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Sars-COV-2 infection leads to neurodegenerative or neuropsychiatric diseases

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***Abstract*---**The current COVID-19 epidemic caused by the new SARS-CoV-2 has severely harmed global healthcare (severe acute respiratory syndrome coronavirus). COVID-19's pulmonary and cardiovascular effects have been known from its inception, but its causes, mechanisms, and neuropath logical consequences remain unknown. Our research focused on neurological problems in COVID-19 patients, as well as probable SARS-CoV-2 infection routes like hematogenous, direct/neuronal, lymphatic tissue, cerebrospinal fluid, or infiltration by infected immune cells. Late December 2019 in Wuhan, China, a mysterious viral pneumonia struck. The disease was caused by a new corona virus. Corona virus infection spread rapidly from person to

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person in 2019. The WHO has called it a global public health emergency (WHO). Activation of NF-B in SARS-CoV-2 infection may be linked to immune cell pathogenicity, cytokine storms, and multi-organ failure. COVID-19's inhibition of the NF-B signaling pathway shows promising therapeutically. Inhibiting IKK phosphorylation, a critical downstream consequence of the NF-B signaling cascade, reduces COVID-19 levels. All three disorders have been linked to COVID-19 gene mutations. This study provides a biological basis for future research on COVID-19-related neurological disease. We also looked at COVID-19's effect on the development of CNS, PNS, and skeletal muscle manifestations, as well as pre-existing neurological illnesses such Alzheimer's, Parkinsonism, and other neurodegenerative diseases. Acute neurologic symptoms in COVID-19 patients were discussed in connection to illness severity, age, gender, comorbidity, and age. The present state of COVID-19 management and therapeutic alternatives were also studied. Finally, this research examines the neurological effects of the ongoing COVID-19 epidemic, emphasizing the significance of early clinical treatment.

***Keywords*---**COVID-19, neurodegenerative diseases, viral RNA, neuropsychiatric disorders.

Introduction

There have been instances in which neurologic symptoms have been present despite COVID-19's most prevalent acute respiratory symptoms. This year's Lancet Neurology2020 According to the1. COVID-19 has a disproportionate effect on people with preexisting neurological disorders. A team of researchers including 2 Medical supply systems have failed, leading in shortages of common medications, which has put patients at risk of infection. This research brief summarises the current understanding of the relationship between neurology and COVID-19: A study published in 2020 by3. The epidemic is causing widespread disease and death, especially among those with pre-existing neurological disorders. Planning for the pandemic's impact on services must take neurological services into account.

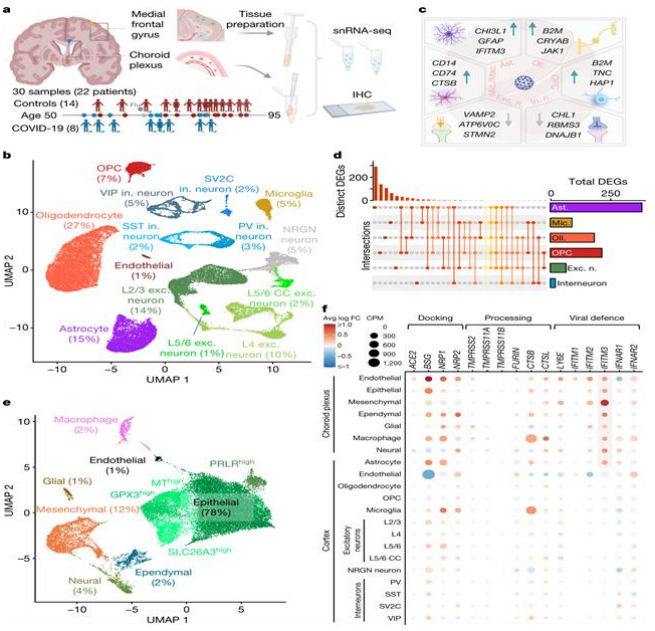

Fig. 1 This diagram shows COVID-19 patients' retinal plexus and brain cells. A study plan The colours of the triangles symbolise the different brain areas studied in each subject. This method is called immunohistochemistry. The medial frontal cortex of eight healthy people and eight COVID-19 patients has 38,217 nuclei. Perivascular cell clusters (containing fibrin-like cells and macrophages) are therefore more difficult to obtain than endothelial cell clusters. OPCs can be stimulated or suppressed. COVID-19 DEGs include astrocytes, oligodendrocytes, microglia, and macrophage (mic2.and mac, respectively). The study involved seven healthy people and eight COVID-19 patients.4

Assume patients with a rare neurological disease may be eligible for covid-19 medication due to a malfunction in lipids transport

ACE2 and TMPRSS2 proteins are required for corona virus infection in cholesterol and sphingolipid-rich PM microdomains. According to 3 NPC1 inactivation at LE/L causes a decrease in PM and ER cholesterol levels. The virion load was restored by administering methyl cyclo dextrin, a medication that lowers cholesterol levels in cell membranes. In 5 SARS-CoV-2 infection may be limited by NPC1 inhibition by lowering the amount of viral S protein binding and priming. In the year 2020, Clathrin and Caveolae-dependent endocytosis occurs in membranes high in cholesterol. When Cathepsin B/L fails to cleave SARS-S CoV-2's protein due to NPC1 deficiency, the virus is unable to enter the cell at a late stage. According to6 As cholesterol accumulates in the LE/L pH, cathepsin's ability to trigger the viral S protein is reduced. Cathepsin inhibition has been linked to an increase in cholesterol. In 3 SARS-CoV-2 infectivity is inhibited by inhibiting viral entry into host cells at many phases when NPC1 is inhibited. Viral replication and budding may be slowed or prevented altogether if NPC1 is inhibited. As of 2020,7DMV production and internal membrane rearrangement

are caused by viral nonstructural proteins that target host cell components in ER expulsions, making them the most likely sites for viral replication centres.

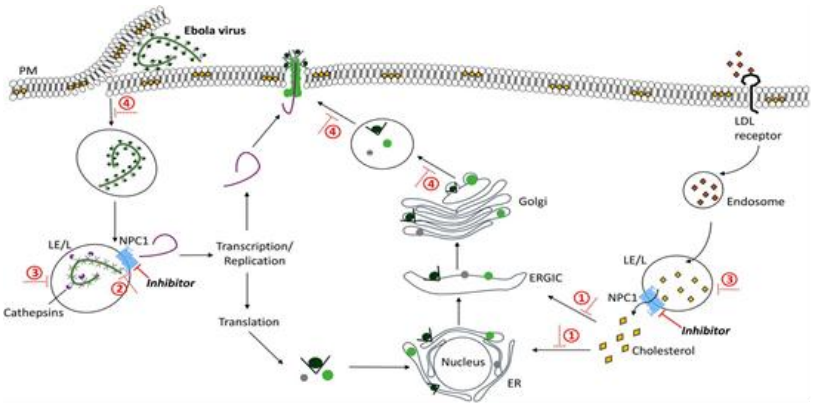

Fig 2. NPC1 promotes filovirus infection and replication. After cathepsin B/macropinocytotic L enters the host cell, the EBOV-GP is activated pH-dependently at the LE/L. When NPC1 is activated by EBOV-GP, the virion enters the cell cytoplasm. The virus then congregates at the PM to prepare for virion replication and transcription. 6

Inflammatory response is communicated over brain defense mechanisms

In 2020 8 Complementary (C1S, C3), IFITM3, STAT3, and other interferon and complement systems are included (Fig. 3).7 RT–qPCR (quantitative PCR with transcription and translation) revealed a substantial.8 COVID-19 has a high amount of brain barrier inflammation, which supports our RNA-seq finding Several SARS-CoV-2 entry genes have been discovered in brain and choroid cells, with varied outcomes. They were screened for SARS-CoV2 using RNA and antibody tests. The study used both snRNA-seq and software-generated RNA-seq datasets to investigate viral. Brain samples had no SARS-CoV-2 RNA. 9 The COVID-19 patients' brains were examined for cell-cell interactions. CCL and CXCL from the plexus epithelial cells increased chromocytokine concentrations in the choroid-to-cortical network. COVID-19 patients' microglia (resident immune cells) should be more receptive to choroid plexus signals.10 Early synapse pruning is associated to increased complement signalling in microglia11 System could track a call. No other antibody could elicit a unique signal in recent tests. Unknown antigen could be bound by 3A2 antibody.12

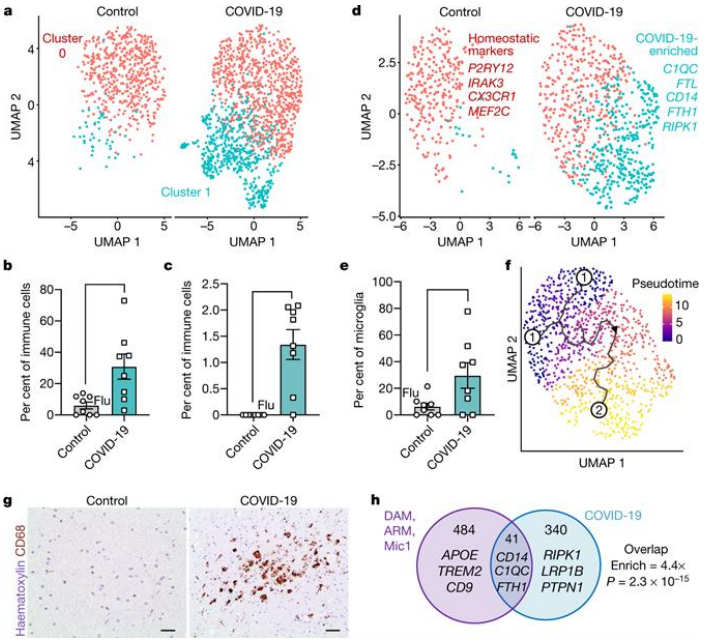

Fig 3. COVID-19 has disease-associated microglia. COVID-19 (swine flu virus) was discovered in swine flu patients (light blue). The first study shows that MRC1 and MRC1+ microglia have unique characteristics. 0.0343 is the significance level. Microglia produce less MRC1 than macrophages (CD206). COVID-19 is associated to light blue microglial cell clusters. Methods shows COVID-19-associated microglia in pseudo-time sequence (Methods). COVID-19 depicts the original and developed populations. Before snRNA-Seq, COVID-19 tissue was IHC for CD68 (brown), a microglial activation marker (blue). IHC staining on a 20-meter scale requires at least two trials. COVID-19 is linked to microglial markers as h, DAM, ARM, and Mic1.14

COVID-19'S initial neurobiological symptoms

Acute neurological symptoms and neurological diagnosis have been documented in 23 cases in the scientific literature. A stroke occurred in one in every 50 COVID-19 patients (n=48 059). The most common neurological symptom in COVID-19 patients over 60 was acute confusion/delirium (34%; 95% CI:23–46%).1

Table 1
In the meta-analysis, it shows neurological symptoms

Disease Variable	No. Of study	No. of event	No. of sample size	% pooled number (%)	96% CI
Cortico spinal Nord	3	129	199	67	59–73
Agitation	4	147	469	46	3–94
Fatigue	170	14 123	45 768	34	30–36
Myalgia	23	620	2 248	33	25–38
Taste impairment	39	2936	12 634	24	15–30
Myalgia	209	12 186	59 822	21	18–24
Impairment smell	53	5647	30 926	20	13–26
Taste & smell impairment	16	618	3 102	19	10–29
Headache	203	9609	51 960	15	12–16
Dizziness	10	776	3 521	14	8–18
Confusion	20	3318	23 923	13	7–17
Disturbance	30	793	15 120	9	5–11
Dizziness	48	909	13 474	8	5–9
Tinnitus	6	32	886	6	1–11
Sight impairment	13	128	2 905	5	1–10
Noisy	8	22	820	4	1–6
Feel impairment	5	24	1 084	3	1–6
Heart impairment	4	23	1 134	3	0–6
Nerve Crazy	4	9	466	3	0–9

The risk of acute confusion/delirium, stroke, seizure, and aberrant movement increased with COVID-19 severity, however the relationships were not statistically significant for all age groups analysed. In non-severe COVID-19, a decreased ability to smell and taste was linked with an OR of 0.44 (95 percent CI: 0.28–0.68) and 0.62 (95 percent CI: 0.42–0.91) 15The study found that people over 60 with neurological symptoms had a significantly increased risk of death (OR: 1.80; 95 percent CI: 1.11–2.91).16

Table 2
Apparent statistical correlation between the prevalence rate of neurological conditions, according to the meta-analysis

Variables	Number of studies	Pooled events	Pooled sample size	P Pooled-prevalence (%)	95% CI
Neuropsychiatric disorders	4	244	1 294	25	2–60
Skeletal muscle injury	5	110	1 546	6	1–13
Myopathy	4	56	5 737	3	0–5
Stroke	30	665	43 025	1	1–3
Ischaemic stroke/TIA	30	528	43 025	2	1–3
Movement disorder	6	49	6 582	2	0–2
CIN/ polyneuropathy	6	49	7 252	2	0–3
Status epilepticus	3	3	283	2	0–6
Hemorrhagic stroke	22	134	36 973	0.32	0.16–0.52
Encephalitis	5	9	4 659	0.31	0–2
Guillain Barré syndrome	5	23	7 404	0.30	0–2
Parainfectious radiculitis	3	4	860	0.26	0–4
Cerebral venous thrombosis	3	6	14 576	0.14	0–4
PRES	4	8	4 315	0.14	0.04–0.27

SARS-CoV-2 has been found to affect the nervous system. Hypoxia, cytokine storm, post-infectious autoimmune responses, hypercoagulability, neurological sequelae of severe systemic disease, and direct neurotropism has all been postulated to explain the neurological signs. The consequences of SARS-neurological CoV-2 on the nervous system are still being studied. To substantiate the link between COVID-19 and GBS, more research is required. Neuropathological and biomarker studies are required to better understand the long- and short-term neurological consequences of TBI. COVID-19 is linked to a wide range of neurological disorders. There is a lack of information about patients with severe cases; hence the present findings are based on a small sample size. Acute and post-acute Covid-19 infection symptoms are hard to distinguish, and long-term effects including cognitive impairment are unknown.16 says The study does not address pre-existing neurological conditions or comorbidities like hypertension and diabetes. They are difficult to generalise to minor symptoms or community residents because they are hospital-based and bias toward more severe symptoms. Neurological disorders demand a diverse range of socioeconomic backgrounds.Studies assessing the impact of mitigation techniques on healthcare also need guidance. Researchers must standardise their methods to make their findings more comparable throughout time. The outbreak has hampered neurology research and training, causing fellowships to be suspended, postponed, or cancelled.

Sars-neuropathogenicity COV-2's

SARS CoV-2's neuroinfective potential has long been known. Covid-19 has been related to numerous neurological issues in studies and case reports worldwide. SARS-CoV-2 RNA was found in the CSF of patients with severe edoema and partial neuronal degeneration (PND). Currently no known method of transmission of SARS-CoV-2 encephalitis. The findings of 17may be used to treat cancer. If the novel virus infects or affects humans, it may cause edoema and altered consciousness. Coronaviruses can infect the CNS via synaptic pathways and retrograde transport. SARS-CoVs and MERS-CoVs are viruses that can enter the brain via the olfactory nerve and quickly infect the brain stem and thalamus.18 These areas regulate neuronal histology. SARS-CoV-2 may be retrogradely transmitted via the olfactory nerve (CNS). Early hyposmia or lack of smell indicates a CNS illness. Blood flow or a breach in the blood-brain barrier could allow SARS-CoV-2 in (BBB). Noroviruses, for example, can directly infect BBB endothelial cells or alter MMP and tight junction protein synthesis to enhance BBB permeability. COVID-19 disrupts the epithelial–endothelial barrier. H. Zhao SARS-CoV-2 may get entrance to the CNS via a "trojan horse" method. Macrophages with ACE2 expression may be involved in SARS-CoV-2 transmission and the inflammatory response in COVID-19 patients." [Yiming Li and a new group] "If SARS-CoV-2 enters the CNS, it can cause permanent damage to neurons in the brain and spinal cord (CNS). SARS-CoV-2 brain damage has been linked to neurodegenerative illnesses like Parkinson's and MS. Due to the high number of COVID-19 cases documented worldwide, doctors should constantly examine patients' early neurologic symptoms19

Molecular pathways in Sars COV-2

36.4 percent of COVID-19 patients exhibit neurological symptoms, according to20. Retroactive studies and case reports from all around the world have documented the CNS effects of Covid-1921 Genome sequencing verified the presence of SARS-CoV-2 RNA in the cerebrospinal fluid (CSF) of seriously ill patients22 SARS CoV-2-associated encephalitis has a mostly unknown aetiology. By infecting or damaging nerves, the new virus may cause edoema and diminished consciousness23 through synapse-connected pathways and retrograde trafficking into the CNS24 Neuronal histopathological alterations in the thalamus and brain stem have been reported following infection with SARS and MERS-CoVs that spread swiftly through the nasal nerves. Netland and colleagues The olfactory nerve can retrogradely transmit SARS-CoV-2 to the central nervous system 26. Early diagnosis of hyposmia, or a lack of sense of smell, is critical in COVID-19 infections27.An alternate hypothesis suggests that SARS-CoV-2 reaches the brain's nervous system through the blood-brain barrier (BBB). By infecting BBB endothelial cells or changing the synthesis of MMPs and TJPs, noroviruses can disrupt the BBB 28. In COVID-19, the epithelial–endothelial barrier has been significantly disrupted 30. Through a Trojan horse mechanism, SARS-CoV-2 could possibly infect the central nervous system(29). COVID-19 patients' inflammatory response may be triggered by macrophages containing SARS-CoV-2 that are CD68+CD169+31. Long-term damage to the

brain and spinal cord from a latent SARS-CoV-2 infection is possible because of the neurons' restricted ability to regenerate and their specialised functions 32. Parkinson's disease or multiple sclerosis (MS) could be caused by the SARS-CoV-2 virus, which has the potential to cause CNS degeneration 33. Since so many people have been exposed to COVID-19, future neurological problems are more likely to occur. In the beginning of the infection, doctors should pay special attention to neurological signs.

Long-term neurological illness effects of COVID-19

The SARS-COV2 virus can kill human brain organoids. However, virus-infected cells had changed metabolic activity. 34 Are due out in 2020. Infections are associated to hypoxia or other cell damage. Antiviral antibodies were recently found in the CSF of a COVID-19 patient, perhaps altering their neurological status. This hasn't happened in a long time 35 ACE2 is now known to exist in both neurons and glia. The olfactory bulb and pericytes associated with the BBB exhibit high Ace2 levels. ACE2 was found in postmortem human amygdala, cortex, and brainstem.36SARS-COV2 may be able to enter the brain and cause neurological harm. Postmortem microglia and CD8+ T cytotoxic lymphocytes coexisted in the medulla of COVID19 patients. 37Microglia may activate invading CD8+ T lymphocytes, preparing them for entrance into the central nervous system. It appears that immune and antigen presentation in the brain are localised.38 No evidence of neurodegeneration were found in any CNS-primed cells, indicating that these people's brains were unaffected. The researchers found in 39 Even if neurons are healthy, neurodegeneration or sickness might occur over time. 40 It is possible that SARS patients had viral particles enter their brains through the blood-brain barrier. Microglia and CD8+ T cells were shown to be stable. The long-term implications of SARS-COV2 are unknown, notwithstanding its minor influence on macroscopic neuropathology. 41 Female mice have a much different ability to learn than male mice, according to 2020 research, Even a healthy brain can be infiltrated by immune cells and soluble substances.42 We just finished studying CD8+ T cells and activated microglia postmortem. 43 COVID19 patients had increased CD68 and TMEM119 microglia activation and CD8+ T cell infiltration than controls. 44Axonal damage (but no necrotic death) was seen in 36–44 percent of COVID19 patients with CD8+ T lymphocytes in their parenchyma, which was connected to the medulla phenotype.45 Microglia activation and immunological T cell invasion, appear to be localised. In 2020, the following papers appeared. 46Acute ischemia in the cerebellum, brainstem, and thalamo-thalamus attracted and activated microglia and T lymphocytes. The brainstems of COVID-19 patients had more CD68-positive microglia than those of Alzheimer's and other dementias. 47Lymphocytes were observed in small numbers near microglia-rich CNS areas.46Mice infected with COVID-19 showed innate microglial and T lymphocyte-driven adaptive immune responses in the brain. No obvious brain illness or neurodegeneration was identified in the brain despite the virus' presence. We haven't seen 48, 49The virus's increased ischemia lesions may make COVID19 patients more prone to early brain stroke. 50

Future implication

Case-control and cohort studies are needed to better understand the cause of COVID-19-related neurological symptoms and to better identify patients at risk for neurological symptoms. Then compare those with and without neurological illnesses. An example of a post-COVID-19 condition CRF is the WHO's post-COVID-19 condition CRF. The EFNA recently conducted an international survey of neurological associations, which was sponsored by members of WHO Neurology and COVID-19 Global Forum.

Conclusion

COVID-19 has been linked to a variety of acute and chronic neurological diseases. Even without respiratory symptoms, clinical and other health care workers should be on the lookout for these issues. Access to key neurologic services and vital pharmaceuticals for individuals with pre-existing neurological disorders should be maintained using remote technology and telemedicine. Covid-19 continues to impact global neurological health, service delivery, and training disparities. These elements must be acknowledged and addressed to improve global neurological care. Antivirals should target NPC1 and its lysosomal function in present and future pandemics.

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Declarations

Conflict of Interest -The authors declare no potential conflicts of interest.
Ethical Approval -This Article does not contain any studies with human participants or animals performed by the author.

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