

Peppi Haavisto

# **ASSOCIATION OF COVID-19 WITH NEUROLOGICAL DISORDERS**

What do we know so far?

Faculty of Medicine and Health Technology  
Bachelor's thesis  
April 2024

# TIIVISTELMÄ

Peppi Haavisto: Covid-19-taudin yhteys neurologisiin sairauksiin  
Kandidaatin tutkielma  
Tampereen yliopisto  
Bioteknologian ja biolääketieteen tekniikan tutkinto-ohjelma  
Huhtikuu 2024

---

COVID-19-tautia aiheuttavan vakavan akuutin hengitystieoireyhtymän koronaviruksen (SARS-CoV-2) leviäminen väestössä johti maailmanlaajuisen pandemian. Virusinfektio on aiheuttanut oireita lievistä flunssan kaltaisista vaivoista vakaviin elinten toimintahäiriöihin, sydän- ja verisuoniongelmiiin sekä ruoansulatuskanavan oireisiin. Virukseen ja sen aiheuttamaan COVID-19-tautiin linkitetyt neurologiset oireet ovat saaneet kasvavissa määrin huomiota.

Tämän kirjallisuuskatsauksen tavoitteena on tutkia SARS-CoV-2:n ja erilaisten neurologisten häiriöiden välistä yhteyttä, tutkia mahdollisia patogeneettisiä mekanismeja ja hypoteeseja, jotka koskevat viruksen roolia yksilöiden altistamisessa tietyille neurologisille sairauksille. On ratkaisevan tärkeää ymmärtää, kuinka SARS-CoV-2 vaikuttaa keskushermostoon, jotta voidaan parantaa käsitystä COVID-19-taudin neurologisista vaikutuksista. Tähän katsaukseen on saatavilla olevan informaation perusteella valittu seuraavat SARS-CoV-2 infekioon liitetyt neurologiset häiriöt: multipeliskleroosi, Alzheimerin tauti, Parkinsonin tauti, Guillain-Barrén oireyhtymä ja epilepsia.

SARS-CoV-2:n ja neurologisten häiriöiden immunopatogeneesien välillä on useita todennäköisiä yhdistäviä tekijöitä, mukaan lukien aktivoituneet mikroglia-solut, neuroinflammaatio, sytokiinimyrsky, oksidatiivinen stressi, muutokset elektrolyyttitasapainossa sekä häiriöt liittyen veri-aivoesteeseen ja veri-hermoesteeseen. Hermosoluissa esiintyvät virusreseptorit voivat mahdollisesti helpottaa viruksen tunkeutumista soluihin. Lisäksi SARS-CoV-2:n ja keskushermoston proteiinien väliset samankaltaisuudet voisivat laukaista autoimmuunivasteen elimistössä.

Yhteydet ovat monitahoisia ja mahdollisesti kaksisuuntaisia, vaikka saatavilla olevissa tutkimuksissa ei ole tästä vakuuttavaa näyttöä. Patogeenisten mekanismien ja niiden yhteyksien lisätutkimus on välttämätöntä, jotta pitkän aikavälin seurauksia voidaan ymmärtää ja tietoa voidaan hyödyntää sairauksien ennaltaehkäisy- ja hoitostrategioissa.

**Avainsanat:** SARS-CoV-2, koronavirus, COVID-19, neurologinen sairaus, neuroinflammaatio, mikroglia, veri-aivoeste, veri-hermoeste, sytokiinimyrsky, oksidatiivinen stressi, molekulaarinen vastaavuus

Tämän julkaisun alkuperäisyys on tarkastettu Turnitin OriginalityCheck –ohjelmalla.

# ABSTRACT

Peppi Haavisto: Association of COVID-19 with neurological disorders  
Bachelor's thesis  
Tampere University  
Degree Program in Biotechnology and Biomedical Engineering  
April 2024

---

The outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV-2) causing COVID-19 led to a global pandemic. Infection with this virus has caused a range of symptoms from mild flu-like ailments to severe organ failures, cardiovascular issues, and gastrointestinal symptoms. Neurological symptoms associated with the virus and COVID-19 have garnered increasing attention.

This thesis aims to explore the link between SARS-CoV-2 and various neurological disorders to date, investigating potential pathogenic mechanisms and hypotheses regarding the viral role in predisposing individuals to specific neurological conditions. Acknowledging the impact SARS-CoV-2 has on the central nervous system is imperative to enhance the understanding of COVID-19's neurological implications. Among the various neurological symptoms and disorders associated with SARS-CoV-2 infection, we have selected the following diseases based on their documented reports: Multiple sclerosis, Alzheimer's disease, Parkinson's disease, Guillain-Barré syndrome, and epilepsy.

Several plausible factors link SARS-CoV-2 with the immunopathogenesis of neurological disorders, such as activated microglia, neuroinflammation, cytokine storm, oxidative stress, electrolyte imbalances, and disruptions to the blood-brain barrier and blood-nerve barrier. Virus receptors expressed in multiple neural cells facilitate viral intrusion. Additionally, similarities between SARS-CoV-2 and central nervous system proteins may trigger autoimmune responses.

The associations are complex and possibly bidirectional, although conclusive evidence is lacking in current research. Further investigation into pathogenic mechanisms and associations is essential for comprehending long-term consequences and utilizing that knowledge in disease prevention and management strategies.

**Keywords:** SARS-CoV-2, coronavirus, COVID-19, neurological disorder, neuroinflammation, microglia, blood-brain barrier, blood-nerve barrier, cytokine storm, oxidative stress, molecular mimicry

The originality of this thesis has been checked using the Turnitin OriginalityCheck -service.

# PREFACE

This bachelor's thesis is done for the degree program in Biotechnology and Biomedical Engineering at Tampere University.

I would like to thank my supervisor, Pabitra Basnyat, for this fascinating topic and for all the time and care in supporting and advising the writing process of this thesis. I also want to thank my loved ones for their unconditional support and reassuring words when I needed them the most.

Tampere, 1.4.2024

Peppi Haavisto

# TABLE OF CONTENTS

1. INTRODUCTION .....	6
2. EPIDEMIOLOGY .....	8
2.1 Symptoms and complications .....	8
3. COVID-19 VIRUS .....	11
3.1 Virus structure and pathogenesis .....	11
3.2 SARS-CoV-2 entry and mechanism of infection .....	12
3.3 Entry and impact to CNS .....	12
4. COVID-19 AND NEUROLOGICAL DISORDERS .....	14
4.1 Multiple sclerosis .....	14
4.2 Alzheimer's disease.....	15
4.3 Parkinson's disease.....	15
4.4 Guillan-Barré syndrome.....	16
4.5 Epilepsy.....	16
4.6 Other complications.....	17
5. DISCUSSION .....	20
5.1 SARS-CoV-2 and neurological disorders.....	20
5.2 Finland's strategy against COVID-19.....	20
6. CONCLUSION.....	22
7. REFERENCES .....	23

## LIST OF ABBREVIATIONS

ACE2	Angiotensin-Converting Enzyme 2
AD	Alzheimer's Disease
APOE $\epsilon$ 4	Apolipoprotein E
BBB	Blood-Brain Barrier
BNB	Blood-Nerve-Barrier
CNS	Central Nervous System
COVID-19	Coronavirus Disease of 2019
CSF	Cerebrospinal Fluid
GBS	Guillain-Barré Syndrome
HCoV-229E	Human Coronavirus 229E
HCoV-HKU1	Human Coronavirus HKU1
HCoV-NL63	Human Coronavirus NL63
HCoV-OC43	Human Coronavirus OC43
IL-6	Interleukin-6
LTP	Long Term Potentiation
MAPK	Mitogen-Activated Protein Kinase
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MS	Multiple Sclerosis
NF- $\kappa$ B	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
PD	Parkinson's Disease
ROS	Reactive Oxygen Species
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
TMPRSS2	Transmembrane Serine Protease 2
WHO	World Health Organization

# 1. INTRODUCTION

Coronaviruses have long been detected in both mammalian and avian species, initially believed to induce only mild symptoms. However, it has become evident that the severity of symptoms can vary significantly depending on the pathogenic strain. The outbreak of severe acute respiratory syndrome (SARS) in China in 2002-2003 highlighted the highly pathogenic nature of the SARS coronavirus (SARS-CoV). A decade later, the Middle East respiratory syndrome coronavirus (MERS-CoV) caused significant distress in Middle Eastern countries. Additionally, four other coronaviruses—HKU1, HCoV-NL63, HCoV-229E, and HCoV-OC43—typically produce milder symptoms compared to SARS-CoV and MERS-CoV. To date, seven human coronaviruses have been identified so far including SARS-CoV-2. (Cui et al., 2019)

In December 2019, the discovery of a novel human coronavirus, SARS-CoV-2, occurred in Wuhan, China, where patients with pneumonia of unidentified etiology sought urgent medical care. By February 2020, the illness caused by SARS-CoV-2 was officially designated as COVID-19. On March 11<sup>th</sup> of the same year, the World Health Organization declared it a pandemic. (Ochani et al., 2021)

Like other highly pathogenic coronaviruses, pinpointing the precise pathogenesis of COVID-19 presents challenges due to symptom similarities with other respiratory illnesses. Nonetheless, a general understanding exists regarding the progression of the infection through the airways and lungs. Upon invading the host, the virus replicates, leading to pneumonia. (Li et al., 2021). Over time, the impaired organ undergoes a gradual recovery process to the best of its capacity, with some tissue potentially becoming fibrotic or progressing into a chronic stage (Li et al., 2021).

With the increasing number of COVID-19 cases, the development of vaccines has become paramount in addressing the global crisis caused by the SARS-CoV-2 virus. Vaccines play a crucial role in mitigating COVID-19 symptoms, and ideally, they can prevent the spread of the disease altogether (Kumari et al., 2022). In Finland, vaccination protocols adhere to recommendations provided by the National Institute for Health and Welfare ([www.thl.fi](http://www.thl.fi)). While most available vaccines, approved by the World Health Organization (WHO), are protein-based or RNA-based, the emergence of rapidly evolving variants poses challenges to effectively curbing the outbreak (Kumari et al., 2022).

While COVID-19 is primarily recognized as a respiratory ailment, numerous studies have documented an array of neurological manifestations, including headaches, dizziness, and in severe cases, seizures or strokes. Existing data indicate that these neurological symptoms are frequently attributed to the immune response triggered by the virus rather than the virus itself. Further investigation is warranted to better understand these correlations, yet hypotheses have emerged suggesting that COVID-19 infection could potentially increase susceptibility to various neurological disorders. (Dale, 2022)

The objective of this review is to provide an updated overview of the relationship between SARS-CoV-2 and neurological disorders based on the available findings published till date. While several studies have suggested potential links between SARS-CoV-2 and conditions such as Multiple Sclerosis, Alzheimer's disease, Parkinson's disease, Guillain-Barré syndrome and epilepsy, conclusive evidence establishing SARS-CoV-2 as a definitive risk factor for these disorders remains elusive. Nevertheless, numerous reports have documented neurological symptoms associated with SARS-CoV-2 infection. This review aims to assess the impact of COVID-19 on the central nervous system (CNS) and explore potential connections between the virus and neurological disorders based on the most recent data. By shedding light on the extent of COVID-19's impact on neurological health and acknowledging the existing knowledge gaps, this review seeks to underscore the urgency of further research in this area.

## 2. EPIDEMIOLOGY

The first case of COVID-19 was detected on December 1st, 2019, in Wuhan, China. Subsequent cases outside of China were initially reported in Thailand, the United States, France, and the United Kingdom (Siddiqui et al., 2022). By the time SARS-CoV-2 was declared a pandemic, a total of 114 countries had reported cases of COVID-19 (Ochani et al., 2021). The WHO has divided the world into six regions: the Americas, European region, Eastern Mediterranean region, Southeast Asia region, Western Pacific region, and African region (Mittal et al., 2021). The Americas region has reported the highest number of confirmed cases, followed by Europe. Overall, the ten countries with the largest number of cases were the United States, Russia, Brazil, Spain, India, the United Kingdom, Peru, Germany, Italy, and Iran (Mittal et al., 2021).

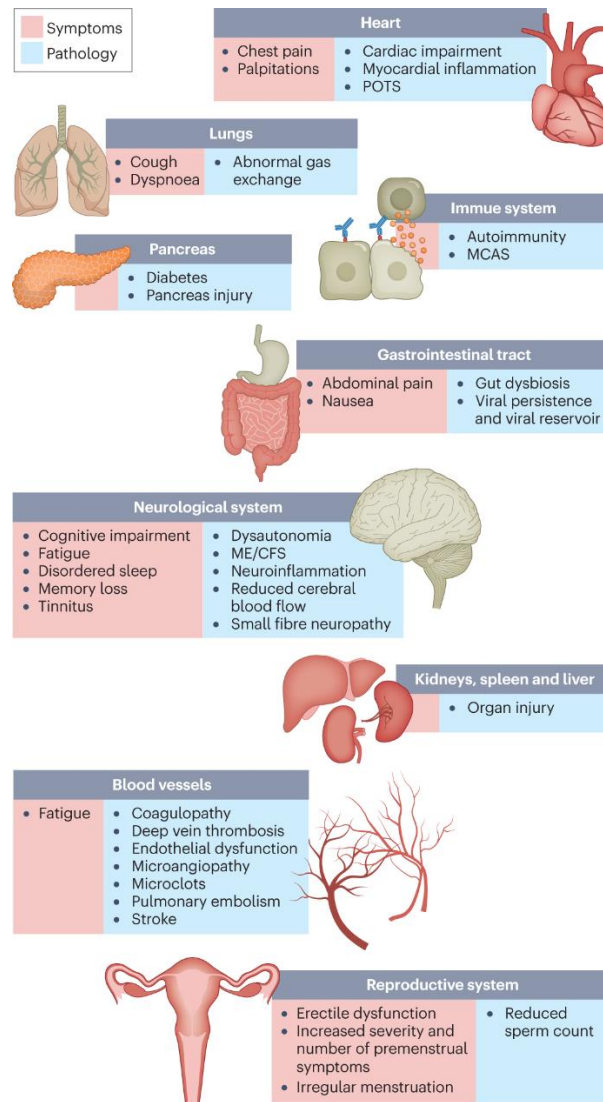
According to WHO, there have been a total of 774,593,066 reported cases of COVID-19 and 7,010,568 reported deaths worldwide (<https://data.who.int/dashboards/covid19/>, accessed on January 20, 2024). These figures may not be entirely precise due to underreporting and lack of testing, and determining a singular cause of death can be challenging. In Finland, the total number of reported cases is 1,515,383 (<https://www.thl.fi/episeuranta/tautitapaukset/koronakartta.html>, accessed on February 22, 2024). According to the Ministry of Social Affairs and Health, COVID-19 is no longer classified as a hazardous communicable disease but rather a monitored communicable disease in Finland. Furthermore, according to WHO, COVID-19 is no longer considered a public health emergency of international concern (<https://stm.fi/korona>, accessed on January 23, 2024).

### 2.1 Symptoms and complications

According to information provided the Finnish Medical Society website, COVID-19 presents a wide range of symptoms and outcomes. The progression of the disease can vary, spanning from mild symptoms resembling a common cold to severe complications, and in some cases, even death. Particularly in the initial stages, symptoms may mimic those of the flu. Common indicators include fever, cough, difficulty breathing (dyspnea), muscle pain, fatigue, nausea, and diarrhea. Distinguishing COVID-19 based solely on these common symptoms is challenging due to their similarity with symptoms of other bacterial or viral infections. Typically, managing the infection involves rest, fever-reducing medication, and adequate hydration; however, this approach may not always suffice (<https://www.terveyskirjasto.fi/dlk01257>, accessed on January 15, 2024). More severe symptoms may include drastic dyspnea, lower blood saturation, lung infiltrates or even respiratory failure (Gao et al., 2021).

Possible risk factors associated with COVID-19 and increased rates of hospitalization and mortality include various factors such as advanced age, male gender, ethnicity, specific symptoms (fever, difficulty breathing, gastrointestinal symptoms), and certain pre-existing medical conditions (hypertension, diabetes, obesity, allergies, chronic obstructive pulmonary disease, interstitial lung disease, chronic liver diseases, chronic kidney diseases, cancer, pregnancy, immunodeficiency). Hospitalized patients may experience various complications arising from the infection, including acute kidney injury, coagulation disorders, and thromboembolism. (Gao et al., 2021)

Following SARS-CoV-2 infection, some individuals develop Long COVID, affecting up to 10% of COVID-19 cases (Davis et al., 2023). Long COVID impacts various organs and systems, including the heart, lungs, immune system, pancreas, gastrointestinal tract, neurological system, kidneys, spleen, liver, blood vessels, and reproductive system (Davis et al., 2023). Figure 1 illustrates the diverse organ impacts and associated pathology. Notably, Long COVID can manifest neurological symptoms, affecting both the central and peripheral nervous systems. This includes cerebrovascular issues, nervous system inflammation, amnesia, delirium, insomnia, headaches, and loss of smell or taste (Dale, 2022). Microvascular function changes can lead to blood-nerve barrier (BNB) damage and hypoxia (Malekpour et al., 2023). Moreover, SARS-CoV-2 has been linked to neurological disorders like Guillain-Barré syndrome (Dale, 2022).

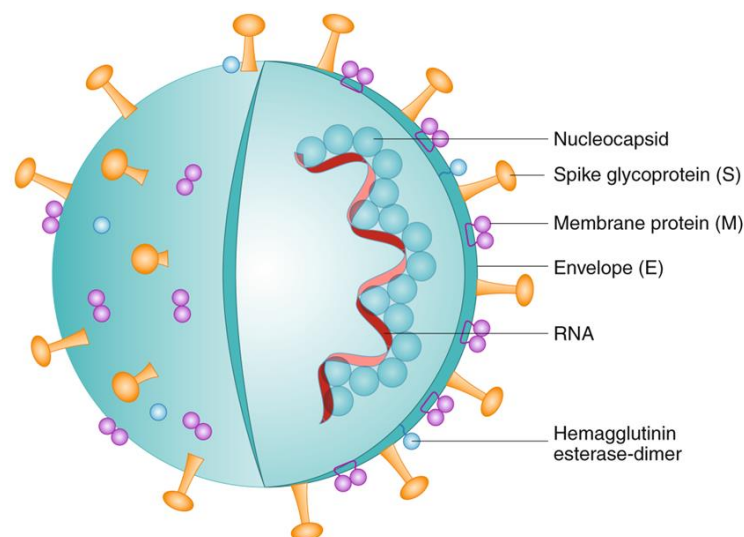


**Figure 1.** The possible impact of SARS-CoV-2 infection on multiple organs. Several symptoms and pathological aspects on the organs are presented. MCAS, mast cell activation syndrome; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; POTS, postural orthostatic tachycardia syndrome. Reproduced with the permission from publisher (Davis et al., 2023).

## 3. COVID-19 VIRUS

### 3.1 Virus structure and pathogenesis

Li and Li (2022) elucidated that SARS-CoV-2, the betacoronavirus accountable for COVID-19, is an enveloped RNA virus characterized by trimeric surface spikes. Its genome, a positive single strand RNA, is the largest among RNA viruses at 29.9 kilobase pairs (kbp), housing six open reading frames encoding non-structural proteins, accessory factors, and structural proteins including spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The glycoprotein spikes consist of S1 and S2 subunits crucial for host cell binding and membrane fusion, respectively (Li and Li, 2022). The structure of SARS-CoV-2 is presented in Figure 2. The receptor binding domain of SARS-CoV-2 interacts with human angiotensin-converting enzyme 2 (ACE2), a key component of the renin-angiotensin-aldosterone system (RAAS) (Bourgonje et al., 2020). Host cell invasion by SARS-CoV-2 necessitates cleavage of its S protein, facilitated by transmembrane serine protease 2 (TMPRSS2), cathepsin L, and furin (Hu et al., 2021). Additionally, other host cell receptors such as Basigin (BSG) and Neuropilin-1 (NRP1) can also facilitate viral entry (Malekpour et al., 2023). Given the pivotal role of the spike protein in virus survival and cellular entry, it remains a primary target for neutralization strategies (Li and Li, 2022).

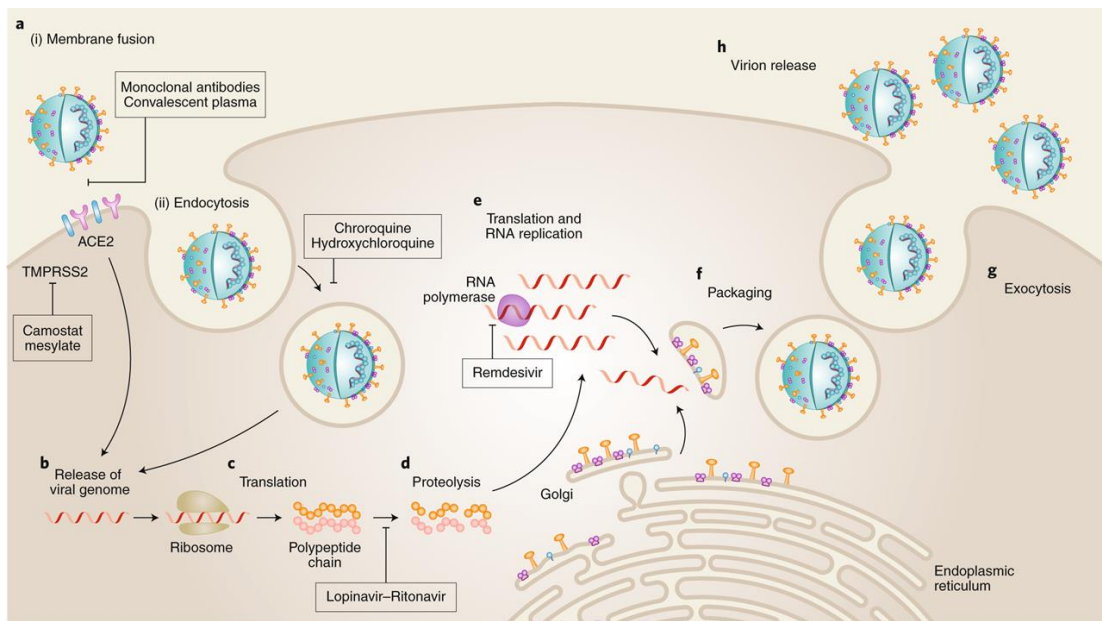


**Figure 2.** *Illustrated structure of SARS-CoV-2. SARS-CoV-2 is an enveloped, positive-sense RNA virus with the following four main structural proteins: spike (S) and membrane (M), envelope (E) and nucleocapsid (N) proteins. Reproduced with the permission from publisher (Florindo et al., 2020).*

The RNA-dependent RNA polymerase is another common clinical target in SARS-CoV-2 due to its role in transcription and replication. Despite the virus possessing a proofreading mechanism in its non-structural protein encoding, the polymerase exhibits a high error rate, leading to the emergence of multiple variants that pose challenges in disease treatment. (Li and Li, 2022)

### 3.2 SARS-CoV-2 entry and mechanism of infection

The infection begins with SARS-CoV-2 attaching to the cell membrane via S protein and ACE2 receptor binding. TMPRSS2 then cleaves the S protein, facilitating fusion between the cell membrane and viral envelope. Within the host cell cytoplasm, the positive-sense viral RNA is replicated, and viral proteins are synthesized. These components are assembled into new virus particles and released via exocytosis. The process is illustrated in Figure 3. The innate immune system detects the virus through pattern recognition receptors, triggering cytokine release. Excessive immune activation, along with the virus itself, can lead to tissue damage in the lungs, causing pneumonia. (Diamond and Kanneganti, 2022)



**Figure 3.** SARS-CoV-2 entry into the cell and new virus formation. The virus can enter the cell (a) by endocytosis or by membrane fusion. In the fusion, the viral receptor binding domain interacts with the angiotensin-converting enzyme 2 (ACE2) and the transmembrane protease serine 2 (TMPRSS2) supports the entry process. After the RNA is released (b), it is translated into proteins (c-e) and the proteins are collected to form new viruses which are then released (g-h). TMPRSS2, transmembrane protease serine 2; ACE2, angiotensin-converting enzyme 2. Reproduced with the permission from publisher (Florindo et al., 2020).

### 3.3 Entry and impact to CNS

Four potential routes for SARS-CoV-2 entry into the CNS have been proposed by Pacheco-Herrero et al. (2021). Firstly, via the hematopoietic pathway, where the virus infects immune cells that breach the blood-brain barrier (BBB). Secondly, through direct entry into the cerebrospinal fluid

(CSF) and subsequent migration to the brain. Thirdly, via transsynaptic viral spreading along nerves like olfactory, gustatory, trigeminal, and vagal. Lastly, through circumventricular organs which lack BBB but express ACE2 receptors. Once in the CNS, the virus can interact with various neural cells expressing ACE2 receptors, such as neurons, oligodendrocytes, and astrocytes (Pacheco-Herrero et al., 2021). Additionally, possibility of entry via the bloodstream through its S1 protein has been suggested (Iacono et al. 2023).

Neurological symptoms stem from inflammation triggered by the body's immune response, leading to elevated levels of inflammatory markers, reactive oxygen species (ROS), interleukin-6 (IL-6), and D-dimer (Malekpour et al., 2023). These markers and ROS correlate with neuronal dysfunction and damage. IL-6 and D-dimers impact cerebrovascular systems, potentially culminating in acute events such as stroke (Malekpour et al., 2023). IL-6 can complicate both long term potentiation (LTP) and hippocampus neurogenesis (Nikbakht et al., 2020). Additionally, elevated levels of TNF- $\alpha$  and other proinflammatory cytokines contribute to a cytokine storm, associated with BBB injury and synaptic loss (Al-kuraishy et al., 2023; MacDougall et al., 2022). Fever and hyperthermia induced by SARS-CoV-2 infection further compromise the BBB integrity, increasing its permeability (Nikbakht et al., 2020).

SARS-CoV-2 activates microglial cells via ACE2 receptors, leading to neuroinflammation. Microglial cells have been identified in brain biopsies of deceased COVID-19 patients (Iacono et al., 2023). Research suggests that SARS-CoV-2 can disrupt microvascular function, particularly the BBB, exacerbating neural cell exposure to autoantibodies associated with severe COVID-19 cases (Malekpour et al., 2023).

## 4. COVID-19 AND NEUROLOGICAL DISORDERS

A growing body of evidence suggested potential impact of SARS-CoV-2 on the CNS, potentially leading to neurological disorders (Wan et al. 2021). The virus has been detected in both CSF and brain tissue of certain patients, with a spectrum of neurological symptoms linked to COVID-19, including dizziness, anosmia, ageusia, seizures, and ischemic stroke. However, many of these symptoms may stem from peripheral pathologies, and the precise mechanisms of SARS-CoV-2 interaction with the CNS remain elusive, necessitating further research (Wan et al., 2021). Our focus is to explore potential links between SARS-CoV-2 and five specific neurological disorders, moving beyond the scope of solely neurological symptoms.

### 4.1 Multiple sclerosis

Multiple sclerosis (MS) is a CNS autoimmune disease characterized by demyelination, damaging the myelin sheath. It leads to impaired neural signal transmission and various motor and sensory issues. Epstein-Barr Virus is implicated in MS development, prompting further investigation into its association with SARS-CoV-2. (MacDougall et al., 2022)

Recent research has suggested parallels between the demyelination observed in COVID-19 patients' brains and that seen in MS (MacDougall et al., 2022). Building on this, Lake and Breen (2023) utilized PEPMatch to investigate similarities between SARS-CoV-2 proteins and CNS proteins, potentially indicating molecular mimicry and triggering autoimmune responses in the brain. Notably, the nucleocapsid protein exhibited significant homology with MS-associated proteins (Lake and Breen, 2023).

MacDougall et al. (2022) further explored integrative factors, including cytokines and neural cell involvement. Cytokines implicated in MS pathogenesis, like Interleukin-6, are upregulated in COVID-19. Oligodendrocytes, responsible for myelination, may suffer direct coronavirus infection, leading to reduced myelin production. While damaged oligodendrocytes are not central in MS pathology, diminished myelin production occurs due to their impairment. Microglia-produced inflammatory cytokines hinder remyelination. Moreover, SARS-CoV-2-induced BBB disruption could facilitate neuroinvasion and increased infiltration of myelin autoantibodies in MS patients (MacDougall et al., 2022). Elevated inflammatory marker production in COVID-19 is similarly associated with MS (Malekpour et al., 2023).

## 4.2 Alzheimer's disease

Alzheimer's disease (AD) is the predominant type of dementia, characterized by cognitive decline affecting memory and personality. It poses increasing challenges for healthcare and families due to rising prevalence and high dependence on resources and caregivers. Emerging evidence suggests a bidirectional relationship between COVID-19 and AD. (Marcello Ciaccio et al., 2021)

According to Ciaccio et al. (2021), common mechanisms exist between COVID-19 and AD, potentially reinforcing their association. Elevated levels of ACE2 receptors in the brains of AD patients, along with increased gene expression, may promote neuroinflammation, impacting AD development through microglia and astrocyte activation. Additionally, the APOE  $\epsilon$ 4 genetic variant, a significant risk factor for AD, has been linked to a higher prevalence and severity of COVID-19, implicating its role in both disrupting the BBB and promoting neuroinflammation. IL-6, an inflammatory cytokine present in COVID-19, is also implicated in neuroinflammation and microglia activation in AD (Marcello Ciaccio et al., 2021).

Gonzalez-Fernandez and Huang (2023) further reviewed evidence suggesting similar signaling and oxidative overload in COVID-19 and the brains of AD patients. SARS-CoV-2 has been shown to damage hippocampal pathways, potentially contributing to dementia development alongside neuroinflammation. Statistical data supports this association, indicating an increased risk of AD diagnosis in older individuals 360 days post-SARS-CoV-2 infection (Gonzalez-Fernandez and Huang, 2023).

## 4.3 Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopamine-producing neurons in the substantia nigra, leading to both motor and non-motor symptoms. Alongside AD, PD constitutes the two most common neurodegenerative disorders. There is an increased risk of PD development associated with infections, and reports suggest a connection between post-encephalitic parkinsonism and COVID-19. Understanding the association pattern is challenging, as similarities in pathogenesis may elevate PD risk, while pre-existing PD could render patients more susceptible to other diseases like COVID-19. (Iacono et al., 2023)

Al-Kuraishy et al. (2023) suggest that the high expression of ACE2 receptors in the substantia nigra, a main affected area in PD, may facilitate the invasion of SARS-CoV-2 into the CNS. Additionally, neuroinflammation or oxidative stress from severe COVID-19 infections could contribute to the loss of dopaminergic neurons in PD (Al-kuraishy et al., 2023).

Iacono et al. (2023) proposed microglia and  $\alpha$ -synuclein may serve as a link between the two diseases, as activated microglia, responsible for neuroinflammation in COVID-19, could exacerbate neuron loss in PD.  $\alpha$ -synuclein, a protein associated with PD, may be transported to the brain due

to viral infection and lung permeability changes, leading to altered protein-protein interactions in the CNS (Iacono et al., 2023).

Furthermore, Al-kuraishy et al. (2023) suggested that IL-6 and NF- $\kappa$ B, components of the cytokine storm, are proposed as potential links between PD and COVID-19, as SARS-CoV-2-induced inflammatory cytokines can activate pathways contributing to dopaminergic neuron loss in PD, such as the mitogen-activated protein kinase (MAPK) pathway (Al-kuraishy et al., 2023).

#### 4.4 Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) is an autoimmune disorder characterized by muscle weakness and paralysis, with a global incidence of 1.1-1.8 per 100,000 individuals annually. GBS occurs when the immune system attacks nerve tissue following infection, surgery, or immunization. Commonly associated with *Campylobacter jejuni* infection, GBS can also be triggered by viruses such as Zika and SARS-CoV-2. Given its potential to cause respiratory failure, GBS compounded with COVID-19 often leads to severe respiratory complications. Approximately 1 in 62,500 COVID-19 patients develop GBS due to the infection. (Malekpour et al., 2023)

Autoantibodies implicated in SARS-CoV-2 pathogenesis may also affect neural cells, potentially leading to GBS (Malekpour et al., 2023). Pre-existing COVID-19 is proposed as a trigger for GBS, possibly through a combination of vascular disruption and autoantibodies (Malekpour et al., 2023). While SARS-CoV-2 antibodies have recently been detected in some GBS cases, their presence in CSF is uncommon (Kocivnik and Velnar, 2022). Despite anecdotal evidence linking COVID-19 and GBS, the precise pathogenic relationship requires further investigation.

#### 4.5 Epilepsy

Epilepsy, a neurological disorder characterized by recurrent seizures, remains poorly understood in terms of its molecular mechanisms (Nikbakht et al., 2020). Seizure initiation can result from either decreased inhibition or increased neuronal excitation, often associated with changes in ion stability triggered by factors such as metabolic abnormalities, infections, trauma, or drug use (Riazi et al., 2010). When linking epilepsy to COVID-19, crucial factors include an increase in glutamate and aspartate levels or a decrease in  $\gamma$ -aminobutyric acid (GABA) neurotransmitter activity (Nikbakht et al., 2020).

COVID-19 neuroinflammation and hypoxia alone can induce epileptic activity. Oxidative stress from SARS-CoV-2 may also be implicated in epilepsy, causing mitochondrial dysfunction and neural electrical disturbances. Electrolyte imbalances, notably hypokalemia seen in COVID-19 patients, can precipitate seizures and brain damage. SARS-CoV-2 binding to ACE2 receptors may down-regulate ACE2 and increase angiotensin II levels, potentially exacerbating hypokalemia. Reduced

LTP and the impact on hippocampus could instigate epilepsy and make it more severe. (Nikbakht et al., 2020)

## **4.6 Other complications**

In addition to aforementioned diseases, various other complications potentially associated with SARS-CoV-2 have been identified. These include ataxia (Malekpour et al., 2023), cases of meningitis and encephalitis, some of which showed positive CSF results for SARS-CoV-2 (Chen et al., 2021). Opsoclonus-myoclonus syndrome and a variant of GBS, Miller-Fischer syndrome, have also been linked to COVID-19 infection (Dale, 2022). Due to the rarity of these conditions, confirming direct associations is challenging.

**Table 1.** Summary of how SARS-CoV-2 affects the CNS and its possible associations with several neurological disorders

<b>SARS-CoV-2 and the CNS</b>	<b>Mechanisms</b>	<b>Potential association with neurological disorders</b>	<b>References</b>
Blood-brain barrier	SARS-CoV-2 infection damages the BBB and can increase its permeability.	Damaged BBB could allow neuroinvasion of autoantibodies into the CNS.	(Nikbakht et al., 2020) (MacDougall et al., 2022)
ACE2 receptors	SARS-CoV-2 binding domain interacts with ACE2 receptors allowing its intrusion into cells. Various neural cells express ACE2, such as microglia and oligodendrocytes.	The amount of ACE2 can be heightened due to diseases such as AD and ACE2 is highly expressed in substantia nigra of PD patients, increasing the SARS-CoV-2 intrusion possibility. Possible downregulation of ACE2 receptors would increase the amount of angiotensin II and cause further problems related to epilepsy.	(Pacheco-Herrero et al., 2021) (Marcello Ciaccio et al., 2021) (Al-kuraishy et al., 2023) (Nikbakht et al., 2020)
Microglia	SARS-CoV-2 activates microglia by intrusion and microglia have been identified in brain biopsies of COVID-19 patients.	Microglia-produced cytokines affect remyelination in MS, activated microglial cells could impact AD development and microglial cells could exacerbate neuron loss in PD.	(Malekpour et al., 2023) (Iacono et al., 2023) (Marcello Ciaccio et al., 2021)
Neuroinflammation	SARS-CoV-2 activated microglial cells lead to neuroinflammation.	Neuroinflammation has conterminous impact with microglia and can cause epileptic activity overall.	(Iacono et al., 2023) (Nikbakht et al., 2020)
Cytokine storm	Cytokine storm is the overproduction of pro-inflammatory cytokines. The SARS-CoV-2 infection activates the immune system triggering the release of cytokines. It is associated with BBB injury and synaptic loss.	The cytokines hinder remyelination in MS, have ability to induce neurodegeneration, activate MAPK in PD and are present in disease pathogenesis in epilepsy, AD and MS. IL-6 can trouble long term potentiation and hippocampus neurogenesis possibly instigating epilepsy.	(Diamond and Kanneganti, 2022) (MacDougall et al., 2022) (Marcello Ciaccio et al., 2021) (Al-kuraishy et al., 2023) (Nikbakht et al., 2020)

Oxidative stress	The immune response to SARS-CoV-2 infection elevates the level of ROS causing oxidative stress. ROS correlate with neuronal dysfunction and damage.	Oxidative stress could lead to loss of neurons in PD and cause mitochondria dysfunction which can further cause abnormal electrical activity in epilepsy. Oxidative overload is also present in AD.	<a href="#">(Malekpour et al., 2023)</a> <a href="#">(Al-kuraishy et al., 2023)</a> <a href="#">(Nikbakht et al., 2020)</a> <a href="#">(Gonzalez-Fernandez and Huang, 2023)</a>
Blood-nerve barrier	SARS-CoV-2 infection can disrupt the function of the BNB exacerbating neural cell exposure to autoantibodies associated with COVID-19.	Autoantibodies interacting with CNS cells provoke neural damage, possibly causing demyelination in MS or leading to diseases such as GBS.	<a href="#">(Malekpour et al., 2023)</a>
Electrolyte imbalance	The oxidative stress in SARS-CoV-2 infection can cause electrolyte imbalances such as hypokalemia.	Hypokalemia can instigate seizures in epilepsy and overall result in brain damage.	<a href="#">(Nikbakht et al., 2020)</a>
Molecular mimicry	Research has shown significant homology between the SARS-CoV-2 nucleocapsid protein with some CNS proteins.	The SARS-CoV-2 triggered immune response could cause an autoimmune response in the CNS. The homologous CNS proteins are especially associated with MS.	<a href="#">(Lake and Breen, 2023)</a>

*ACE2, Angiotensin-Converting Enzyme 2; AD, Alzheimer's Disease; BBB, Blood-Brain Barrier; CNS, Central Nervous System; COVID-19, Coronavirus Disease of 2019; GBS, Guillain-Barré Syndrome; MAPK, Mitogen-Activated Protein Kinase; MS, Multiple Sclerosis; PD, Parkinson's Disease; ROS, Reactive Oxygen Species; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.*

## **5. DISCUSSION**

### **5.1 SARS-CoV-2 and neurological disorders**

The potential links between SARS-CoV-2 and neurological conditions are varied, yet commonalities exist among the disorders under investigation. These potential links between SARS-CoV-2 and neurological conditions based on published reports are compiled in Table 1. Our objective was to analyze how SARS-CoV-2 impacts the CNS and establish connections between these impacts and hypothesized associations with various neurological disorders. This association could be bidirectional: COVID-19 potentially heightens the risk of future neurological disorders, while pre-existing neurological conditions might render individuals more susceptible to COVID-19 infection. Key factors contributing to this development include disruption of the BBB and BNB, locations of ACE2 receptors, activation of microglia leading to neuroinflammation and cytokine storms, oxidative stress, electrolyte imbalances, and the potential molecular mimicry between SARS-CoV-2 and CNS proteins.

Numerous studies explore the potential link between COVID-19 infection and certain neurological disorders, yet discerning SARS-CoV-2 as the definitive cause remains challenging. Limited data, particularly for rare disorders like GBS, hinder reliable conclusions with statistical significance. Confirmation of this association awaits further data.

Moreover, the broader impact of COVID-19 warrants consideration. During the pandemic's onset, even individuals not infected with COVID-19 may have experienced exacerbated symptoms due to various factors. Social distancing measures may have adversely affected mental health, while limited access to resources such as physical therapy could worsen physical symptoms.

Even if SARS-CoV-2 serves as a risk factor rather than the sole cause of a disorder, understanding its influence is crucial for disease prevention and management. Further research is imperative, both in elucidating the pathogenesis of neurological disorders and comprehending SARS-CoV-2's impact on the CNS. However, comparing pathogenesis poses challenges, particularly for diseases like PD, where aspects remain unclear. The emergence of different SARS-CoV-2 variants adds another layer of complexity to ongoing research efforts.

### **5.2 Finland's strategy against COVID-19**

According to the Finnish Institute for Health and Welfare, COVID-19 vaccines are recommended for individuals aged 6 months and older, with specific dosage guidelines. Individuals aged 18 and above are recommended to receive at least three doses. Booster shots are recommended for those

over 12 with immunodeficiency, 18-year-olds in high-risk groups, and individuals over 65. Vaccination is both free and voluntary. Finland utilizes BioNTech-Pfizer's Comirnaty and Novavax's Nuvax-ovid vaccines, both adapted for the XBB.1.5 variant. (<https://thl.fi/aiheet/infektiotaudit-ja-rokotukset/rokotteet-a-o/koronarokotteet>, accessed on February 10, 2024). It has been proposed that mRNA vaccines might lead to an excessive production of SARS-CoV-2 spike proteins, interfering with prion-like proteins and resulting in harmful protein aggregates (Iacono et al., 2023). However, further research is required to validate these claims.

## 6. CONCLUSION

In late 2019, hospitals began receiving patients with respiratory issues of unknown origin, culminating in the identification of the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in early 2020. Symptoms range from flu-like manifestations such as fever, cough, tiredness, and headache to more severe complications including organ failure, cardiovascular issues, and gastrointestinal symptoms. Reports have also indicated neurological symptoms like seizures, delirium, and loss of smell and taste. (Nikbakht et al., 2020)

This thesis explores the pathogenesis of SARS-CoV-2, particularly its impact on the CNS, and investigates potential connections between COVID-19 and various neurological disorders, including MS, AD, PD, GBS, and epilepsy.

SARS-CoV-2 enters cells by binding to ACE2 receptors, which are present in many CNS cells and highly expressed in PD affected substantia nigra. Diseases like AD may increase ACE2 levels. The infection can damage both the BBB and BNB, facilitating neuroinvasion of autoantibodies associated with COVID-19. Microglia activation leads to neuroinflammation, possibly contributing to the loss of neurons seen in PD, affecting AD development and remyelination in MS. Inflammatory cytokines produced during infection could disrupt myelination in MS, induce neurodegeneration, and play a role in the pathogenesis of epilepsy, AD and MS. Oxidative stress and mitochondrial dysfunction, observed in Alzheimer's and Parkinson's, may also result from the infection. Electrolyte imbalances like hypokalemia can lead to epileptic seizures and long-term brain damage. Additionally, similarities between SARS-CoV-2 and CNS proteins may trigger autoimmune responses.

The associations between COVID-19 and neurological diseases are complex and possibly bidirectional. While COVID-19 may predispose individuals to neurological disorders, pre-existing neurological conditions might increase susceptibility to the infection. However, due to incomplete understanding of the pathogenesis of both SARS-CoV-2 and neurological disorders, establishing definitive associations remains challenging. The understanding of COVID-19 and its neurological effects is still evolving, and more research is needed to fully comprehend the extent and long-term consequences of these neurological complications.

## 7. REFERENCES

- Al-kuraishy, H.M., Al-Gareeb, A.I., Kaushik, A., Kujawska, M., Ahmed, E.A., Batiha, G.E.-S., 2023. SARS-COV-2 infection and Parkinson's disease: Possible links and perspectives. *Journal of Neuroscience Research* 101, 952–975. <https://doi.org/10.1002/jnr.25171>
- Bourgonje, A.R., Abdulle, A.E., Timens, W., Hillebrands, J.-L., Navis, G.J., Gordijn, S.J., Bolling, M.C., Dijkstra, G., Voors, A.A., Osterhaus, A.D., van der Voort, P.H., Mulder, D.J., van Goor, H., 2020. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). *The Journal of Pathology* 251, 228–248. <https://doi.org/10.1002/path.5471>
- Chen, X., Laurent, S., Onur, O.A., Kleineberg, N.N., Fink, G.R., Schweitzer, F., Warnke, C., 2021. A systematic review of neurological symptoms and complications of COVID-19. *J Neurol* 268, 392–402. <https://doi.org/10.1007/s00415-020-10067-3>
- Cui, J., Li, F., Shi, Z.-L., 2019. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol* 17, 181–192. <https://doi.org/10.1038/s41579-018-0118-9>
- Dale, L., 2022. Neurological Complications of COVID-19: A Review of the Literature. *Cureus* 14, e27633. <https://doi.org/10.7759/cureus.27633>
- Davis, H.E., McCorkell, L., Vogel, J.M., Topol, E.J., 2023. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 21, 133–146. <https://doi.org/10.1038/s41579-022-00846-2>
- Diamond, M.S., Kanneganti, T.-D., 2022. Innate immunity: the first line of defense against SARS-CoV-2. *Nat Immunol* 23, 165–176. <https://doi.org/10.1038/s41590-021-01091-0>
- Florindo, H.F., Kleiner, R., Vaskovich-Koubi, D., Acúrcio, R.C., Carreira, B., Yeini, E., Tiram, G., Liubomirski, Y., Satchi-Fainaro, R., 2020. Immune-mediated approaches against COVID-19. *Nat. Nanotechnol.* 15, 630–645. <https://doi.org/10.1038/s41565-020-0732-3>
- Gao, Y., Ding, M., Dong, X., Zhang, J., Kursat Azkur, A., Azkur, D., Gan, H., Sun, Y., Fu, W., Li, W., Liang, H., Cao, Y., Yan, Q., Cao, C., Gao, H., Brügggen, M.-C., van de Veen, W., Sokolowska, M., Akdis, M., Akdis, C.A., 2021. Risk factors for severe and critically ill COVID-19 patients: A review. *Allergy* 76, 428–455. <https://doi.org/10.1111/all.14657>
- Gonzalez-Fernandez, E., Huang, J., 2023. Cognitive Aspects of COVID-19. *Curr Neurol Neurosci Rep* 23, 531–538. <https://doi.org/10.1007/s11910-023-01286-y>
- Hu, B., Link to external site, this link will open in a new tab, Guo, H., Link to external site, this link will open in a new tab, Zhou, P., Link to external site, this link will open in a new tab, Zheng-Li, S., Link to external site, this link will open in a new tab, 2021. Characteristics of SARS-CoV-2 and COVID-19. *Nature Reviews. Microbiology* 19, 141–154. <https://doi.org/10.1038/s41579-020-00459-7>
- Iacono, S., Schirò, G., Davì, C., Mastrilli, S., Abbott, M., Guajana, F., Arnao, V., Aridon, P., Ragonese, P., Gagliardo, C., Colomba, C., Scichilone, N., D'Amelio, M., 2023. COVID-19 and neurological disorders: what might connect Parkinson's disease to SARS-CoV-2 infection. *Front Neurol* 14, 1172416. <https://doi.org/10.3389/fneur.2023.1172416>
- Kocivnik, N., Velnar, T., 2022. A Review Pertaining to SARS-CoV-2 and Autoimmune Diseases: What Is the Connection? *Life (Basel)* 12, 1918. <https://doi.org/10.3390/life12111918>
- Kumari, M., Lu, R.-M., Li, M.-C., Huang, J.-L., Hsu, F.-F., Ko, S.-H., Ke, F.-Y., Su, S.-C., Liang, K.-H., Yuan, J.P.-Y., Chiang, H.-L., Sun, C.-P., Lee, I.-J., Li, W.-S., Hsieh, H.-P., Tao, M.-H., Wu, H.-C., 2022. A critical overview of current progress for COVID-19: development of vaccines, antiviral drugs, and therapeutic antibodies. *J Biomed Sci* 29, 68. <https://doi.org/10.1186/s12929-022-00852-9>
- Lake, C.M., Breen, J.J., 2023. Sequence similarity between SARS-CoV-2 nucleocapsid and multiple sclerosis-associated proteins provides insight into viral neuropathogenesis following infection. *Sci Rep* 13, 389. <https://doi.org/10.1038/s41598-022-27348-8>
- Li, C., He, Q., Qian, H., Liu, J., 2021. Overview of the pathogenesis of COVID-19 (Review). *Experimental and Therapeutic Medicine* 22. <https://doi.org/10.3892/etm.2021.10444>

- Li, Y., Li, J.Z., 2022. SARS-CoV-2 Virology. *Infect Dis Clin North Am* 36, 251–265. <https://doi.org/10.1016/j.idc.2022.01.004>
- MacDougall, M., El-Hajj Sleiman, J., Beauchemin, P., Rangachari, M., 2022. SARS-CoV-2 and Multiple Sclerosis: Potential for Disease Exacerbation. *Front Immunol* 13, 871276. <https://doi.org/10.3389/fimmu.2022.871276>
- Malekpour, M., Khanmohammadi, S., Meybodi, M.J.E., Shekouh, D., Rahmanian, M.R., Kardeh, S., Azarpira, N., 2023. COVID-19 as a trigger of Guillain-Barré syndrome: A review of the molecular mechanism. *Immun Inflamm Dis* 11, e875. <https://doi.org/10.1002/iid3.875>
- Marcello Ciaccio, Bruna Lo Sasso, Concetta Scazzone, Caterina Maria Gambino, Anna Maria Ciaccio, Giulia Bivona, Tommaso Piccoli, Rosaria Vincenza Giglio, Luisa Agnello, 2021. COVID-19 and Alzheimer's Disease. *Brain Sciences* 11, 305. <https://doi.org/10.3390/brainsci11030305>
- Mittal, N., Bhadada, S.K., Katare, O.P., 2021. COVID-19: Diagnosis and Management - Part I. Bentham Science Publishers, Sharjah, UNITED ARAB EMIRATES.
- Nikbakht, F., Mohammadkhanizadeh, A., Mohammadi, E., 2020. How does the COVID-19 cause seizure and epilepsy in patients? The potential mechanisms. *Mult Scler Relat Disord* 46, 102535. <https://doi.org/10.1016/j.msard.2020.102535>
- Ochani, R.K., Asad, A., Yasmin, F., Shaikh, S., Khalid, H., Batra, S., Sohail, M.R., Mahmood, S.F., Ochani, R., Arshad, M.H., Kumar, A., Surani, S., 2021. COVID-19 pandemic: from origins to outcomes. A comprehensive review of viral pathogenesis, clinical manifestations, diagnostic evaluation, and management.
- Pacheco-Herrero, M., Soto-Rojas, L.O., Harrington, C.R., Flores-Martinez, Y.M., Villegas-Rojas, M.M., León-Aguilar, A.M., Martínez-Gómez, P.A., Campa-Córdoba, B.B., Apátiga-Pérez, R., Corniel-Taveras, C.N., Dominguez-García, J. de J., Blanco-Alvarez, V.M., Luna-Muñoz, J., 2021. Elucidating the Neuropathologic Mechanisms of SARS-CoV-2 Infection. *Front Neurol* 12, 660087. <https://doi.org/10.3389/fneur.2021.660087>
- Riazi, K., Galic, M.A., Pittman, Q.J., 2010. Contributions of peripheral inflammation to seizure susceptibility: Cytokines and brain excitability. *Epilepsy Research, Special Issue on San Servolo Epilepsy Courses Alumni Meeting* 89, 34–42. <https://doi.org/10.1016/j.epilepsyres.2009.09.004>
- Siddiqui, S., Alhamdi, H.W.S., Alghamdi, H.A., 2022. Recent Chronology of COVID-19 Pandemic. *Front Public Health* 10, 778037. <https://doi.org/10.3389/fpubh.2022.778037>
- Wan, D., Du, T., Hong, W., Chen, L., Que, H., Lu, S., Peng, X., 2021. Neurological complications and infection mechanism of SARS-CoV-2. *Signal Transduct Target Ther* 6, 406. <https://doi.org/10.1038/s41392-021-00818-7>