COVID-19 AND THE BRAIN:
Neurological Changes in COVID-19

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ABSTRACT
Coronavirus disease 19 (COVID-19) is a highly transmissible viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in Wuhan, China and has since spread rapidly around the world resulting in a global pandemic that has caused millions of deaths. Although primarily a disease of the respiratory tract, the spectrum of pathology in COVID-19 is wide and this has been linked to the ability of the virus to attack several organs of the human body such as the heart, kidney and even the brain. A growing body of evidence shows that neuro-tropism is one common feature of coronaviruses.[1]

Neurologic manifestations of COVID-19 are abundant and highly variable involving the central nervous system (dizziness, headache, impaired consciousness, ataxia, seizure and acute cerebrovascular disease), peripheral nervous system (smell impairment, vision impairment, (taste impairment, and nerve pain), and muscular-skeletal system.[1] *It can occur prior to its diagnosis or as a complication of the viral infection. The involvement of the nervous system can be due to its direct action on the nervous tissue or an indirect action through the activation of immune-mediated mechanisms.*[1] *Neurological complaints at any point during the course of the illness is associated with a higher risk of death.*
This review elaborates on the neurological changes associated with the brain, potential mechanisms of these changes and their clinical presentations.

INTRODUCTION
The Corona virus pandemic is the largest global health crisis the world has witnessed in recent times, with its effects causing disruptions in all sectors of the economy in various countries worldwide. The report of a cluster of cases with history of contact with live animals in Huanan seafood wholesale market of Wuhan city who developed an unexplained course of pneumonia marked the beginning of the pandemic. This novel viral infection was later identified and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[2] eventually progressed to a worldwide pandemic as declared by the WHO on March 11, 2020.[3] As at 18th May, 2022, the WHO had reported about 520+ million cases and about 6 million deaths.[4]

At the inception of this pandemic, much of the focus was on the cardiovascular, pulmonary, and haematologic complications; however, there is growing evidence showing that the virus has effects on other parts of the body such as the heart, kidney, and even the brain. Hence, neurologic complications have become a recognized area of morbidity and mortality,[5] with the first official report of a neurologic change caused by the virus in Japan[6] and numerous similar reports from other parts of the world.

EPIDEMIOLOGY: Reported Neurological Changes
Studies carried out in various countries across the world have shown that neurological manifestations are not uncommon. A retrospective observational case series from Wuhan, China, reported that 36.4% of 214 patients hospitalized for COVID-19 had neurological manifestations.[7] Another study from Sub-Saharan Africa reported an incidence of 63.8% (113 patients) of the 241 COVID-19 patients who were studied.[8] Though the prevalence of neurological manifestations varies from 3.5% to 84% across reports due to various factors,[8] it has been observed that about 80% of COVID-19 hospitalized patients are likely to have neurologic manifestations at some point during or after the acute illness.[9]

Another important fact about the neurologic manifestations associated with COVID-19 is that they are so widely varied. Neurologic manifestations that have been reported worldwide include self-reported symptoms like headaches, anosmia, ageusia, syncope, myalgia, etc., and clinically confirmed signs or syndromes like acute encephalopathy/encephalitis, stroke, cerebral haemorrhage, paralysis, meningitis, myelopathy, Guillain-Barre syndrome, etc.[9,10] However, the most frequently reported

neurological symptoms have been headaches, dizziness, taste and smell dysfunctions, and impaired consciousness, which is more common in more severe forms of the disease.[10,11]

Neurological manifestations have been reported to be associated with an increased risk of mortality;[10] however, there are still debates as to how neurological manifestations are linked to the severity of the infection as various neurological manifestations seem to have diverging epidemiological data regarding the subject.

PATHOPHYSIOLOGY

The broad spectrum of the neurological effects caused by SARS-CoV2 indicates that the neurological injuries caused by the virus are mediated via several mechanisms. A very likely mechanism is direct invasion of the brain tissue by the virus, majorly via neuronal routes like infected olfactory nerves, or haematogenous routes like infected vascular endothelia or leukocyte migration across the blood-brain barrier.[11,12] This is supported by the proven neurotropic and neuro-invasive potential of viruses including previous coronaviruses such as HCoV-OC43, HCoV-229E, and SARS-COV.[13]

Once in the brain, the virus can then mediate its effects directly via Angiotensin-Converting Enzyme 2 (ACE2) receptors and the serine protease known as transmembrane protease serine 2 (TMPRSS2) which are widely distributed throughout the brain.[14] Furthermore, the exhaustion of the ACE2 receptors in the brain could result in an increase in Angiotensin II. This could develop into a myriad of effects such as elevated blood pressure, vasoconstriction, pro-coagulation effects and, thus, injury to the tissues within the brain.[15]

However, studies have reported some patients with very little or no SARS-CoV2 virus in their brain samples who showed neurological manifestations associated with the virus.[16,17] This suggests that there are other mechanisms underlying neurological injury associated with the virus. One of such mechanisms is via hypoxic-ischemic/hypoxic injuries to the brain[15]. Severe hypoxia caused by damage to the respiratory system could contribute to encephalopathy, demyelination or even white matter micro-haemorrhages.

The virus can also cause injury to the brain via inflammation-mediated mechanisms.[15] Upon infection with COVID, like in cases of other infections, there is a surge of cytokines, chemokines and free radicals in the blood. These chemical substances disrupt the blood-brain barrier which then permits the entrance of immune/inflammatory cells into the brain. The entrance of these cells into the brain results in the activation of microglial cells and astrocytes and a chain of neuro-inflammatory reactions which, depending on the intensity, might result in encephalitis, stroke or even Alzheimer's disease, to mention a few.[18]

Another potential mechanism is the induction of hypercoagulability in the body by the virus.[19] Due to the use of ACE2 receptors by SARS-CoV2, upon infection, there would be a significant reduction in the amount of circulating ACE2 receptors and a corresponding increase in the serum level of angiotensin II. This will put the body in a "hypercoagulable" state, predisposing organs of the body, including the brain, to damage via thrombosis, acute clots or stroke.

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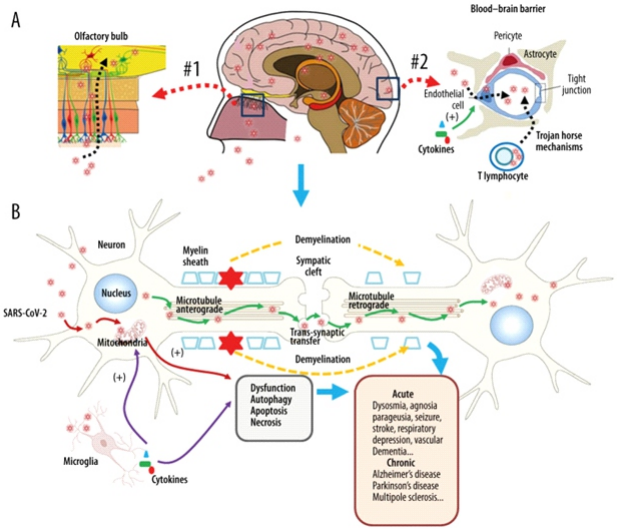

Figure 1: The long-term neurological effects of SARS-CoV-2 infection[20]

CLINICAL FEATURES & COMPLICATIONS

The clinical manifestations of COVID-19 range from a mild disease with nonspecific signs and symptoms to acute respiratory symptoms to severe pneumonia with respiratory failure and septic shock;[21] the severity of which depends on the course of the illness. Neurological symptoms observed in COVID-19 are grouped into several categories including: central nervous system symptoms, peripheral nervous system symptoms, and symptoms related to skeletal muscle injury or neuromuscular junction (NMJ) disorders.[22] Other symptoms include: sensory abnormalities, neuralgia, and sphincter disturbances.[2]

Cerebrovascular events such as acute ischaemic stroke, intracranial haemorrhage, cerebral venous sinus thrombosis have been reported in COVID-19 patients and it was shown that venous and arterial thromboembolic complications are seen in 5–15% of patients with severe COVID-19.[22] The final common pathway for this has a multifactorial etiology which includes a global inflammatory response and a hypercoagulable state evidenced by increased D-dimers, prolonged prothrombin time, and disseminated intravascular coagulation.[5]

Non-specific symptoms such as dizziness and headache have been observed in about 8% - 34% of patients and could occur in the setting of intracranial infections[2] (encephalitis and encephalopathy) with symptoms like fever, vomiting, seizures, and disturbance of consciousness. Acute necrotizing encephalopathy (ANE) is a rare neurologic complication caused by cytokine storm and damage to the blood-brain barrier; however, it is not associated with demyelination and treatment is with intravenous immunoglobulin (IVIg).[5] Para-infectious neurological diseases such as Guillain–Barré syndrome, transverse myelitis, or acute disseminated encephalomyelitis could also result from mechanisms other than direct viral invasion of the CNS.[23]

Peripheral nervous system symptoms include: hypogeusia, hyposmia, deficit in visual function and neuralgia.[24] Muscle damage-related symptoms such as fatigue, myalgia and elevated muscle enzyme levels are associated with the inflammation and muscle damage caused by the virus.[2] Cognitive impairment has been identified as a long-term complication.

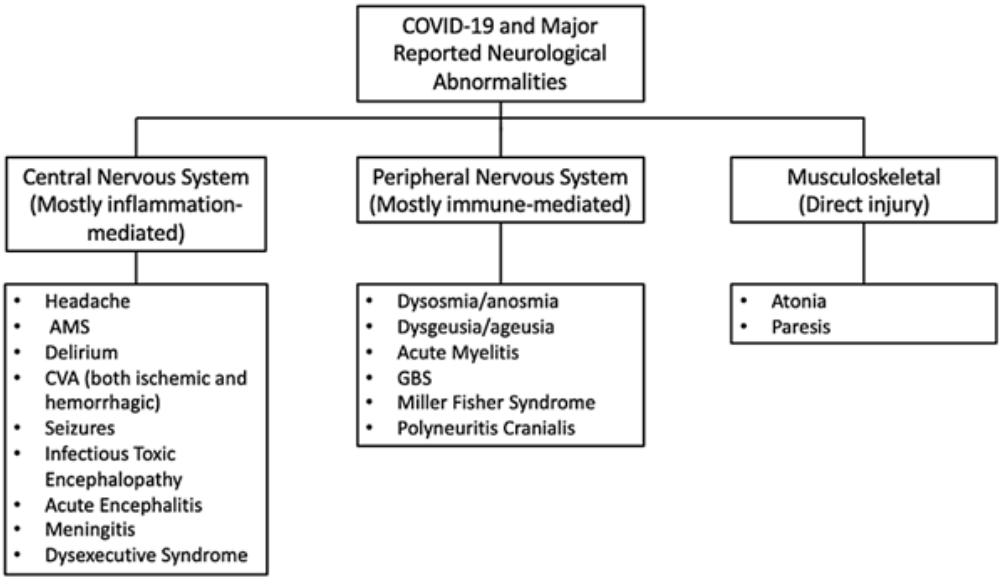

Figure 2: Summary of major neurological abnormalities in COVID-19.[24]

MYTHS

Myths have functioned as 'narrative theories' and are a way of making sense of reality but, in a crisis, the lack of information can open the gateways for uncertainties and disorientation.[25] In times of public health crises, misconceptions could result in life-or-death effects and make individuals and societies vulnerable to false or misleading information.

While on one hand you have the ignorant, uneducated group who deny the existence of the pandemic and consider it a major political game; the other group is comprised of educated people who believe the virus exists and took exaggerated preventive measures, including the use of masks sprayed with sterilizers and chlorine, resulting in cases of poisoning and chemical pneumonitis as well as anxiety and obsessive-compulsive disorders.[26]

Misconceptions that have been associated with the COVID-19 pandemic include the belief that the disease is a "white illness" and does not affect the "black population"; prolonged use of masks can harm the brain; and the use of cannabinoids to treat COVID-19-associated health effects including anxiety, depression, and substance use disorders.[25,27] During a public health crisis, people seek informa-

tion to help understand and make sense of risks as well as to make decisions on how to respond, and the scarcity of reliable information opens avenues for rumours and misinformation[24] which then spread like wild fire. Formal news channels and, of recent, social media are key to information dissemination and have roles in filtering myths and rumours through fact-checking and constant verification; this should however be a collective effort.

TREATMENT

The definitive treatment of these neurological manifestations is to treat the underlying primary viral infection, as some of the manifestations are self-limiting, resolving with recovery from the COVID-19 infection. Examples are anosmia, ageusia, headaches, e.t.c. However, a number of other neurological manifestations may require more specific treatments, but this do not usually differ from their normal treatment in the absence of Covid. Adequate care must be taken in cases where there might be conflicting pharmacological reactions between the drugs treating covid and the drugs treating the neurological manifestations.

Treatment can be considered broadly in three categories: Central Nervous System (CNS) manifestations, Peripheral Nervous System (PNS) manifestations and Musculoskeletal manifestations.

Treatments of CNS Manifestations

A very common CNS manifestation is headache. Headaches can be relieved through the administration of NSAIDs and other pain relievers. However, a study reported that Ibuprofen (a NSAID) has the potential to increase ACE2 expression, which is dangerous since ACE2 is the receptor for entry of SARS-CoV2.[28] Yet, this claim has been rejected by another study and there is no reason to stop the use of NSAIDs. However, caution should be taken when prescribing NSAIDs for headaches related to Covid.[29]

Impaired Consciousness is another common CNS manifestation. It could be linked to toxic or septic encephalopathy caused by systemic inflammation. Like encephalopathy due to other causes, it is managed mainly by treating the underlying disease which is Covid in this instance.

For cerebrovascular diseases like strokes, their management should follow the same standards of care as for patients without COVID-19 but with necessary precautions related to infection control.

Treatment of PNS manifestations

Guillain-Barré syndrome (GBS) is one of the PNS manifestations associated with Covid. Some treatment approaches of GBS include the usage of Intravenous Immunoglobin (IVIG), plasmapheresis and corticosteroids.[30] Another PNS manifestation is immune-mediated necrotizing myopathy (IMNM). A study made the following recommendations for its treatments: corticosteroids (IV, 0.5–1 g/day, 3–5 days) and IVIG for refractory disease, which may be considered as monotherapy for patients who have contraindications to the use of steroids (IVIG 2 g/kg in 5 days).[31]

Other PNS manifestations that have been reportedly associated with Covid are neuro-ophthalmological disorders, sensorineural hearing loss, neuromuscular junction disorders and multiple cranial neuropathies.[31] The general approach is to treat the underlying disease, the systemic inflammation caused by Covid and then the manifestation itself.

Treatment of Musculoskeletal symptoms

Some of the musculoskeletal symptoms associated with covid are fatigue, myalgia and arthragia. NSAIDs[32] and multidisciplinary care (such as orthopedic rehabilitation) are used in the management of musculoskeletal symptoms.[32] Other musculoskeletal problems like osteoporosis, reduced bone mineral density, and osteonecrosis tend to arise in hospitalized patients. Therefore, physicians should take note of these possibilities and make necessary arrangements to prevent these complications.

CONCLUSION

COVID-19 mostly presents with a mild flu-like illness; however, the presence of co-morbidities results in severe disease and death. While the pulmonary complications of COVID-19 have been well outlined and described, its effects on other organs have lagged behind and the neurological manifestations of SARS-CoV-2 is no exception. Simply put, not enough attention has been paid to it.

Although pulmonary complications are profound, the neurological system is also significantly affected and neurological manifestations have been shown to be an important component of the disease spectrum both during the acute and post-acute phases of infection. Hence, familiarizing neurologists with the clinical course of the disease is critical in treating and controlling the disease as neurological complications have a detrimental effect on the overall quality of life of patients.

ACKNOWLEDGEMENT

We would like to express our very great appreciation to Prof. M.A. Komolafe (Head, Department of Medicine) and Dr A. Adebowale (Consultant Neurologist, Department of Medicine, OAUTHC, Ile-Ife) for their guidance and contribution by providing constructive suggestions during the development of this manuscript. Their willingness to give their time to review the article is much appreciated.

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