

## COVID-19- BIOCHEMICAL AND OTHER MECHANISMS ASSOCIATED WITH NEUROPATHY AND STROKE: NARRATIVE REVIEW

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### How to cite this article

Umedani LV, Javaid Q. Covid-19- Biochemical and Other Mechanisms Associated With Neuropathy and Stroke: Narrative Review. J Gandhara Med Dent Sci.2024;11(2):55-62

**Date of Submission:** 09-03-2024

**Date Revised:** 05-03-2024

**Date Acceptance:** 24-03-2024

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<https://doi.org/10.37762/jgm.11-2.583>

### **ABSTRACT** **OBJECTIVES**

*The objective of this narrative study was to explore the mechanisms associated with neuropathy and stroke in COVID-19 subjects.*

### **METHODOLOGY**

*The study employed was to search for related articles from PubMed. After scrutiny and exclusion, we selected 47 articles from January 2021 to January 2023. The initial pooling of the virus in nasal mucosa was followed by spread to respiratory and other tissues.*

### **RESULTS**

*The main mechanisms of ischemic stroke were DNA methylation, raised D-dimers, platelet activation, clotting factor receptors antibodies, protease cleavage, and brain injury markers. Hemorrhagic strokes had decreased ACE2, raised BP, cytokine storm, anticoagulant use, endothelial ACE2 expression, and ferroptotic mechanisms. Neuropathy mechanisms included blood-brain barrier and endothelial damage, inflammasomes, reactive astrogliosis, cytokine storm, immune dysregulation, and retrograde axonal viral transport.*

### **CONCLUSION**

*The role of receptors, enzymes, proteins, and genes in neuropathological mechanisms is highlighted. The vascular endothelial effects, choroid plexus, and blood-brain barrier disruptions were noted. The epigenetic neuropathological mechanisms need further exploration to help design the new therapeutic modalities. The post-vaccination neurological manifestations, as well as the post-COVID effects, both require additional attention to diagnose and start treatment promptly.*

**KEYWORDS:** COVID-19, SARS-CoV-2, Biochemical Mechanisms, Stroke, Neuropathy

## INTRODUCTION

### The SARS-CoV-2 and COVID 19 Disease:

The coronavirus was first identified in 1962. It mainly affected the respiratory tract, but in China, at the end of December 2019, a more serious variety of cases of pneumonia occurred due to a new SARS-CoV-2 strain producing COVID-19 disease with a global pandemic.<sup>1</sup> The higher genomic size of this virus favored recombinations and mutations for its spread from lower species and from one human to the others.<sup>2</sup> COVID-19 presented as asymptomatic without clinical or radiological signs despite a positive laboratory test, to Mild case (sneezing, pyrexia, body ache, throat irritation with abdominal pain, nausea, vomiting and diarrhea), Moderate (as pneumonia with positive lesions on chest CT scans), Severe case (pneumonia with SpO<sub>2</sub> level <92%) and a most serious Terminal stage requiring intensive care unit admission having acute respiratory distress, vital organ failure, shock,

neuropathy and coagulation issues.<sup>3</sup> The injury to the nervous system occurs in the moderate to severe stages.<sup>4</sup> The severe neurological complications occur in approximately 13% of COVID-19 patients. Apart from the olfactory, gustatory, and cranial nerve manifestations, it produces encephalitis, strokes, neuropathy, and demyelination of white matter of the nervous system. This was observed in MRI studies, immunohistochemistry, biopsies, and RT-PCR of the brain, showing nucleocapsids of the virus in the neurons.<sup>5</sup> Some COVID-19 cases presented directly with neurological manifestations.<sup>6</sup> The stroke incidence was less in COVID-19, e.g., ischemic 0.4-2.7% versus hemorrhagic stroke 0.2-0.9% cases.<sup>7</sup> Various structural areas of the nervous system express ACE2, e.g., choroid plexus, para ventricular thalamic nuclei, astrocytes, oligodendrocytes, endothelial cells of middle temporal gyrus, cingulate cortex, hippocampus, olfactory sustentacular cells, olfactory bulb pericytes, and olfactory stem cells.<sup>8</sup> The main contributors were microglial and astrocytic activation due to viral immune

responses.<sup>9</sup> COVID-19 is regarded as an endothelial disease. New research has shown that in severe COVID-19, more than 1000 genes are implicated.<sup>10</sup> The capillary dysfunction results in the impairment of oxygen, glucose, and lactate exchange from astrocytes to nerve cells, causing brain fog, anxiety, and depression.<sup>11</sup> The blood-brain barrier (BBB) is affected secondary to damage to the astrocytic process, producing ease of entry of inflammatory cytokines and resulting in neurological symptoms.<sup>12</sup> This review contains general information about the COVID-19 disease and SARS-CoV-2, followed by information about mechanisms for neurological manifestations to get guidelines to explore the treatment strategies in the future.

### **Basic and General Mechanisms for Neurological Manifestations:**

The chief contributors are the viral spike protein and host cell surface proteins, mainly ACE2 and TMPRSS2.<sup>13</sup> The viral N (Nucleocapsid) protein contains the viral RNA genome, whereas the S, E, and M (Spike, Envelope, and Membrane) proteins constitute the viral envelope. The S1 glycoprotein helps in the attachment of the virus, and S2 works for its fusion with the host cell membrane. ACE2 has an affinity for S proteins to internalize the virus on the host cell. The host serine proteases called TMPRSS2, TMPRSS4, furin, neuropilin, and endothelial cathepsins help in membrane fusion and viral entrance in target cells.<sup>14</sup> The degree of infectivity depends on the receptor binding domain (RBD) of the S1 viral spike protein that attaches to the peptidase domain of ACE2. The genetic mutations at RBD (e.g., single nucleotide polymorphism G614) produce a dominant strain with infectivity variations in various regions of the world during the pandemic.<sup>15</sup> In the host cell, the viral genome replicates polyproteins (1a, 1ab) tagged with genes about open reading frames called ORF-1a and ORF-1b. These mechanisms take over the control of target cell ribosomal functions to produce viral proliferation.<sup>15</sup> The ORF play various roles, e.g., ORF3a, ORF3b, ORF6, and ORF7a cause host cell apoptosis, ORF7a increases cytokine expression, ORF6 is interferon inhibitor, ORF9b for cell autophagy by mitochondrial dysfunction, ORF8b causes activation of inflammasome complex, release of interleukin-1 beta, stress response of endoplasmic reticulum, malfunction of lysosomes and caspase-independent cell necrosis; and ORF6 and ORF10 produce amyloid assembly and neurotoxicity (Table 1).<sup>16</sup>

### **The Cytokines Play a Marked Role in Inflammation and Produce Neurological Manifestations:**

The infiltration of CD8<sup>+</sup> T-cells in 70% of subjects, neutrophils, and activated microglial cells was found in brain autopsies of COVID-19 cases.<sup>17</sup> About 40% of cases had microglial nodules due to microgliosis (Table 2).<sup>17</sup> The virus and cytokines passed through barriers (BBB and Blood CSF Barrier) by hematogenous route to the target cells (Table 2).<sup>18</sup> The immune system autoantibodies were noted in these complications. The stroke, neuropathy, choroid plexus damage, BBB damage, direct cranial nerve damage, gene regulation problems, glial cell damage, and their underlying mechanisms are addressed in this review. The severity of the disease was related to complement hyperactivation, mainly C3, C5a, and C5b, which causes thrombi and damage to endothelial cells (Table 2).<sup>19</sup> The immune-based endothelial damage was evidenced by raised levels of D-dimers, soluble vascular cell adhesion molecules, plasma fibrinogen, thrombomodulin, von Willebrand factor, TNF receptor 1, heparan sulfate, alpha-2 antiplasmin, and plasminogen activator inhibitor.<sup>20</sup> Changes in hippocampus cells were noted in autopsies with a reduced number of microglia, astrocytic cells, and processes of both, and less granular layer neurons and reduced pyramidal cell dendritic length to affect neuronal metabolism and cognition. The encephalopathy is multifactorial, e.g., disturbed cellular metabolism, low oxygen tension, medication effects, intensive care unit environment, and vascular problems in the serious states and post-COVID period.<sup>21</sup> This review aimed to highlight the mechanisms related to neuropathy and stroke. This will help future researchers to carry up the studies further along that line. It will also help future researchers explore the treatment strategies targeted to the mechanisms indicated in this study.

### **MATERIAL & METHODS:**

This narrative review analyzed the mechanisms underlying neurological manifestations related to COVID-19 subjects, except those for smell, taste and cranial nerve disorders. The data source was articles selected from January 2021 to January 2023 using PubMed. For this purpose, the relevant keywords were utilized, first by putting the term COVID-19 followed by the type of neurological complication and mechanism. For instance, COVID-19 mechanisms in stroke or cerebrovascular events, COVID-19

by the type of neurological complication and mechanism. For instance, COVID-19 mechanisms in stroke or cerebrovascular events, COVID-19 mechanisms in neuropathy and cognitive dysfunction. These articles included comprehensive reviews, case studies, and original research manuscripts. This review included the articles indicating the 6-month post-COVID period and after that. Due to less work done in the initial COVID-19 period, the articles published in the most recent years, mainly 2022, were targeted to get the latest information. The articles references were also reviewed to obtain the related mechanisms. The inclusion criteria were the year of publication, relevance with the title, and aim of the related article. The exclusion criterion was accessory and non-relevant information. The relevant data was extracted from a total number of selected 47 articles. Among these, 30 articles belonged to the stroke and neuropathy, and 17 were attributed to miscellaneous neurological manifestations. After obtaining the related information, the concluding remarks in the discussion section indicated that they would help future workers design therapeutic strategies.

### Specific Mechanisms for Stroke and Neuropathy: The Background of Hemorrhagic Stroke:

Mechanisms for hemorrhagic strokes were increased blood pressure, decreased ACE2 levels, coagulopathy, and cerebral vascular thrombosis. The viral S protein-ACE2 receptor interaction cleaves angiotensin I into both types, i.e., Angiotensin type 1-7 (vasoconstrictors) and type 1-9 (vasodilators and anti-inflammatory functions). Reduction in the quantity of ACE2 raises the Angiotensin II, producing vasoconstriction, inflammation, and hemorrhagic stroke. The therapeutic anticoagulants in cerebral thrombosis also lead to hemorrhage.<sup>22</sup> The cytokine storm produces acute hemorrhagic necrotizing encephalopathy due to alteration in BBB by matrix metalloprotease-9 and trypsin.<sup>23</sup> The pulmonary hypoxia produced an additional hypertensive state due to ACE1 and ACE2 imbalance. (Table 1). The biomarkers associated with brain damage and stroke in COVID-19 include GFAP, neurofilament light chain, S100B calcium-binding proteins, tau, neuron-specific enolase (NSE), and inflammatory markers like D-dimers, LDH, and C-reactive proteins. The lymphocytes, procalcitonin, creatinine, and antiphospholipid antibodies were higher in COVID-19 strokes.<sup>24</sup> The micro-bleeds commonly occur in white matter areas in the brain, causing strokes. These produce biodegradation of hemoglobin to release heme-producing lipid peroxidation, breaks in DNA strands, and ferroptosis.<sup>25</sup> Ferroptosis iron toxicity degrades heme to bile salts, producing iron-mediated

neuronal death, oxidative stress, and cell death.<sup>26</sup> (Table 1).

### The Background of Ischemic Stroke:

Multiple mechanisms were responsible, e.g., cytokine overproduction, endothelial damage, and hypercoagulable state involving biological processes like DNA methylation, modifications of non-coding RNAs, and histone tails. These were related to the inflammatory complexes like Tumor Necrosis Factor- $\alpha$  and Interferons in the cytokine storm. The genetic aspects were related to micro RNAs controlling immune system genes, viral structural protein genes, and proinflammatory signaling of epigenetic modulations.<sup>27</sup> The thrombotic effects of thromboxane levels activate the platelets, causing infarctions. This activation is due to Anti  $\beta 2$  glycoprotein (Anti- $\beta 2$ GPI) autoantibodies cross-linking the von Willebrand Factor receptor glycoprotein Iba and apolipoprotein E receptor-2.<sup>28</sup> The ablation of protein nuclear factor- $\kappa$ B (NEMO) in brain endothelium induces necrosis, reduction of capillaries, inflammation and damage to BBB (Table 1).<sup>26</sup> The protease in the coronavirus causes replicase polyprotein to cleave the NEMO, which is considered a drug target against viral replication.<sup>26,32</sup> The virus reaches the brain by crossing the BBB with raised brain injury markers like glial fibrillary acidic protein, neurofilament-light chain, T-tau, and Interleukin-8.<sup>29</sup> The hematogenous spread hypothesis was noted due to viral particles found in the neuronal cytoplasmic vacuoles and endothelial cell vesicles in vitro.<sup>29</sup> Thromboembolic spread from remote sites caused strokes due to ACE2 expression from the arterial and cardiac epithelial sources.<sup>30</sup> The intracerebral thrombosis was observed with raised levels of Interferon (IL-2, IL-6), D-dimers, and raised serum anti-phosphatidylserine or prothrombin antibodies (Table 1).<sup>31,33</sup>

**Table 1: Main mechanisms in the strokes and microhemorrhages with their therapeutic aspects**

Ischemic stroke Mechanisms	Therapeutic Comments
Methylation of DNA.	**
Serum anti-phosphatidylserine/prothrombin antibodies & raised D-dimers produced microemboli.	Cortisone in the early stages of disease later careful usage considering side effects.
Platelet activation (by thromboxane & Anti β2GPI autoantibodies cross-linking the von Willebrand Factor receptor glycoprotein Iba & Apo lipoprotein E receptor2).	Anticoagulants and protease inhibitors reduce hospitalization.
Protease cleavage by NEMO.	Anticoagulation, **
Brain injury markers, e.g., glial fibrillary acidic protein, neurofilament-light chain, T-tau, & IL8	**
Hypoxia & Remote thromboembolism.	O2, ICU, Antivirals, Aspirin, Dual antiplatelet therapy (platelets <50X10 <sup>9</sup> , Hb <8g/dl), Heparinize if D- dimers >upper limit, ICU. Dexamethasone, O2. Below are uncertain: anti-cytokine (Tocilizumab) & anti-IL1 (Anakinra), anti-JAK (Ruxolitinib, Tafocitinib, Baricitinib), Renin inhibitor Aliskirin.
Hemorrhagic stroke	Therapeutic Comments
Decreased ACE2 raises angiotensin II, causing vasoconstriction, inflammation, & Pulmonary hypoxia to raise BP	-For BP regulation, ACE2 inhibitors are harmful.
Administration of anticoagulants	Anticoagulant usage with care.
Micro bleeds	Therapeutic Comments
Cytokine storm causing acute hemorrhagic necrotizing encephalopathy due to matrix metalloprotease-9 & trypsin & Endothelial ACE2 expression	Antivirals and corticoids. Blood pressure regulation, O2, ICU with concomitant antivirals and care.
Ferroptosis & hemoglobin breakdown	α- tocopherol

Legend: \*Immunoglobulins, \*\*Needs further research

**BBB Disruption Mechanisms:**

The expression of matrix metalloprotease damages the basement membrane collagen IV by protease, which cleaves the NF-κB modulator protein (NEMO) for controlling transcription of antiviral interferons type1, resulting in endothelial damage, inflammation, and gliosis.<sup>32</sup> The T lymphocytes could cross the BBB to infect the neural tissue directly.<sup>17</sup>

**Gene Regulation Problems:**

A downregulation of signaling pathway working with interleukin six and nucleotide-binding domain leucine-rich family pyrin domain 3 (NLRP3) inflammasome with the transcription activators like Janus kinase signal transducing (JAK/STAT) pathway promoted B lymphocytes proliferation and antibody production by the transforming growth factor-beta.<sup>33,35</sup> The cytokines

cause P2X7 purinergic receptor activation, resulting in a fast inflow of sodium and calcium and an outflow of potassium ions, producing problems in cell division, disintegration of cells, generation of reactive O2 species, interleukin production, and increased BBB permeability.<sup>34</sup> The permeability also increases in inflammation due to activation of G-protein coupled 5a receptor-1 (C5aR1).<sup>18</sup> Downregulation of neurotransmission genes in excitatory neuron synapses and overexpression in inhibitory neurons are implicated in cognitive deficits observed by Electroencephalograms from the frontal lobe associated with elevated levels of IL-6 and CSF oligoclonal bands.<sup>26</sup> Upregulation of coreceptor cofactor CD147 raises the transcripts for proinflammation notably, S100 calcium binding protein A9 (S100A9) called migration inhibitory factor-related protein 14 (MRP14 / calgranulin B) and lectin galactoside binding soluble-3 binding protein (LGALS3BP).<sup>32</sup>

**Damage to the Choroid Plexus:**

As indicated above, the mechanisms damaged the choroid plexus, resulting in cognitive dysfunction and headache due to reduced CSF volume affecting layers 2 and 3 of the cerebral cortex.<sup>18</sup>

**Mechanisms Producing Damage to Astrocytes and Microglia:**

An astrocytic marker (glial fibrillary acidic protein-GFAP) was detected in plasma and CSF. Astrocytic hypertrophy and microglial activation with immune mechanisms were also found.<sup>36</sup> Astrocytes utilize GABA and glutamate synthesis for synaptic function. The astrogliosis increased glutamate to produce cognitive symptoms, an increase in reactive oxygen species, and ischemic damage<sup>36</sup> (Table 2). The microglia acquire amoeboid morphology in immunological gliosis and release the TNF-α interleukins (IL-1β, IL-6), damaging the BBB, causing apoptosis and ineffective T cell response (Table 2).

**Mechanism by Retrograde Viral Axonal Transport:**

The path of the virus to multiple brain regions involving the trigeminal, olfactory, facial, glossopharyngeal, and vagus nerves was observed by autopsies.<sup>29</sup>

**Other Mechanisms Producing Damage to Nervous Tissue:**

The other body parts displayed cytokine storm-producing inflammation, secondarily causing akinesia, seizures, mutism, and encephalitis. (Table 1).<sup>37</sup> The encephalitis cases manifested elevated cytokines, i.e., Interleukins1β, IL2, IL6, IL8 and Tumor Necrosis

Factor. The chemokine C-C Motif Ligand 2 (CCL2) and macrophage chemo-attractant protein-1 (MCP-1) caused inflammation and microglial activity to damage the BBB. The neuronal-enriched extracellular vesicle (nEV) proteins are normally produced by cells, including neurons with functions like structural, nutritional, and metabolic support, but in COVID-19, these produce neurodegeneration and memory effects due to being transferred from neurons to outside.<sup>38</sup> (Table 2) Vitamin D is an immune modulator and protector of coronavirus infection with therapeutic significance. The research on the RNA-based vitamin D receptor expression mechanism is meager and needs further exploration.<sup>39</sup> The toll-like receptors (e.g., TLR4 for innate immunity) and nuclear factor-κB were noted for binding with viral S protein, causing oxidative stress, apoptosis, and neurodegeneration.<sup>40</sup> The increased pro-oxidants like lactic dehydrogenase and oxidative stress gene expression caused the regulation of glutathione antioxidants enzymes<sup>41</sup> to increase poly ADP-ribose polymerase-1 needed in the viral life cycle. Its inhibition is considered as a therapeutic target<sup>42</sup> (Table 2). The effect of SARS-CoV-2 on the dopaminergic neuron α-synuclein and thromboembolic cytokines in substantia nigra produce Parkinson's disease.<sup>43</sup> The acetylcholine antibodies were positive in the COVID-19 period in Italian subjects, mimicking the myasthenia gravis mechanism.<sup>44</sup> Guillain Barre Syndrome-like paralysis was noted due to IL-6 antibodies against myelin.<sup>45</sup> The headache was due to effects on trigeminal endings, and usual analgesics did not relieve it.<sup>46</sup> The peripheral sensory and motor neuropathy was attributed to ACE2-based inflammatory mediators with antibody production, as seen in dorsal root ganglions, and a positive response to immunoglobulin and corticosteroid therapy evidenced this.<sup>47</sup>

**Molecular Mimicry Mechanisms:**

The auto-immune-based encephalitis mechanisms were also reported (Table 2).

**Table 2: Main Mechanisms in Neuropathy with Related Therapeutic Aspects**

Neuropathy related mechanisms	Therapeutic Comments
BBB disruption by ACE2, Cytokines, Neuropilin 1 receptor, Metalloproteases.	Remdesivir, Lopinavir, Ritonavir, Oseltamivir antivirals recommended.
Endothelial damage (coagulopathy, angiogenesis, Chemokine ligands, Endothelin, Interleukins, JAK pathway, Plasminogen activator inhibitors, Toll-like receptors, Adhesion molecules, Growth factors)	Steroids, Anticoagulation, All such mechanisms need ** Senolytics (Quercetin/ Dasatinib combination*)
NLRP3 inflammasome activation generates P2X7 receptors on T cells to disturb ionic flow.	Tocilizumab & Anakinra, ionic P2X2 antagonists.
Host cell coreceptor inflammatory cofactor (CD 147) activation.	Like ACE2, CD147 is a therapeutic target** Meplazumab is in trial.
Choroid plexus damage due to ACE2 expression & cytokines.	Antivirals & Steroids.
Reactive astrogliosis-based ischemia.	Corticoids, Ig***, IL6 inhibitors, **
T cell infiltration in inflammation causes microgliosis to release TNF 1α, IL 1 beta & IL 6 & causes ineffective T cells & neural damage.	Corticosteroids, antagonists of IL6R & IL1, e.g., tocilizumab & anakinra.
Cytokine storm: (IL 4, 7, 10, 12, 13, 17), interferon, Macrophage inflammatory protein-1, HGF, TNF, GCSF, MCSF. (Interleukins1β, 2, 6, 8 & TNF produce apoptosis).	Eculizumab (antibodies) after three weeks to inhibit complement, IL inhibitors, and corticoids.**
Immune dysregulation for neuronal damage by C3, C5a, C5b.	Corticoids.
Ferroptosis, DNA breakdown & lipid peroxidation.	α-Tocopherol; **
Sensory & motor neuropathy with perivascular macrophage infiltrates.	Analgesics, Corticoids & general antivirals.
ACE2 & TMPRSS2 with viral ORF 1a & 1b interaction for apoptosis, mitochondrial dysfunction & IL 1 beta release.	Corticoid genomic inhibitor research is needed.
BBB endothelial leakage with cytokine release.	Antivirals, anti-cytokines.
Metalloprotease-based Basement membrane collagen IV damage with T cell crossing.	** , antivirals and Phytochemicals from Camellia sinensis.
Encephalitis with Molecular mimicry basis due to antibodies (Antimyelin, Anticontactin associated protein-like-2, Anti-N-methyl- D-aspartate receptor, Antiganglioside, Anti- glutamic acid decarboxylase antibodies.	** , Steroids, Ig***, Plasmapheresis.
Retrograde axonal transport to neurons & glia.	Steroids, Ig***, **
Neuronal-enriched extracellular vesicle (nEV) proteins for neuropathy.	**
NOTE: Methylprednisolone, Ig., Blood purification, Azithromycin, Chloroquine (HSP90 inhibitor), Geldanamycin, Antibodies for viruses in synapses, and rho-kinase inhibitors (Fasudil) were used with variable benefits.	

**Legend:** \*need clinical trial, \*\*Need further research, \*\*\*Immunoglobulins

## DISCUSSION

The COVID-19 neurological manifestations had multifarious mechanisms. The SARS-CoV-2 produced direct infection of the peripheral sensory neurons by the entry component ACE2. The molecular mechanisms produced this. The genes get changed and undergo expression by the viral infection. Paying attention to and working on the gene expression pattern becomes important for exploring and understanding the basic background for designing appropriate remedies. The neurological manifestations were less than those of pulmonary in the case of COVID-19. The time of occurrence of the neurological signs was variable, i.e., they could happen during the active phase and in the post-COVID-19 prolonged phase. Although they had lesser incidences, they produced grave consequences and morbidity. Hence, they should never be ignored. The earlier diagnosis and prompt treatment of such manifestations are highly important. The global geographical variation in disease severity, e.g., lower in Asia versus the West, was attributed to a genetic variation in the viral spike proteins or host cell receptor polymorphisms of ACE2 or at transmembrane serine protease 2. Hence, a viral genealogic lineage variation at one end and host proteins on the other end need attention as they changed the pattern and infectivity of the SARS-CoV-2. Neuropilin-1, vascular endothelial growth factor, and semaphorin are also found as host cell receptor factors for viral infection.<sup>48</sup> The critical ICU patients of COVID-19 had encephalitis, which was mainly related to the cytokines. In these cases, the soluble markers to activate the endothelial cells showed higher levels, such as angiopoietin-like 4, tumor necrosis factor- $\alpha$ , and soluble E-selectin.<sup>49</sup> It is important to note that the COVID-19 headaches, isolated cranial nerve damage, and stroke cases did not have a worse functional prognosis. Mortality in such cases happens due to adverse effects produced by other organs, such as pulmonary. Confirmatory mechanisms underlying headaches were scarce. In this regard, the prolonged headaches were hypothesized to occur due to trigeminal nerve-ending activation due to cytokines, direct CNS invasion, hypercoagulation states, and hypoxic effects. It was also noted that the usual headache analgesics were less effective, which points to research being needed in this area. The encephalopathy also happened due to effects from other organs, such as poor oxygenation due to pulmonary pathology. Corticosteroids play a main role in limiting neuroinvasion and encephalitis. The CSF's immunoglobulins, cytokines, and albumin were associated with the Blood CSF Barrier disintegrity. Some biomarkers are important for assessing the severity and mortality of COVID-19, like cytoskeletal

proteins of neurofilament light chains, which specifically indicate axonal degeneration. The medium and heavy chain neurofilaments, e.g., NfM 150 kDa and NfH 200 kDa of axons, are affected in these cases.<sup>50</sup> Therefore, a raised level of neurofilaments should be regarded as an adverse prognostic sign needing urgent treatment for protective perspectives and structural integrity of nervous tissue. A successful treatment is indicated once the normal levels of neurofilaments are achieved. Any additional and continuous rise in neurofilament level warrants progressive axonal injury needing intensive treatment. Some authors regarded the role of astrocytes to only indicate disease severity but paid no importance to pathogenicity.<sup>51</sup> Some of the therapeutic agents used in COVID-19, such as benzodiazepines, opioids, antipsychotics, and vasopressors, showed a higher risk of delirium, except haloperidol. The benzodiazepines and anticholinergics had a greater risk of respiratory depression and confusion.<sup>52</sup> It is found that administration of corticosteroids causes psychiatric adverse effects like sudden mania, depression, or both. The possible mechanism was considered a disruption of the hypothalamic-pituitary-adrenal axis. The workers hypothesized that the corticosteroids may alter the nervous system's transcription of receptor genes and transmitter genes.<sup>53,54</sup> The limitation of this review was that it did not include further findings of the workers who published their research after January 2023. Other search engines and browsers, such as Google Scholar, were not explored as they could have some additional information about the mechanisms. It is recommended that future workers explore the results obtained after January 2023, including information from all other portals. It is also recommended that apart from other mechanisms, the molecular mechanisms must be focused on for future workers to design possible drugs. There is a need to update the data about the long-term complications of vaccinations and COVID-19.

## CONCLUSION

The role of receptors, enzymes, proteins, and genes in the neuropathological mechanisms shows the effects on vascular endothelium, choroid plexus, BBB, and blood CSF barrier disruptions. The role of microRNAs in the molecular pathology of inflammations points towards future research to elucidate the epigenetic mechanisms that facilitate the design of novel treatment strategies. The cytokine-related pathogenesis, immune mechanisms, and direct neuroinvasions were highlighted. Although the COVID-19 incidence decreased globally through care and vaccinations, the long-term post-vaccination and COVID-19 effects need attention and exploration due to strokes and morbidity.

The earlier diagnosis of these effects and their timely treatment are mandatory.

**CONFLICT OF INTEREST:** None

**FUNDING SOURCES:** None

## REFERENCES

- Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med.* 2003;348(20):1967–1976.
- Li B, Si H-R, Zhu Y, et al. Discovery of bat coronaviruses through surveillance and probe capture-based next-generation sequencing. *mSphere.* 2020;5:1.
- Khaled Habas, Chioma Nganwuchu, Fanila Shahzad, Rajendran Gopalan, Mainul Haque, Sayeeda Rahman, Anwarul Azim Majumder & Talat Nasim. Resolution of coronavirus disease 2019 (COVID-19), Expert Review of Anti-infective Therapy, 2020;18(12):1201-1211.
- Kanberg N, Ashton NJ, Andersson LM, Yilmaz A, Lindh M, Nilsson S. Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. *Neurology.* 2020;95(12):e1754–e1759.
- Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med* 2005;202:415-424.
- Najafloo R, Majidi J, Asghari A, Aleemardani M, Kamrava SK, Simorgh S, Seifalian A, Bagher Z, Seifalian AM. Mechanism of Anosmia Caused by Symptoms of COVID-19 and Emerging Treatments. *ACS Chem Neurosci.* 2021 Oct 20;12(20):3795-3805.
- Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145–147.
- Chen R, Wang K, Yu J, Howard D, French L, Chen Z, et al. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain. *Front. Neurol.* 2021;11:573095.
- Klein, Robyn S. Mechanisms of coronavirus infectious disease 2019-related neurologic diseases. *Current Opinion in Neurology.* 2022;35(3):392-398.
- Brola W, Wilski M. Neurological consequences of COVID-19. *Pharmacol Rep.* 2022;30:1–15.
- Marshall M. COVID and the brain: researchers zero in on how damage occurs. *Nature.* 2021;595(7868):484-485.
- Ribeiro DE, Oliveira-Giacomelli Á, Glaser T, et al. Hyperactivation of P2X7 receptors as a culprit of COVID-19 neuropathology. *Mol Psychiatry.* 2021;26(4):1044-1059.
- Butowt R, von Bartheld CS. Anosmia in COVID-19: Underlying Mechanisms and Assessment of an Olfactory Route to Brain Infection. *Neuroscientist.* 2021;27(6):582-603.
- Cantuti-Castelvetri L, Ojha R, Pedro LD, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science* 2020 Nov 13;(370):856-860.
- Prajapat M, Sarma P, Shekhar N, Avti P, Sinha S, Kaur H, Kumar S, Bhattacharyya A, Kumar H, Bansal S, Medhi B. Drug targets for corona virus: A systematic review. *Indian J Pharmacol.* 2020 Jan-Feb;52(1):56-65.
- Shi CS, Nabar NR, Huang NN, Kehrl JH. SARS-coronavirus open reading frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. *Cell Death Discov.* 2019;5:101.
- Schurink B, Roos E, Radonic T, Barbe E, Bouman CSC, de Boer HH, et al. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *Lancet Microbe.* (2020);1:e290–9.
- Zhang L, Zhou L, Bao L, Liu J, Zhu, H, Lv Q, Liu R, Chen W, Tong W, Wei Q, et al. SARS-CoV-2 crosses the blood–brain barrier accompanied with basement membrane disruption without tight junctions alteration. *Signal Transduct. Target. Ther.* 2021 Sep 6;6(1):337.
- Afzali B, Noris M, Lambrecht BN, Kemper C. The state of complement in COVID-19. *Nat Rev Immunol.* 2022 Feb;22(2):77-84.
- Billoir P, Alexandre K, Duflot T, Roger M, Miranda S, Gorla O, et al. Investigation of Coagulation Biomarkers to Assess Clinical Deterioration in SARS-CoV-2 Infection. *Front Med* (2021);8:670694.
- Uginet M, Breville G, Hofmeister J, Machi P, Lalive PH, Rosi A, et al. Cerebrovascular Complications and Vessel Wall Imaging in COVID-19 Encephalopathy-A Pilot Study. *Clin Neuroradiol.* 2022 Mar;32(1):287-293.
- Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. *Rev Neurol.* 2020 May 1;70(9):311-322.
- Poyiadji N, Shahin G, Noujaim D, et al. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. *Radiology.* 2020;296(2):E119–E120.
- Esenwa C, Cheng NT, Luna J, Willey J, Boehme AK, Kirchoff-Torres K, et al. Biomarkers of Coagulation and Inflammation in COVID-19-Associated Ischemic Stroke. *Stroke.* 2021;52(11):e706-e709.
- Dharmalingam P, Talakatta G, Mitra J, Wang H, Derry PJ, Nilewski LG, et al. Pervasive Genomic Damage in Experimental Intracerebral Hemorrhage: Therapeutic Potential of a Mechanistic-Based Carbon Nanoparticle. *ACS Nano.* 2020 Mar 24;14(3):2827-2846.
- Yang AC, Kern F, Losada PM, Agam MR, Maat CA, Schmartz GP, et al. Dysregulation of brain and choroid plexus cell types in severe COVID-19. *Nature.* 2021;595(7868):565–571.
- Sen R, Garbati M, Bryant K, Lu Y. Epigenetic mechanisms influencing COVID-19. *Genome.* 2021 Apr;64(4):372-385.
- Urbanus RT, Pennings MT, Derksen RH, de Groot PG. Platelet activation by dimeric beta2-glycoprotein I requires signaling via both glycoprotein Ib alpha and apolipoprotein E receptor 2'. *J Thromb Haemost.* 2008 Aug;6(8):1405-12.
- Reynolds JL, Mahajan SD. SARS-COV2 alters blood brain barrier integrity contributing to neuro-inflammation. *J. Neuroimmune Pharmacol.* 2021;16(1):4-6.
- Valderrama EV, Humbert K, Lord A, Frontera J, Yaghi S. Severe acute respiratory syndrome coronavirus 2 infection and ischemic stroke. *Stroke.* 2020 Jul;51(7):e124-e127.
- Du F, Liu B, Zhang S. COVID-19: the role of excessive cytokine release and potential ACE2 down-regulation in promoting hypercoagulable state associated with severe illness. *J Thromb Thrombolysis.* 2021 Feb;51(2):313-329.
- Wenzel J, Lampe J, Müller-Fielitz H, Schuster R, Zille M, Müller K, Krohn M, Körbelin J, Zhang L, Özorhan Ü, et al. The SARS-CoV-2 main protease Mpro causes microvascular brain pathology by cleaving NEMO in brain endothelial cells. *Nat. Neurosci.* 2021;24:1522–1533.
- Mitra J, Kodavati M, Provasek VE, Rao KS, Mitra S, Hamilton DJ, Horner PJ, Vahidy FS, Britz GW, Kent TA, Hegde ML. SARS-CoV-2 and the central nervous system: Emerging insights into hemorrhage-associated neurological consequences and therapeutic considerations. *Ageing Res Rev.* 2022;80:101687.
- Kopp R, Krautloher A, Ramírez-Fernández A, Nicke A. P2X7 interactions and signaling - making head or tail of it. *Front Mol Neurosci.* 2019;12:183.
- Paniri A, Akhavan-Niaki H. Emerging role of IL-6 and NLRP3 inflammasome as potential therapeutic targets to combat COVID-19: Role of lncRNAs in cytokine storm modulation. *Life Sci.* 2020 Sep 15;257:118114.
- Tavčar P, Potokar M, Kolenc M, Korva M, Avšič-Županc T, Zorec R, Jorgačevski J. Neurotropic Viruses, Astrocytes, and COVID-19. *Front. Cell. Neurosci.* 2021;15:662578.

37. Welcome MO, Mastorakis NE. Neuropathophysiology of coronavirus disease 2019: neuroinflammation and blood brain barrier disruption are critical pathophysiological processes that contribute to the clinical symptoms of SARS-CoV-2 infection. *Inflammopharmacology*. 2021 Aug;29(4):939-963.
38. Sun B, Tang N, Peluso MJ, Iyer NS, Torres L, Donatelli JL, et al. Characterization and Biomarker Analyses of Post-COVID-19 Complications and Neurological Manifestations. *Cells*. 2021 Feb 13;10(2):386.
39. Taheri M, Rad LM, Hussen BM, Nicknafs F, Sayad A, Ghafouri-Fard S. Evaluation of expression of VDR-associated lncRNAs in COVID-19 patients. *BMC Infect Dis*. 2021;21:588.
40. Choe K, Park HY, Ikram M, Lee HJ, Park TJ, Ullah R, Kim MO. Systematic Review of the Common Pathophysiological Mechanisms in COVID-19 and Neurodegeneration: The Role of Bioactive Compounds and Natural Antioxidants. *Cells*. 2022;11(8):1298.
41. Chernyak BV, Popova EN, Prikhodko AS, Grebenchikov OA, Zinovkina LA, Zinovkin RA. COVID-19 and oxidative stress. *Biochem*. 2020;85:1543–1553.
42. Dash S, Dash C, Pandhare J. Therapeutic significance of microRNA-mediated regulation of PARP-1 in SARS-CoV-2 infection. *Non-Coding RNA*. 2021;7(4):60.
43. Mahalaxmi I, Kaavya J, Mohana Devi S, Balachandar V. COVID-19 and olfactory dysfunction: a possible associative approach towards neurodegenerative diseases. *J Cell Physiol*. 2021; 236(2):763–70.
44. Restivo DA, Centonze D, Alesina A, Marchese-Ragona R. Myasthenia gravis associated with SARS-CoV-2 infection. *Ann Intern Med*. 2020;173(12):1027–1028.
45. Aladawi M, Elfil M, Abu-Esheh B, Abu Jazar D, Armouti A, Bayoumi A, Piccione E. Guillain Barre Syndrome as a Complication of COVID-19: A Systematic Review. *Can J Neurol Sci*. 2022;49(1):38-48.
46. Ahmad SJ, Feigen CM, Vazquez JP, Kobets AJ, Altschul DJ. Neurological Sequelae of COVID-19. *J Integr Neurosci*. 2022;21(3):77.
47. Oaklander AL, Mills AJ, Kelley M, Toran LS, Smith B, Dalakas MC, Nath A. Peripheral Neuropathy Evaluations of Patients with Prolonged Long COVID. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(3):e1146.
48. Benton DJ, Wrobel AG, Xu P, et al. Receptor binding and priming of the spike protein of SARS-CoV-2 for membrane fusion. *Nature* 2020; 588:327–330.
49. Victor Altmayer, Jason Ziveri, Corinne Frère, Joe-Elie Salem, Nicolas Weiss, Albert Cao, et al. Endothelial cell biomarkers in critically ill COVID-19 patients with encephalitis Wiley Online Library *Journal of Neurochemistry (JNC)*. 2022;161(6):492-505.
50. Alirezaei Z, Pourhanifeh MH, Borran S, Nejati M, Mirzaei H, Hamblin MR. Neurofilament light chain as a biomarker, and correlation with magnetic resonance imaging in diagnosis of CNS-related disorders. *Mol Neurobiol*. 2020;57(1):469- 491.
51. Sahin BE, Celikbilek A, Kocak Y, Saltoglu GT, Konar NM, Hizmali L. Plasma biomarkers of brain injury in COVID-19 patients with neurological symptoms. *J Neurol Sci*. 2022;439:120324.
52. Ostuzzi G, Gastaldon C, Papola D, Fagiolini A, Dursun S, Taylor D, Correll CU, Barbui C. Pharmacological treatment of hyperactive delirium in people with COVID-19: rethinking conventional approaches. *Therapeutic Advances in Psychopharmacology*. 2020;10:2045125320942703.
53. Dubovsky AN, Arvikar S, Stern TA, et al. The Neuropsychiatric Complications of Glucocorticoid Use: Steroid Psychosis Revisited. *Psychosomatics*. 2012;53(2):103–115.
54. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. *Trends Neurosci*. 2008;31(9):464-468.

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