matter hyperintensities as a result of chronic ischemia and consequently impacts lesion load (S. P. Chen & Eikermann-Haerter, 2020).

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There have been a variety of hypotheses regarding stroke in migraine patients. Cortical spreading depression (CSD) that leads to altered vascular permeability of the endothelial membrane is the stream of depolarization of the neurons and glial cells during a migraine aura. It is partly influenced by matrix metalloproteinases and restricted penetration (50%) or hypoperfusion small arteries (Pietrobon & Moskowitz, 2013), further resulting in hypoxic brain injuries, which appear as white matter lesions on MRI.Neuropeptide (i.e., calcitonin gene related peptides (CGRP), substance P and neurokinin A), inflammatory cytokines, plasma protein (bradykinin and prostanoids) are released by the consequences of neurogenic inflammatory disease induced by both CSD and exogenous stimulating the Trigeminovascular System (Weber et al., 1993). It may trigger cerebral ischemia through cerebral blood flow impacts (Goadsby, 2012).

Migraine and cerebrovascular disorder has been studied for genetic correlations, where migraine was found to be a critical factor for stroke in combination with methylenetetrahydofolate reductase (MTHFR) C677T homozygosity, a genotype version linked with hyper homocysteinemia (Scher et al., 2006) . In accordance with this, high levels of homocysteine were seen in the cerebrospinal fluid (CSF) and serum of migraine patients (both with and without aura).

The risk of cerebrovascular events can be affected by migraine treatment. Various abortive migraine medications, particularly triptans or ergot alkaloids, may substantially contribute to ischemic events by vasoconstriction (Barra et al., 2010). Thus the risk of vascular adverse effects in migraineurs with triptan treatment is being continuously studied in broad population studies. However, overuse of drugs needs to be monitored, as in case with all medications. Excess use of ergot-derived drugs (over 90 days a year) showed that the chances of ischemic attacks increased (coronary, peripheral or cerebrovascular).

Patent foramen ovale (PFO) occurs at great rate among migraineurs. The incidence of PFOs is 27% in the general public and 4.9% large shunts. However, 60% migraineurs suffer from shunts, which include 38% having large PFOs (Dowson et al., 2008). It has been debated whether PFO is responsible for migraine pathogenesis, and whether closure of PFOs may be advantageous.

The comorbid association between stroke and migraine includes the finding that migraine maximizes adiposity, decreased response to insulin, an adverse lipid profile and hypertension, certain metabolic syndrome characteristics, also common leading causes for cerebrovascular disorders (Sinclair & Matharu, 2012). Relevant risk factors affect the migraine-ischemic stroke relationship; such as (1) Patent foramen ovale or endothelial impairment and more prevalent in specific states such as unconstrained cervical artery sectioning (2) Migraine is

linked to higher prevalence of cardiovascular risk; (3) Migraine-specific drugs; (4) Genetic factors (Etminan et al., 2005).

5. Possibilities of migraine to become a comorbid situation for COVID-19 infected patients

Co-morbidity may be defined as the statistical link between two or more simultaneous disorders in a patient. COVID-19 patients with co-morbidities such as hypertension or high blood pressure, asthma, respiratory system disease and cardiovascular disease have been shown health issues in contrast to non-severe patients (Yang et al., 2020).

Neurological co-morbidities are significant predictors of the incidence of COVID-19 and should be extensively evaluated throughout earlier infection phases. In order to target vulnerable patients impacted by the neurological diseases. In general, there was neurologic comorbidity in 22.4 percent (n = 77) patients. These were overwhelmingly found to be more prevalent among serious COVID-19 in patients comparing to patients who are not affected by any neurological disorders ($p<0.001$). Antecedent cerebrovascular conditions are perhaps the most common comorbidities, which influenced 39.0% of patients. These were often accompanied by mental conditions (Silberstein, 2004) .

Migraine aura is vital factor connecting migraine and stroke; it doubles the chances of ischemic stroke. Cortical depression associated with migraine aura is a sustained depolarization of neuronal and glial membranes, steadily spreading through the cerebral mantle (Ayata & Lauritzen, 2015; Charles, 2018).

The cause of cortical depression human remains unknown, although it can easily be elicited by certain immediate stimuli in animals, such as electrical and mechanical stimulation, ischaemic disorder, hypoxia, thromboembolism and various substances like, air bubbles,

cholesterol, crystals and endothelial substances (Ayata & Lauritzen, 2015). Migraine Aura (MA) is related to lower initiating limit for cortical spreading depression, leaving the migraine-sensitive brain more susceptible to cerebral ischemia.

Neurological symptoms (e. g., febrile seizure, convulsions, changes of mind and encephalitis) are concerned with coronavirus infections (C. Huang et al., 2020). The neurotropic and neuro invasive nature of coronaviruses have been identified in humans. The deadly coronavirus gets into the CNS via the olfactory bulb after nasal infection, triggering inflammation and demyelination (Y. C. Li et al., 2020).

Additionally, a deteriorating prognosis of chronic neuroimmune disease (CND) patients may be directly associated with immune senescence, an increased inflammatory status, promoting angiotensin II stimulated vasoconstriction and inflammation, progressing to lymphopenia, cytokine discharge and activation of macrophage (Romoli et al., 2020).

The aura and hypercoagulability of migraine shown that CSD induces blood brain barrier impairment and endothelial injury and hence the inflammatory cascade of neurons and glial cells triggering successive stimulation of peripheral and central trigemino vascular neurons. This improvement leading to CSD facilitates thrombophilia. Studies showed elevated incidence, and overall lifespan of migraine being aligned with greater likelihood of ischemic stroke through an acyclic process under which chronic migraine encourages hypercoagulability (CTietjen & Ollins, 2018).

Migraine aura is closely linked with generating coagulation factors and endothelial dysfunctions, which may intensify the chances of thrombosis and ischemic stroke. Persons with migraine and migraine aura in particular are also at a higher risk for comorbid disorders (e.g. PFO) and problems (e.g. arterial dissection). Similarly, variations in cerebrovascular reactions in migraine aura patients may raise the chances of ischaemic stroke events,

particularly under vascular stress circumstances (eg, arterial emboli) (Simona Sacco & Kurth, 2014).

Furthermore, in several organs of patients COVID-19, microthrombi were found in bloodstream, supposedly created by dissemination of intravascular coagulation (DIC). Therefore, these can also exist inside the CNS microvascular system and contribute greatly in neurological problems (Archie & Cucullo, 2020).

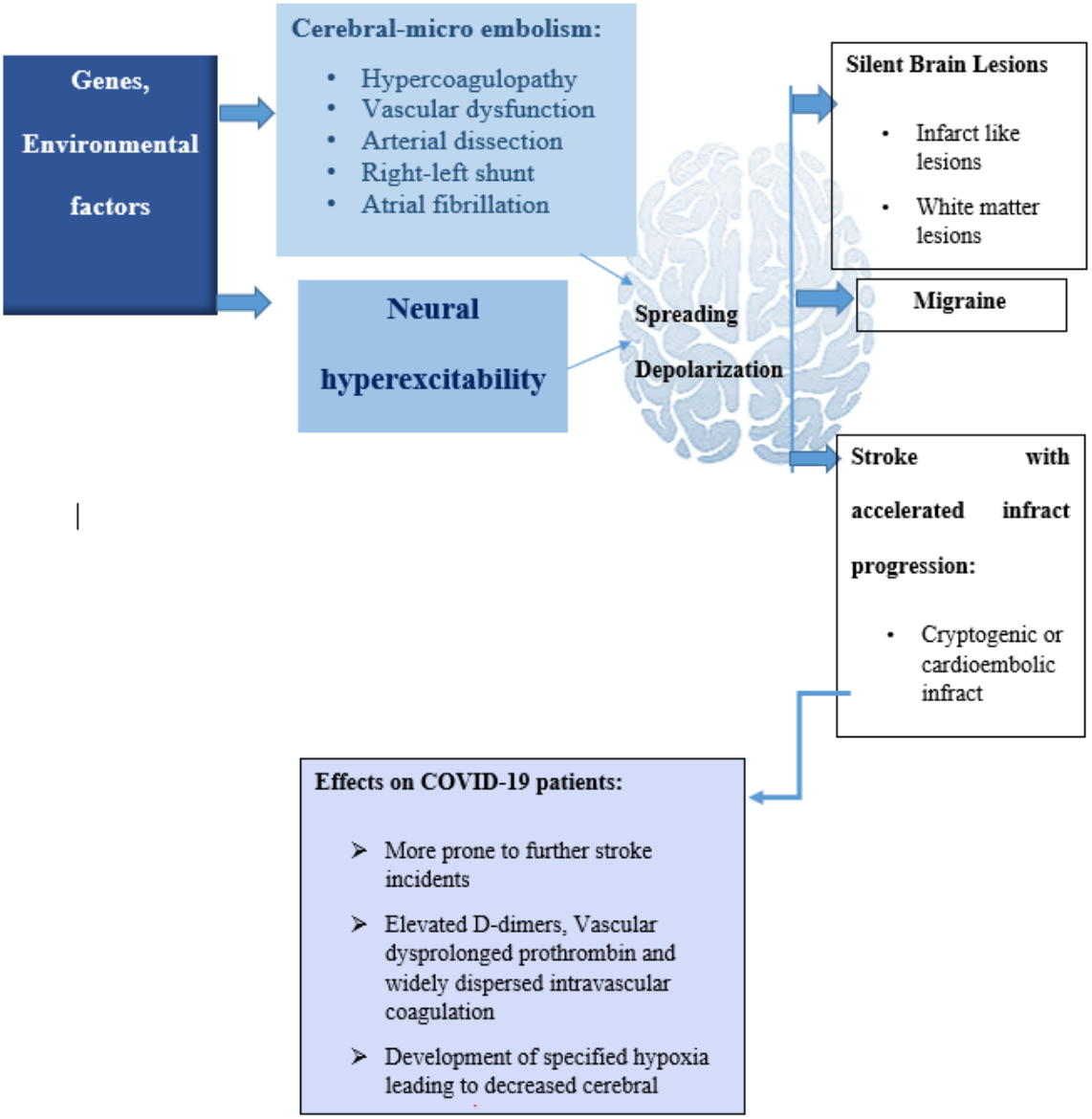

Figure 17: Comorbid Role of Migraine to Deteriorate COVID-19 infection severity

Migraine prior to COVID-19 might raise the probabilities of cerebral ischemia and boost the regulation of coagulation factors, an interaction could occur among migraines and strokes. In order to validate this theory, however, comprehensive well-designed and monitored animal studies are required

6. Treatment protocol for COVID-19 and migraine

(1) Treatment agents for COVID-19 can be usually categorized into anti-viral drugs (inhibits viral entry and pathogenesis) and immuno-modulators (hyperimmune activation prevention and cytokine storm). The major immune-modulators with initial promising effects are hydroxychloroquine /chloroquine, interferon-l, glucocorticoids, interleukin antagonist, ulinastatin, intavanous immunoglobulins and plasma. Some of the most effective antiviral agents with initially promising effects are umifenovir, lopinavir and ritonavir, ribavirin, remdesivir and ravipiravir. Multi-drug treatment, a mixture of the immunomodulatory agent and the antiviral agent, is the most effective scheme (Shaikh, Shrestha, & Dutta, 2020).

Adjunctive Therapy

In addition to antiviral medications and immunomodulators, adjuvant therapies are commonly used in COVID-19 patients to improve conditions.

1. Whenever an acute ischemic stroke is suspected or confirmed in COVID-19 positive patients, urgent treatment should be provided. Prophylactic anticoagulation therapy is recommended for ischemic stroke patients having elevated D-dimer levels. These patients require special attention are thus moved to the isolation ward (Jin et al., 2020).

Heparin with low molecular weight or non-fractionated heparin is favored in hospitalized, critically-ill patients over oral anticoagulants due to its shorter half-lives, intravenous or subcutaneous administration potential and less drug-drug interactions. For example, dalteparin, nadroparin (Fraisse et al., 2000).

2. A deficiency in vitamin D, identified as 25-hydroxyvitamin D serum concentration less than 20 ng/mL, is identified in Hispanic and Black people. The vitamin D deficiency is more prevalent in elderly, obese and hypertension patients; this has been responsible for poor patient outcomes in COVID-19 patients. These are highly represented in cases of COVID-19 in the USA (Forrest & Stuhldreher, 2011).

Low vitamin D in adults and children in the epidemiological trials were related to a high risk of acquired pneumonia. In healthy people and autoimmune disease patients, vitamin D supplements improve production and activity of T cells (S. A. Fisher et al., 2019). A meta-analysis of RCT indicated it also provides protection against acute respiratory tract infection. Thus, use of vitamin D is largely dependent on immune support (Martineau et al., 2017).

3. Vitamin C shows antioxidant and anti-inflammatory also acts as free radical remover. It increases cell immunity, vascular integration, and acts as a cofactor in producing endogenous catecholamines (B. J. Fisher et al., 2011). Since severe COVID-19 causes systemic infection and acute respiratory distress syndrome (ARDS), vitamin C doses in prevention of in COVID-19 inflammation is under investigation (Fowler et al., 2019).

4. Increased intracellular zinc levels have effectively influenced replication of many RNA viruses (te Velthuis et al., 2010). The use of zinc in vitro with zinc ionophorus (e.g.,

chloroquine) has been shown to improve cytotoxicity and induce apoptosis. Chloroquine also has been shown to enhance intracellular zinc absorption in vitro (Xue et al., 2014). Zinc supplementation, alone or in conjunction with hydroxy chloroquine to prevent and treat COVID-19, has been explored in this case (Calder, Carr, Gombart, & Eggersdorfer, 2020). Zinc deficiency can affect the intensity of COVID-19 and thus zinc supplements may improve clinical outcomes. Different doses of zinc in clinical trials for COVID-19 patients, are being investigated, for example zinc-sulphate (220 mg, 50 mg of elemental zinc) and 8 mg for non-pregnant women at a daily basis (National Institute of Health, 2019).

Official guidelines recommend non-steroidal anti-inflammatory drug (NSAIDs), with triptans and narcoleptics for migraine. Some initial concerns regarding ibuprofen were raised, if it was safe to use for COVID-19 patients, but in accordance with the latest FDA guideline, scientific data indicating NSAID's role in deteriorating COVID-19 symptoms were not given, although the agency is researching it even further (‘World Health Organization: Could Ibuprofen Worsen... - Google Scholar’, n.d.). Acute treatment should also consider triptans and antiemetics such as metoclopramide, chlorpromazine and prochlorperazine. Some of the later treatment choices, approved by the FDA in 2019, include small molecules of the gene-related peptide such as calcitonin gene related peptide (CGRP) antagonists called Gepants, which may be recommended in combination to alleviate a severely acute attack (ubrogepant and rimegepants) and 5HT-1F agonist called “ditans” (lasmiditan) (Szperka et al., 2020).

Regular therapeutic treatments containing class I confirmation such as propranolol, metoprolol, divalproex, topiramate, flunarizine, and amitriptyline can all be administered safely. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) such as candesartan and lisinopril have been proven to be helpful for migraine prevention (Dorosch, Ganzer, Lin, & Seifan, 2019). Moreover, no clinical or experimental data are available for the unfavorable effects of ACEI, ARB and RAAS in COVID-19

patients. Therefore, the clinician can judge on a specific instance analyzing the risk/benefit ratio for the continuation of these drugs in patients who are already on these medications due to migraine and probably can develop COVID-19 infection ('ACEIs/ARBs and Risk of Death in COVID-19 Patients With Hypertension - American College of Cardiology', n.d.). In patients with migraine who need to start a new preventive drug, however, ACEI and ARB cannot be used as the first option.

7. Conclusion

COVID-19 pandemic has affected individuals and families all over the world, resulting in confusion of the health care professionals and researchers regarding the treatment and organs affected. It can be mentioned that this virus can invade the CNS; it can also affect the gastrointestinal, lung and heart systems in the above-described case reports. These cases indicate that in patients with COVID-19 are up to 36.4% have neurological disorders (Mao, Wang, et al., 2020). Nevertheless, the process of the COVID-19 CNS intrusion remains unclear. One logical explanation is it can enter the brain via olfactory nervous system in the nasal cavity (Y. C. Li et al., 2020). An alternative CNS penetration mechanism for such viruses was suggested within the CSF (Y. Wu et al., 2020). While BBB is responsible for defending the brain against infections by virus and bacteria, disruption of the BBB may result in the buildup of the virus in the CNS.

Migraine aura and hypercoagulability migraine signify that CSD tends to degrade the blood barrier and the endothelial, as well as to a subsequent activation of inflammatory cascade within the periphery or central trigemino vascular system (CTietjen & Ollins, 2018). Migraine can therefore affect the viability and integrity of BBB, leading to acute SARS-CoV-2 infection. Moreover, migraine aura associated with dissemination of coagulation factors and systemic endothelial dysfunction may increase the chances of ischemic and arterial

thrombosis (CTietjen & Ollins, 2018). Migraine individuals, particularly those who have the aura, are also at comorbid conditions (such as PFO), that may lead to, or cause ischemic stroke, or complications (such as arterial dissections). The risk of ischemic stroke can be elevated by migraine aura. From that point, additional testing of samples from deceased patients belonging to migraine or non-migraine COVID-19 affected patients should be done and the results can be used to identify the impact of migraine on brain and neurological dysfunctions as well as the pathogenesis of SARS-CoV-2.

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