A Comprehensive Review on Investigations of Chronic neurological Impact of SARS-COV-2 on human biological samples and on animal model (In vitro or In vivo)

By

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

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Declaration

It is hereby declared that

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

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Approval

The thesis/project titled ‘’A Comprehensive Review on Investigations of Chronic neurological Impact of SARS-COV-2 on human biological samples and on animal model (In vitro or In vivo)” submitted by Md. Mujahid Chowdhury of Spring, 2024 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

No living organism were harmed during this project.

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Abstract/ Executive Summary

Introduction: This study investigates COVID-19's neurological impacts using biological materials, recognizing a gap in understanding long-term brain effects amidst extensive respiratory research.

Method: Screening 4132 papers yielded 89 relevant studies, including cohort (41), case (16), investigational (26), and animal model (6) experiments, encompassing 455,129 cohort participants, 500 investigators, and 77 case patients.

Results: Post-SARS-CoV-2 neurological difficulties include seizures, sleep disorders, and post-COVID-19 syndrome. Neuroinflammation and neuronal cell dysregulation may contribute. Secondary autoimmunity, CSF abnormalities, and autoantibodies suggest immune-mediated neuroimmunological diseases. COVID-19 severity can differ in MS patients. Recovering cognitively may have long-term immune system effects. Animal models of neutralizing antibodies, medicines that interact with viral proteins, and melatonin and cannabinoids that may reduce viral entrance and inflammation offer therapeutic insights.

Conclusion: This research underscores COVID-19's neurological manifestations, proposing potential treatments and emphasizing ongoing research's critical role in shaping clinical management and public health guidelines.

Keywords: Seizures, neuroinflammation, autoimmunity, auto-antibody.

Dedication

Dedicated to my parents.

Acknowledgement

I am grateful to Allah for enabling me to choose Pharmacy as my field of study. Without His powerful blessings, I would be unable to finish this project and submit it to obtain my Bachelor's degree in Pharmacy.

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Table of Contents

List of Tables

List of Figures

List of Acronyms

ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
aPL	Antiphospholipid
NE	Neurological events
PASC	Post-acute sequelae of SARS-CoV-2 infection
MS	Multiple sclerosis
QSART	Quantitative sudomotor axonal reflex testing
SSNHL	Sensorineural Hearing Loss
ChP	Choroid plexus
mAb	Monoclonal antibody

Chapter 1

Introduction

1.1 Background

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has resulted in a wide range of clinical manifestations, spanning mild respiratory symptoms to severe pneumonia and multi-organ failure. While the virus's primary respiratory effects have been thoroughly researched, new data shows that SARS-CoV-2 may also have a substantial influence on the neurological system, both immediately and potentially long term. Numerous studies indicate anosmia, ageusia, headaches, dizziness, and more serious signs such as encephalopathy and stroke in COVID-19 individuals.

In order to comprehend the long-term neurological effects of SARS-CoV-2, scientists are focusing on studying human biological samples like blood, tissue, cell etc. Because these samples contain biomarkers, chemical fingerprints and other molecular indicators that can provide light on the systemic effects of the virus on the central nervous system, it is an invaluable source of information.

The intent of this comprehensive review is to synthesize and analyze the existing literature on investigations of chronic neurological impact, with an emphasis on such which utilise human biological samples. Through the analysis of blood biomarkers, cytokine profiles, and other molecular indicators, a possible correlation between the residual symptoms and the SARS-CoV-2 infection is investigated.

1.2 Research gap:

Given the highly contagious nature of the virus and its rapid global spread, there was an urgent need to understand and manage the primary mode of transmission, which was through respiratory droplets. The main goal of COVID-19 research in its initial stages was to on understanding the acute respiratory aspects of the infection. However, as the pandemic progressed, a noticeable research gap became evident, particularly in the realm of neurogenic manifestations. While significant attention was directed towards immediate respiratory consequences, there was a limited and concise understanding of how COVID-19 might impact the nervous system over the long term. The research gap in neurogenic manifestations remained conspicuous, indicating a need for more comprehensive investigations into the neurological aspects of the virus.

The research gap is very noticeable because scientists often use clinical assessments, neurological examinations, neuroimaging techniques, etc. to look into the long-term neurological effects. Scientists are currently concentrating on examining biological samples in an effort to understand the long-term neurological repercussions of SARS-CoV-2. This systematic review aims to make a substantial contribution to our comprehension of the enduring neurological effects of SARS-CoV-2.

1.3 Objectives:

The following are the objectives of this study:

- Outline the studies of neurological Impact of SARS-COV-2 that are investigated on biological samples.
- To shed light on neurological problems or disorders that are identified during the examination of human biological samples.

- Address the neurological issues that have been studied using in vitro or in vivo models.

1.4 Significance:

This review is a crucial resource since it goes beyond just focusing on the respiratory system. It includes the synthesis of existing research, the examination of biological samples, and the incorporation of preclinical models. The results of this study have the capacity to provide valuable insights for medical treatment, direct public health approaches, and influence future research endeavors, ultimately assisting in the comprehensive response to the intricate and changing difficulties presented by the COVID-19 epidemic.

Chapter 2

Methods:

2.1 Criteria for inclusion and exclusion:

The following were the stated requirements for inclusion:

- Original Articles
- Full text
- The article must be written in English.

The following criteria were used to exclude articles:

- Review article
- Systematic Review
- Vaccination studies

2.2 Literature Search Strategy:

In order to investigate the chronic neurological impact of SARS-CoV-2, a systematic search was conducted, spanning the period from December 12, 2019, to April 11. Five prominent search engines, including PubMed, Google Scholar, Springer, ScienceDirect, and Scopus, were utilized to identify relevant research articles in English. The search strategy involved the use of specific keywords such as "SARS-CoV-2," "post COVID-19," and "Neurological Investigations." The outcomes of the search across these electronic databases were compiled, and the findings from each source were synthesized to provide a comprehensive overview of the research related to the persistent neurological effects of SARS-CoV-2 infection.

2.3 Quality Assessment

In order to critically approve prevalence studies, some criteria were used in this review: (i) a clear and acceptable objectives/aim; (ii) complete investigations with a conclusion; and (iii) application of results. Relevant article titles and abstracts that satisfy the aforementioned selection criteria were included in this evaluation.

2.4 Data Extraction

A total of 4132 articles were identified through systemic search spanning the period from December 12, 2019, to April 11, using specific keyword such as SARS-CoV-2, post COVID-19, Neurological investigation. Following the inclusion criteria-based screening process, 461 papers were accessed to determine their eligibility for the research. Following a comprehensive text evaluation of these papers, 118 studies that used human blood samples for their investigations were included for the systemic analysis. From there, 89 papers met the required criteria and were included in the systemic review; the remaining 29 reviews were omitted due to the exclusion criteria. The steps involved in the eligibility evaluation, screening, and literature review are shown in Figure 1.

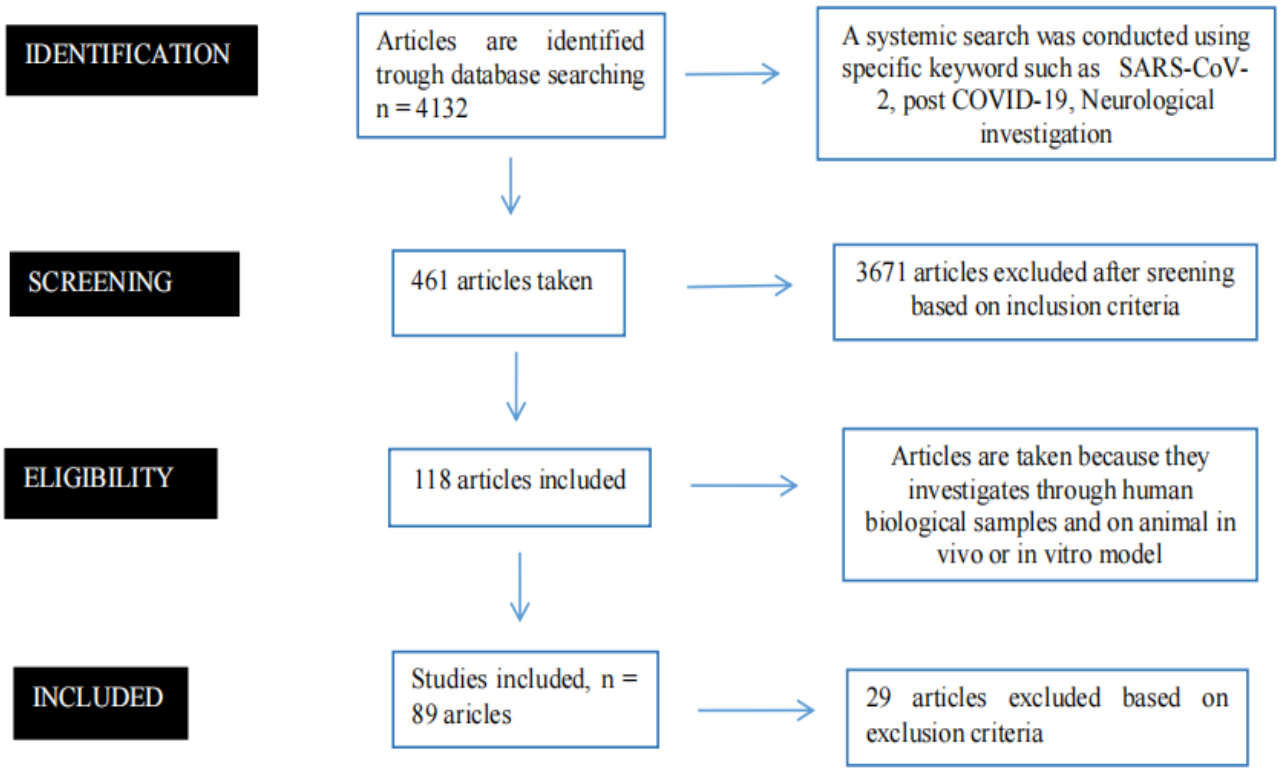

Figure 1: Flow diagram showing literature searching process of the study

Chapter 3

Results:

In the analysis of 89 studies, various research methodologies were employed, comprising 41 cohort studies, 16 case studies, 26 investigational studies, and 6 studies conducted on animal models. Cohort studies, being a prevalent approach, utilizing the highest total number of participants, amounting to 4,55,129 human subjects. . Investigational study have combined 500 number of participants while Case studies predominantly focused on observing specific cases, encompassing 77 participants in total. Furthermore, 6 studies were centered on experimenting with animal models. The participants number, methods and the result of each article of the studies are given below:

Table 1: Summary of findings from Cohort studies

Number	Participants	Methods/ tools	Result	Reference
1.	439 patients	Observational, retrospective cohort study and laboratory data	Among the 19 individuals, 3 experienced seizures for the first time after contracting COVID-19, whereas 2 had a pre-existing diagnosis of controlled epilepsy.	Khedr et al., 2021
2.	47 patients	Blood markers, An analysis of group comparisons and linear regression models.	The incidence of sleeplessness rose from 10.6% to 27.3% following the onset of COVID-19. 41.5% of patients exhibited substandard sleep quality.	Pellitteri et al., 2022
3.	50 patients	Blood markers	Comparatively, hospitalised individuals had heightened levels of inflammatory indicators, such as CRP, procalcitonin, TNFa, and sIL-2R, in contrast to non-hospitalized patients.	Bungenberg et al., 2022
4.	14,399 patients	EHR-based cohort study	The PASC cohort included a higher representation of older	Lorman et al., 2023

			children and girls compared to younger children and boys, with an overall distribution of 54.9% and 45.1% respectively and majority (55.8%) had a chronic condition.	
5.	359 elderly patients	The demographic, clinical, radiological, and laboratory test data	The mortality rate for COVID-19 patients was 5.45 times higher compared to TBI patients who did not have COVID-19.	Reza Bagheri et al., 2021
6.	194 patients	the measurement of respiratory rate (RR), dyspnea status, arterial blood gas (ABG), heart rate (HR), temperature, C-reactive protein (CRP), and Alveolar-arterial (A-a) gradient	Patients brought to the hospital with COVID-19 often exhibit poor regulation of breathing, characterised by rapid breathing (tachypnea) even when there is low carbon dioxide levels (hypocapnia) leading to alkalosis.	Jareonsettasin et al., 2022
7.	15 patients	Lumbar puncture with CSF examination, Serum anti-gangliosides antibodies testing, CSF PCR for SARS-CoV-2	Para-infectious encephalitis and polyradiculitis in SARS-CoV-2 infected patients are linked to the presence of CSF lymphocytic pleocytosis and/or blood-CSF barrier disruption.	Guilmot et al., 2021
8.	71 patients	evaluate the anti-phospholipid autoantibody titre	A total of 21 patients, out of the 71 individuals examined, tested positive for at least one type of antiphospholipid (aPL) antibody.	K.Bitzogli,2021
9.	91 patients	Collection and analysis of medical records and data	The majority of patients with neuroimmunological problems and SARS-CoV-2 infection experienced mild cases of COVID-19, with 84.6% of patients having mild disease. There were 3 cases (3.3%) of severe disease and 7 cases (7.7%) of critical disease.	Moura et al., 2022
10.	45 patients	Nerve conduction study (NCS). Mann-Whitney test, Sensory studies.	The instance had neurophysiological anomalies in both sensory and motor nerve fibres.	Stępień & Pastuszak, 2023
11.	171 patients	Pulmonary function tests and peripheral	The most common post-COVID-19 grievances	Fleischer et al., 2022

		oxygen saturation measurement, Blood analysis for routine parameters, full blood count, and analysis of inflammatory parameter.	encompassed weariness, cognitive impairments, and memory deficiencies. Neurological evaluation revealed no abnormal findings in the majority of patients (85.8%).	
12.	1,916 patients	Logistic regression	Patients infected with Covid-19 are at a greater risk of experiencing acute ischemic stroke as compared to patients with influenza.	Merkler et al., 2020
13.	501 participants	a comprehensive test battery	Young, previously healthy people recover from moderate covid infection with less multi-system damage than older or hospitalised patients.	Werner Deuel et al., n.d.
14.	83 pediatric patients	NF	Most cases of acute COVID-19 in children are not severe, although children with pre-existing comorbidities are more susceptible to developing severe acute COVID-19 compared to those without comorbidities.	Biharie et al., 202
15.	582 patients	A standardized, predesigned, interviewer-administered checklist was developed following a review of the literature.	Neurological events (NE) were seen in 283 individuals (48.63%) and showed a significant correlation with severe COVID-19 at the beginning and a higher mortality rate.	Mekkawy et al., 2022
16.	NF	Clinical trial, Post-marketing cohort, Real-world data (RWD) stud, and the OPTUM ® de-identified COVID-19 EHR database.	Most ocrelizumab-treated MS patients have mild to moderate COVID-19, which does not require hospitalisation. Risk factors associated with severe COVID-19 outcomes in the general population also appear to affect severity.	Hughes et al., 2021
17.	62 persons	Tele-consultation and/or evaluation during hospital visits	COVID-19 can have severe and persistent effects on people with Multiple Sclerosis who are undergoing treatment with Rituximab.	Iyer et al., 2022
18.	20 patients	Autonomic function testing, including	All individuals experienced a consistent deterioration or	Varma-Doyle et al., 2023

		cardiovascular indices, sympathetic cholinergic/sudomotor testing, skin biopsies	new occurrence of sudomotor (sweat gland) dysfunction as a result of COVID-19.	
19.	334 patients	A prospectively maintained database of subarachnoid hemorrhage patients	There was a noticeable increase in ruptured internal carotid artery blister aneurysms among patients with aneurysmal subarachnoid haemorrhage during the height of the COVID-19 pandemic in 2021, as compared to the years before the pandemic (2017-2019).	Hudson et al., 2023
20.	131 patients	Clinical, lung function assessment, and serum neurofilament light chain measurement.	ME/CFS-like symptoms were detected in 27% of COVID-19 survivors who had a comprehensive evaluation, which included assessing lung function and measuring blood neurofilament light chain levels.	Mantovani et al., 2021
21.	58 patients	Laboratory tests.	Mild cases of COVID-19 can lead to functional and anatomical problems in the central nervous system, such as brain microhemorrhages.	Udzik et al., 2023
22.	1354 patients	A web-based survey and telephone interviews	MS patients with COVID-19 reported fever, cough, exhaustion, and dyspnea as the most common symptoms. Smoking was a risk factor for many symptoms.	Schiavetti et al., 2022
23.	1252 patients	K-means algorithm based on unsupervised learning and ihe Stable Sparse Classifiers procedure (SSC)	Based on symptoms, comorbidities, and age, it defined six clinical phenotypes. Phenotypes 1 and 3 had the greatest in-hospital mortality rates (25.79%).	Morales Chacón et al., 2022
24.	367 patients	Electronic medical records (EMR) and Statistical analysis.	95 (26%) of 367 individuals had AMS as a major or presenting symptom. Most neurological primary complaints were AMS.	Chachkhiani et al., 2021
25.	18 patients	Electrodiagnostic studies, concentric needle	There were various comorbidities present in the subjects, with hypertension	Hameed et al., 2021

		electromyography examination, Nerve conduction study(NCS), Nicolet Viking machine.	being the most prevalent comorbid disease (67 percent, n = 12), followed by diabetes mellitus (50 percent, n = 9), and asthma (22 percent, n = 4).	
26.	91 patients	Retrospective analysis	Out of the total of 1795 patients observed at the neuroimmunology outpatient clinic, 91 were diagnosed with proven SARS COV 2 infection.	Joao Maura ,2022
27.	70 patients	Investigate the potential therapeutic effects of HD-tDCS.	The HD-tDCS had a clear impact on the cognitive and psychosocial aspects, but there was no notable variation between groups on the physical subscale.	Kelly Santana,2023
28.	236,379 patients	TriNetX electronic health records network	Neurological and psychological health issues are common over the 6 months following a COVID-19 infection. The dangers were most pronounced in patients with severe COVID-19, albeit not exclusively limited to them.	Taquet et al., 2021
29.	199 patients	Demographic, medical history, clinical presentation data and complete physical and neurological examination.	A total of 199 individuals diagnosed with mild-to-moderate COVID-19 were included in this study. Among them, 83% exhibited at least one neurological symptom, with an average duration of 8 +/- 6 days.	Carcamo Garcia et al., 2021
30.	56 patients	Rehabilation unit during pandemic period	A high number of post-covid patients had abnormal scores in one or more neuropsychological tests, suggesting cognitive consequences.	Rota et al., 2022
31.	66 COVID -19 survivor s and 79 healthy controls (HCs)	Demographic data and basic clinical information, Serum sample collection and analysis.	Significant variations in I-TAC, IL-8, and TNF-伪 levels were found between COVID-19 and healthy control groups.	He et al., 2023

32.	112700 patients	Disease Analyzer database (IQVIA), Poisson regression models.	Depression and anxiety disorder were not substantially greater in the COVID-19 group than in the upper respiratory infection group (IRR = 1.02, 95% CI = 0.95–1.10).	Jacob et al., 2022
33.	178 patients	Evaluate the effect of previous CVD on mortality rates of critically ill CPVID 19	178 crucial covid In 19 ICU patients, previos CVD was substantially related with increased fatality rates.	Teixeira-Vaz et al., 2022
34.	72 datasets	Behavioral measurements, and serum testing	The concentrations of two inflammatory biomarkers, interleukin-16 and monocyte chemoattractant protein-1, were shown to be increased in persons after the lockdown period.	Brusaferri et al., 2022
35.	11 patients	A retrospective observational study, Data collection and analysis.	All 11 hospitalised neurosurgical patients (0.68%) had COVID-19 with comorbidities. The average stay was 13.4 days (4-30 days).	Marenco-Hillembrand et al., 2021
36.	62 patients	Data collection, data analysis & comparing, MAC.	During the COVID-19 lockdown period in 2020, there was a notable decrease in the total number of neurosurgery cases compared to 2019. This decrease was particularly evident in elective spine procedures.	Sudhan et al., 2021
37.	1500 patients	NF	Immunosuppressors, smoking, hypertension, and epilepsy increased mortality. Mortality was also linked to asthma, obesity, diabetes, migraine, cerebrovascular illness, encephalitis, and cardiovascular problems.	Azab et al., 2021
38.	80,388 patients	Multilevel logistic regression and survival models, the International Severe Acute Respiratory and Emerging Infections Consortium WHO Clinical	Forty-nine point seven percent of the patients who were admitted to the hospital for the treatment of COVID-19 had at least one problem. Renal difficulties, severe respiratory issues, and systemic complications were	Drake et al., 2021

		Characterisation Protocol UK	the most common types of complications.	
39.	127 patients	NF	The pandemic did not increase the incidence of surgical complications including fever and respiratory distress compared to a well matched pre-pandemic group.	Louie et al., 2020
40.	254 individuals	NF	Out of the 249 instances that experienced symptoms in the acute phase, 64.1% reported having at least one symptom in the post-acute phase.	Sadat Larijani et al., 2022
41.	417 infants	Periodic clinical assessments, telephonic contacts, laboratory evaluations, and instrumental evaluations	This study presents the findings of a comprehensive follow-up study conducted in the outpatient clinic of the Paediatric Infectious Diseases Unit on children who were hospitalised due to SARS-CoV-2 infection.	Garazzino et al., 2023

Table 2: Summary of findings from Case studies

Number of study	Participants	Methods/ tools	Result	Reference
1.	1 patient	Patient's biochemical investigations.	It showed low sodium (123 mmol/L), high C-reactive protein (44 mg/L), and plasma and urine osmolality (252 and 291).	Butt et al., 2020
2.	1 patient	Specific cerebrospinal fluid investigation	A female patient with normal routine examination exhibited persisting cerebrospinal fluid anti-SARS-CoV-2 antibodies 6 months after moderate COVID-19.	Borsche et al., 2021
3.	1 patient	Serum testing, cell-based assay (CBA), and prolonged steroid course of treatment	This article presents a documented instance of longitudinally extensive transverse myelitis (LETM) accompanied by the presence of anti-myelin oligodendrocyte glycoprotein (MOG) antibodies subsequent to SARS-CoV-2 infection.	Dias da Costa et al., 2021
4.	1 patient	Euroimmun (Lübeck, Germany) provided SARS-CoV-2 ELISA IgA/IgG and PCR. Two ELISA IgG tests from Abbott (Sligo, Ireland) and DiaSorin (Sasluggia, Italy).	The patient exhibited subacute ocular symptoms of myasthenia gravis following a typical COVID-19 infection, which also included neurological manifestations such as headache and loss of smell/taste.	Huber et al., 2020
5.	1 patient	NF	This report details a solitary instance of post-infectious cerebellar ataxia occurring after COVID-19 in a patient with epilepsy. It encompasses the patient's clinical manifestation, diagnosis, and treatment.	Chattopadhyay et al., 2022
6.	1 patient	Comprehensive laboratory work-up, Quantitative sudomotor axonal	The decreased sweat production in the forearm and foot areas indicates a dysfunction in the	Agnihotri et al., 2022

		reflex testing, Head-up tilt table test, skin punch biopsy, HIV titers.	postganglionic sympathetic cholinergic sudomotor system, which is caused by autonomic neuropathy.	
7.	1 patient	Laboratory investigations, patient's medical history	The patient tested positive for IgG antibodies against this infection. All other identified reasons for this syndrome were ruled out.	Fernandes & Puhlmann, 2021)
8.	1 patient	PMCT, Microscopic examination, Virology studies, Bacteriology studies, Histology studies	SARS-CoV-2 infection has been documented to cause both direct harm to organs and an abnormal immune response leading to viral sepsis.	Ducloyer et al., 2020
9.	1 patient	Clinical presentation, radiological and pathological evaluation and management	The nerve conduction investigation indicated the presence of an uneven distribution of sensory and motor polyneuropathy.	R Ojha et al., 2021
10.	6 cases	Analysis of brain biopsies and autopsies from COVID-19 patients, NGS-based transcriptomic analysis, NGS-based target capture, immunohistochemistry, and detection of SARS-CoV-2 spike protein in brain endothelial cells	COVID-19 associated cerebral microangiopathy (CCM) is characterised by alterations in the brain endothelial cells surrounding blood vessels, where the spike protein of the SARS-CoV-2 virus is detected in the Golgi apparatus. This presence is tightly associated with furin.	Boluda et al., 2023
11.	1 patient	Patient's medical history, physical examination, scintigraphic evaluation	Intravenous immunoglobulin effectively addressed the patient's autoimmune gastrointestinal dysmotility (AGID) that occurred as a result of SARS-CoV-2 infection.	Montalvo et al., 2022
12.	1 patient	Routine blood tests, Lumbar puncture for cerebrospinal fluid analysis.	The patient had treatment with lamotrigine and haloperidol, resulting in the eventual resolution of the symptoms.	Russo et al., 2021

13.	1 patient	Blood work, Urine culture.	The blood analysis revealed a low white blood cell count (3.81k/microliter), low sodium levels (134 mmol/L), and high fibrinogen levels (627 mg/dL).	Sirbu et al., 2022
14.	5 cases	Clinical, radiological and laboratory investigation	The diverse range of neurological symptoms observed in paediatric patients with COVID includes headache, ataxia, and seizures.	Aljomah et al., 2021
15.	1 patient	Lumbar puncture and nerve conduction studies	The subject of the case report underwent treatment with intravenous immunoglobulin (IVIG) and received supportive care, leading to a partial restoration of health.	Miyajan et al., 2021
16.	53 cases	NF	COVID-19 could contribute to the occurrence of sudden sensorineural hearing loss (SSNHL). Out of the 53 cases of verified COVID-19, there was one patient who had received a COVID-19 vaccine and developed sudden sensorineural hearing loss (SSNHL).	Elmoursy et al., 2023

Table 3: Summary of findings from Investigational studies

Number of study	Samples	Methods/ tools	Result	Reference
1.	Post-mortem tissues	Histological sections of multiple organs, Luxol fast blue staining, Immunohistochemistry, Immunostaining, RT-qPCR	The data suggest the presence of microthrombosis, pulmonary congestion, interstitial edoema, lymphocytic infiltrates, bronchiolar damage, collapsing alveolar gaps, cortical atrophy, and significant neuronal loss.	Gomes et al., 2021
2.	Single cell RNA sequencing of human tissues	In silico analysis of immune system protein-protein interactcome network	15 immune system proteins, 4 approved medications, 9 investigated compounds, and 16 experimental chemicals.	López-Cortés et al., 2021
3.	The frontal cortex tissue	qRT-PCR. ddPCR. RNA-seq. EnrichR web tool and clusterProfiler, CORALL Total RNA-Seq Library Prep Kit, Illumina NextSeq 500 Sequencing, STARRSEM software. R package EBSeq and DESeq.2. qPCR validation	SARS-CoV-2 does not actively invade and reproduce in the brain. However, it may influence the expression of genes in the brain by downregulating key genes related to the hypoxia-inducing factor system (HIF).	Gagliardi et al., 2021
4.	Blood samples	Bioassay	Each of the 31 individuals possessed 2–7 receptor-agonist GPCRfAABs. These activate their target receptors, which have positive or negative chronotropic effects on cells.	Wallukat et al., 2021
5.	Blood samples	Blood tests	It shows the incidence and severity of chronic/post-COVID multiorgan symptoms and their correlations with acute illness characteristics,	Busatto et al., 2021

			sociodemographic variables, and individual- and neighborhood-level environmental variables.	
6.	Biological samples specifically cells of the neurovascular unit.	qPCR, immunoblotting, and immunostaining.	The neurovascular unit's cells, specifically astrocytes and microglial cells, possess functional receptors that are implicated in SARS-CoV-2 infection.	Torices et al., 2021
7.	Cortical organoids and blood vessel organoids	Characterization, culturing, observation of AD pathologies, and analysis of gene and protein expression.	The cortical-blood vessel assembloids display characteristics of Alzheimer's disease by stimulating glia following SARS-CoV-19 infection.	Kong et al., 2023
8.	Cerebrospinal fluid and serum samples	Proteomics, immunoassays and semiquantitative cytokine arrays, Autoantibody screening, RNA sequencing, DESeq2, Functional analysis	The cerebrospinal fluid (CSF) of COVID-19 patients exhibits comparable but significantly reduced inflammatory alterations compared to individuals with herpes simplex virus encephalitis (HSVE). This is characterised by a decrease in the expression of apolipoproteins and extracellular matrix proteins.	Reinhold et al., 2023
9.	Gene/protein sets	Network medicine methodologies, Clinical and multi-omics observations, interactions, transcriptomics, and proteomics.	It has been determined that the use of melatonin is linked to a reduced likelihood of contracting a COVID-19 infection.	Zhou et al., 2020
10.	Cerebrospinal fluid and plasma	Multiplex cytokine assay, Quantitative reverse transcriptase polymerase chain reaction, sequencing, and culturing,	The onset of COVID-19 may initially emerge as neurological symptoms, and the presence of inflammation in the central nervous system may be linked to the neurological	Farhadian et al., 2020

		Hydroxychloroquine and tocilizumab	manifestations of the disease.	
11.	Brain tissue	Systematic neuropathologic examinations, Modified Bielschowsky silver-stained sections, Aβ immunohistochemistry, α-synuclein immunostains, a semiquantitative scale	The study revealed that acute tissue damage and microglial activation were the predominant abnormalities observed in the brains of individuals with COVID-19. Although no virus was detected, distinct signs of encephalitis-like alterations were observed.	Agrawal et al., 2022
12.	Plasma samples	ELISA and neutralization assays, RT-qPCR	The study examined the humoral immune response to SARS-CoV-2 in COVID-19 patients who were either hospitalised or not, as well as in vaccinated volunteers.	Lucas et al., 2021
13.	Cerebrospinal fluid	Ultra performance liquid chromatography (UPLC)	NeuroCOVID patients exhibit signs of immunological activation and damage to the central nervous system, along with poor processing of amyloid.	Chaumont et al., 2023
14.	Spike glycoprotein	Computational biology validation, molecular docking analyses, multiple sequence alignment, relative phylogenetic analysis, homology modelling and validation.	The medication candidates Camostat, Favipiravir, Tenofovir, Raltegravir, and Stavudine exhibited substantial interactions with the spike RBD of SARS-CoV-2, indicating their potential as viable options for designing and developing innovative combinations of therapeutic formulations.	Toor et al., 2021
15.	Human pluripotent stem cells-derived neurons	Immunocytochemistry, Published reports, Previous studies, Autopsy studies	The article examines the presence of ACE2 in human neurons and suggests the potential for SARS-CoV-2 to invade and harm neurons in the	Xu & Lazartigues, 2022

			central nervous system of humans.	
16.	Blood sample	Siemens Healthineers Atellica IM sCOVG, B cell depleting therapies	In COVID-19 patients with reduced B cells, RBD antibody responses spike at lower and variable titers.	Bazzi et al., 2022
17.	Biological samples	Intergroup (anosognosic vs. nosognosic) analyses, nonparametric Mann-Whitney U tests, chi-square tests, characteristic (ROC) analysis	Circulating monocytes in the blood during the early stage of SARS-CoV-2 infection are linked to long-term post-COVID-19 anosognosia..	Nuber-Champier et al., 2022
18.	Spike protein	Membrane Optimal Docking Area (MODA) analysis, PPM server;	This study identifies several membrane binding sites on the closed spike head of the SARS-CoV-2 spike protein. These sites have a preference for convex membranes and are susceptible to the influence of pH, fatty acids, and post-translational modifications.	Tran et al., 2022
19.	Plasma samples	Longitudinal multi-omics analysis, consensus clustering, construction of an affinity matrix and sc-RNA-seq analysis.	Several early indicators can predict post-acute COVID-19 sequelae (PASC), such as autoantibodies, viremia, and comorbidities.	Su et al., 2022
20.	Peripheral blood and plasma samples	Transcriptomics, proteomics, metabolomics, Student's t-tests, random forest modelling -tests.	The immunopathology of COVID-19 leads to multi-organ damage due to dysregulated immunological responses, metabolic dysfunction, and organ impairment.	Chen et al., 2020
21.	Human iPSC-derived cardiomyocytes (hiPSC-CMs)	iPS-cardiomyocyte, SARS-CoV-2 propagation, PCR, Immunofluorescence staining, Neutral	WIN decreased the concentrations of interleukins six, eight, 18 and tumour necrosis factor-alpha (TNF-a)	Aragão et al., 2021

		red uptake cell viability assay, Western blotting, Statistical analyses.	generated by infected cells, and reduced cytotoxic damage as determined by the release of lactate dehydrogenase (LDH).	
22.	Peripheral blood samples	Enzyme linked immunosorbent assay method	The levels of Serum GFAP were markedly elevated in the severe group of COVID patients compared to the control group, although the levels of Serum S1ooB were comparable between the control and disease groups.	Sahin et al., 2022
23.	Human neurosphere	Investigate SARS COV 2 infection in human neural cells	SARS COV 2 infection of neural tissue is non-permissive, indicating that the virus is unable to reproduce in the brain's parenchyma.	da S.G. Pedrosa et al., 2021
24.	Blood sample	Sample collection and processing, multi omics analysis, statistical analysis, pathway analysis	Offer a comprehensive understanding of the immunological response to covid and contribute to the advancement of novel therapy and therapeutic approaches.	Ahern et al., 2022
25.	Brain tissue	neuropathological workshop including histological staining and immunohistochemical staining	The neuropathological abnormalities observed in patients with COVID-19 appear to be relatively modest, with the most commonly observed findings being pronounced neuroinflammatory changes in the brain.	Matschke et al., 2020
26.	Cortical neurons, astrocytes, microglia from stem cells	Induction method.	The original strain of SARS-CoV-2, as well as the delta and omicron variants, were incapable of infecting cortical neurons and astrocytes, but were able to infect microglia.	Kase et al., 2023

Table 4: Summary of findings from Animal model studies (In vitro or In vivo)

Number of study	Participants	Methods/ tools	Result	Reference
1.	Murine (lung tissue)	Quantitative PCR and Western blot, immunoassay, flow cytometry, bacterial cultures.	The study reveals a twofold rise in the quantity of ACE2 protein in mouse lungs within 24 hours following post-ischemic-reperfusion injury, but the levels of ACE protein remained constant.	Singh et al., 2021
2.	Hamster (monoclonal antibodies)	The isolation and characterization of potent human monoclonal SARS-CoV-2 neutralizing antibodies, crystal structures of two antibodies in complex with SARS-CoV-2 RBD, and evaluation of in vivo efficacy using the hamster model of COVID-19.	The antibody CV07-209 was specifically selected for assessment in the hamster model of COVID-19. The study illustrates that the administration of CV07-209, either as a preventive measure or as a treatment, effectively shielded the hamsters from experiencing weight loss and lung damage resulting from SARS-CoV-2 infection.	Kreye et al., 2020
3.	Rat (brain tissue)	Immunohistochemistry	ACE2 was discovered to be widely distributed in brain blood vessels, with the greatest concentration of ACE2-expressing capillaries observed in certain brain areas.	Hernández et al., 2021
4.	Transgenic mice (brain vascular pericytes)	cell based assay, in vivo experiments, protein analysis using BCA assay	Exposure to the spike protein of SARS COV 2 hampers the vascular and immunological regulatory functions of brain pericytes, leading to damage in the brain caused by vascular dysfunction.	Khaddaj-Mallat et al., 2021
5.	Mouse (Brain tissue,	Electron microscopy, recombinant mouse CCL11, gene	Mild respiratory COVID-19 affects the cells responsible for	Fernández-Castañeda et al., 2022

	serum and CSF)	expression analysis and cytokine analysis.	generating myelin and hippocampus neural precursors, while also boosting harmful substances and the activity of microglial cells in the white matter of the brain.	
6.	K18-hACE2 mice	Molecular modeling analyses, experimental studies in cells, in vitro binding assay of spike S1 to ACE2 in the absence or presence of melatonin, and measurement of exopeptidase activity of ACE2.	Melatonin and its derivatives, agomelatine and ramelteon, possess the ability to hinder the entry of SARS-CoV-2 into the brain and mitigate the detrimental effects caused by the virus on small cerebral blood vessels, infiltration of immune cells, and inflammation in the brain.	Cecon et al., 2022

Chapter 4

Discussion

4.1 Chronic neurological problems and abnormalities caused by SARS-CoV-2 :

As on the most recent information that I have, the long-term neurological effects of SARS-CoV-2, are still being actively observed and researched. Although most individuals who get COVID-19 have mild to moderate symptoms and recover fully, there is increasing evidence that a subset of people may develop persistent neurological issues and abnormalities after the initial phase of the illness. The chronic neurological issues identified in the investigation are as follows:

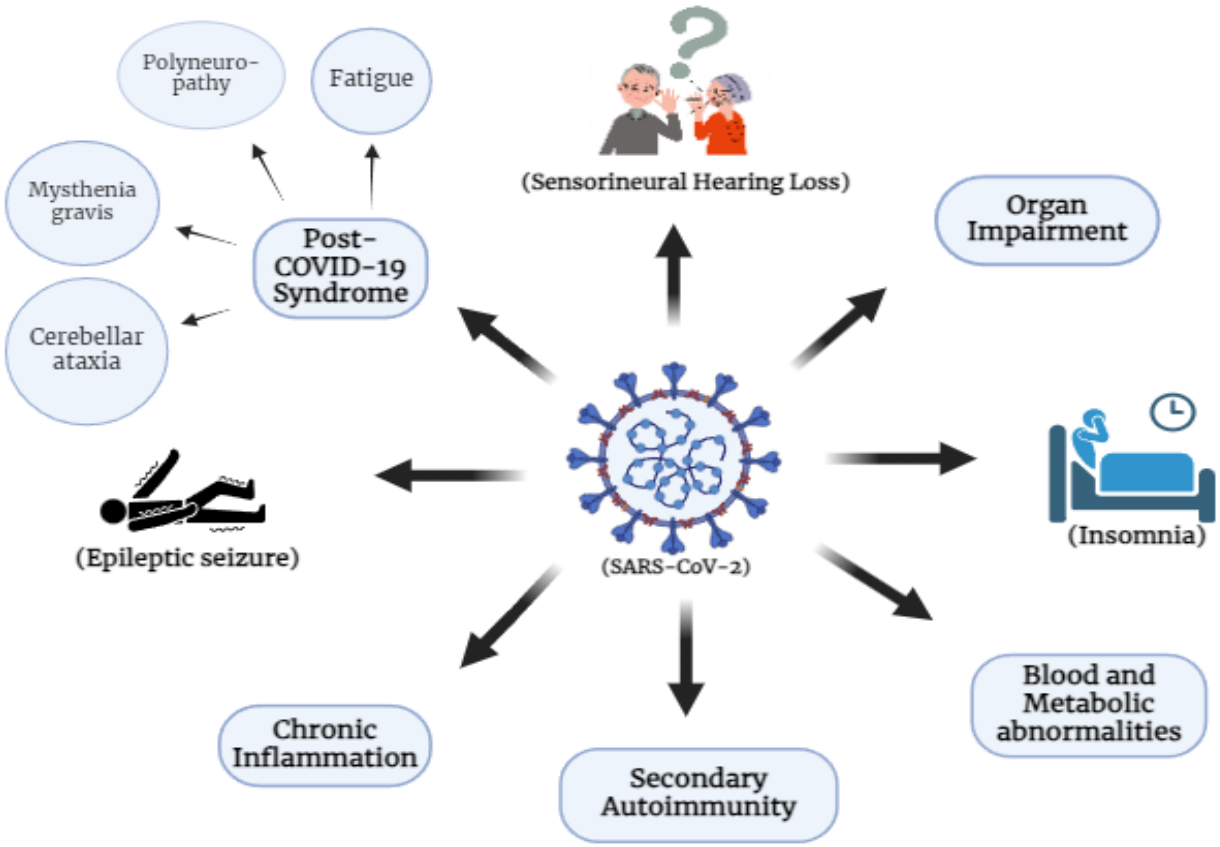

Figure 2: Chronic neurological problems and abnormalities due to SARS-CoV-2

4.1.1 Seizures and Epilepsy:

Within the population of individuals infected with COVID-19, a specific group of patients encountered seizures, and a portion of them developed seizures for the first time after being infected (Figure-2). A study conducted in a hospital revealed that 4.3% of individuals diagnosed with COVID-19 experienced acute symptomatic seizures. These seizures included both new onset seizures and breakthrough seizures in patients who had previously been diagnosed with epilepsy. The precise mechanisms behind seizures in COVID-19 are not completely understood. However, potential explanations include retrograde movement from the olfactory nerve, entry into the central nervous system (CNS) via circulating lymphocytes, or entry through the permeable blood-brain barrier (Khedr et al., 2021). It is important to mention that seizures are linked to pre-existing epilepsy, indicating that the virus may worsen or activate the condition. Additional investigation is required to comprehensively comprehend the precise methods via which the virus infiltrates the central nervous system in individuals affected with COVID-19.

4.1.2 Sleep Disorders :

Patients with COVID-19 have been found to experience insomnia and a decline in the quality of their sleep (Figure-2). A considerable proportion of patients experienced chronic sleep disturbances, which were correlated with distinct inflammatory biomarkers. The sleep disturbances observed in COVID-19 patients may be caused by an increase in inflammation, which affects both the immune system and the brain. This is indicated by elevated levels of neurofilament light chain and inflammatory cytokines. Poor sleep quality has been linked to these factors in patients who were previously hospitalized with moderate-to-critical symptoms (Pellitteri et al., 2022).

4.1.3 Post-COVID-19 Syndrome and Neurological Abnormalities:

The predominant post-COVID-19 syndrome encompasses symptoms such as fatigue (Figure-2), memory impairment, and cognitive difficulties sometimes referred to as "brain fog". A study was conducted to observe a group of 171 patients with post-COVID-19 syndrome. The most often reported issues among these patients were weariness, difficulties in attention, and memory loss. In a separate study, it was discovered that 27% of individuals who had recovered from COVID-19 exhibited symptoms similar to those of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). This conclusion was reached after conducting a comprehensive evaluation that included assessing lung function and measuring the levels of neurofilament light chain in the blood serum (Mantovani et al., 2021). The group exhibiting symptoms similar to ME/CFS demonstrated poorer sleep quality, increased fatigue, heightened pain, depressive symptoms, subjective cognitive complaints, and higher levels of baseline dyspnea on the 6-minute walking test, in comparison to individuals without ME/CFS-like symptoms. And mild respiratory COVID can lead to deregulation of neuronal cells and myelin in the brain. This mechanism entails an inflammatory reaction to COVID that triggers an increase in neurotoxic cytokines/chemokines, activation of microglial cells, and subsequent disruption of myelin-producing oligodendrocytes and hippocampal neural precursor cells. This mechanism could potentially contribute to the cognitive decline observed in certain individuals with COVID, including the condition commonly referred to as "COVID fog" or "brain fog" (Fernández-Castañeda et al., 2022).

Neurophysiological abnormalities remain present even 6 months from the onset of COVID-19. Neurophysiological abnormalities were observed in both sensory and motor nerve fibers within the research group. SARS-Cov-2 has the ability to damage the peripheral nerve fibers, leading to the development of polyneuropathy. The etiopathogenesis of peripheral neuropathy in patients with post-COVID remains unclear. Peripheral nerve injury in COVID-19 survivors

can be attributed to molecular mimicry, hyperinflammation, and deregulation of the immune system (Stępień & Pastuszak, 2023). The persistent abnormalities in sensory and motor nerve fibers, even after a span of six months following COVID-19, emphasize the prolonged effect on the neurological system. A further investigation revealed that mild cases of COVID-19 lead to functional and structural abnormalities in the central nervous system, with brain microhemorrhages being observed in patients with non-severe symptoms. The study additionally revealed that 49.06% of patients with EEG recordings that met the criteria displayed aberrant brain activity. Furthermore, 27.59% of the overall study group exhibited MRI results related with COVID-19 (Udzik et al., 2023).

In one study, 83% of the individuals had at least one neurological symptom, with an average duration of 8 +/- 6 days. The most prevalent neurological symptoms reported were headache (72%), reduced or loss of taste (41%), reduced or loss of smell (40%), and dizziness (34%) (Carcamo Garcia et al., 2021). Examine the various neurological symptoms seen in patients after being infected with SARS-CoV-2, including conditions including transverse myelitis, myasthenia gravis, cerebellar ataxia, and sensory motor polyneuropathy (Figure-2). The patient exhibited subacute ocular signs of myasthenia gravis following a normal COVID-19 infection, which included neurological symptoms such as headache and loss of smell or taste. The myasthenic syndrome was effectively treated with intravenous immunoglobulins and oral pyridostigmine (Huber et al., 2020). A solitary instance of post-infectious cerebellar ataxia has been seen in a patient with epilepsy and COVID-19. The research emphasises the significance of promptly identifying and managing neurological consequences of COVID-19, such as post-infectious cerebellar ataxia, in order to enhance patient outcomes (Chattopadhyay et al., 2022) . Quantitative sudomotor axonal reflex testing (QSART) revealed decreased sweat production in the forearm and foot areas, indicating a dysfunction in the postganglionic sympathetic

cholinergic sudomotor system caused by autonomic neuropathy. Autonomic dysfunction is anticipated to occur concurrently with or after to COVID-19 due to several factors. There is a strong correlation between a commonly occurring autonomic disease called POTS and previous or simultaneous infections. Other additional variables may also contribute to the onset or exacerbation of orthostatic tachycardia. The heart rate exhibited a continuous tachycardic response during the latter half of the tilt period, which corresponded with symptoms of orthostatic intolerance such as palpitations, exacerbation of headache, and dizziness (Agnihotri et al., 2022).

4.1.4 Neuroimmunological Disorders and Autoimmunity:

Certain individuals infected with COVID-19 may experience neuroimmunological problems and display symptoms of secondary autoimmunity (Figure-2). The majority of patients with neuroimmunological problems and SARS-CoV-2 infection experienced a mild form of COVID-19, with 84.6% of patients falling into this category (Moura et al., 2022). The research discovered that the presence of CSF lymphocytic pleocytosis and/or blood-CSF barrier dysfunction is linked to para-infectious encephalitis and polyradiculitis in patients infected with SARS-CoV-2. In specific cases, certain patients showed the presence of anti-GD1b and anti-Caspr2 autoantibodies, which raises the possibility of secondary autoimmunity induced by SARS-CoV-2 (Guilmot et al., 2021). CSF abnormalities and the presence of specific autoantibodies raises concerns about the potential of SARS-CoV-2 to trigger secondary autoimmune. A portion of the patients exhibited positive antiphospholipid antibodies, indicating a possible association between COVID-19 and autoimmune reactions. Out of the total of 71 patients, 21 tested positives for at least one type of aPL antibody. It is possible that anti phospholipid antibodies could contribute to the development of thrombosis in patients with

COVID-19 (K.Bitzogli,2021). These findings indicate that the virus could initiate immunological reactions that result in neurological problems.

4.1.5 MS Patients and COVID-19 Severity:

Multiple sclerosis (MS) patients with COVID-19 commonly have symptoms such as fever, cough, fatigue, and dyspnea. Additionally, smoking increases the probability of suffering several symptoms during COVID-19 (Schiavetti et al., 2022). The effect of COVID-19 on patients with pre-existing conditions, such as multiple sclerosis (MS), is diverse. The severity of COVID-19 in individuals with multiple sclerosis (MS) who are treated with ocrelizumab is mostly mild to moderate. Most patients do not need to be hospitalised. Additionally, the risk factors that are known to be associated with severe COVID-19 outcomes in the general population also seem to affect the severity of COVID-19 in ocrelizumab-treated individuals with MS. The mortality rates among individuals with MS who received ocrelizumab were consistent with the rates reported for the general population and other groups of individuals with MS (Hughes et al., 2021). However, it is important to note that Multiple Sclerosis patients who are treated with Rituximab may experience unpredictable results if they contract COVID-19. There is a possibility of developing severe symptoms and experiencing a prolonged infection due to the depletion of B-cells caused by Rituximab. This highlights the importance of humoral immunity in the recovery process. Disease severity was impacted by factors such as age, type of MS progression, time elapsed since Rituximab infusion, and dosage (Iyer et al., 2022). It is recommended to use caution when using Rituximab during COVID-19 and consider reducing the frequency and dosage if needed.

4.1.6 Cognitive Sequelae and Immune Response:

Neuropsychological testing revealed cognitive consequences in patients after recovering from COVID-19. A significant proportion of individuals who have recovered from COVID-19 exhibited abnormal scores in one or more neuropsychological tests, indicating the potential presence of cognitive sequelae within the clinical group (Rota et al., 2022). Post-lockdown people have heightened levels of inflammatory markers, suggesting possible long-term impacts on the immune system beyond the acute phase of the infection. Inflammatory markers, such as CRP, procalcitonin, TNFa, and sIL-2R, were found to be higher in hospitalised patients compared to non-hospitalized patients. Additionally, hospitalised patients showed significant associations with altered lipid metabolism markers, including increased levels of triglycerides and decreased levels of HDL-cholesterol (Bungenberg et al., 2022). Nevertheless, comparative examinations unveiled notable disparities in the amounts of I-TAC, IL-8, and TNF-伪 cytokines between the COVID-19 group and the group of healthy individuals. The I-TAC and IL-8 levels were higher in the healthy control group compared to the COVID-19 group, however the TNF-伪 level was raised in the COVID-19 group (He et al., 2023). The correlation analysis revealed a negative connection between TNF-伪 levels and cognitive ability.

Several early variables, including as autoantibodies, viremia, and comorbidities, can predict the occurrence of post-acute COVID-19 sequelae (PASC). The reactivation of latent viruses after the initial infection could potentially lead to Post-Acute Sequelae of SARS-CoV-2 (PASC), and the presence of subclinical autoantibodies is inversely related to the levels of anti-SARS-CoV-2 antibodies. Gastrointestinal PASC is characterized by the distinct occurrence of cytotoxic T cell proliferation throughout the post-acute phase (Su et al., 2022). Severe instances of COVID-19 exhibit persistent neutrophil activation, IFN-I signaling, and elevated levels of

inflammatory cytokines, whereas less severe cases demonstrate strong T-cell responses. Additionally, possible biomarkers have been identified to assist in predicting prognosis based on viral load (Chen et al., 2020). The utilization of melatonin and its derivatives, including agomelatine and ramelteon, was linked to a reduced likelihood of contracting COVID-19 (Cecon et al., 2022).

4.1.7 Blood Anomalies and Metabolic Imbalances:

The blood work showed abnormalities including a low white blood cell count (3.81k/microliter), low sodium levels (134 mmol/L), high fibrinogen levels (627 mg/dL), and increased Creatine Kinase (CK) levels (Figure-2). Furthermore, a urine culture tested positive for E. Coli with a concentration of more than 100,000 cfu/mL, suggesting possible systemic involvement (Sirbu et al., 2022)(Figure-2). Leucopenia signifies a reduction in the quantity of white blood cells, hyponatremia denotes abnormally low concentrations of salt in the bloodstream, and hyperfibrinogenemia suggests increased amounts of fibrinogen, a protein that plays a role in blood clotting. These data indicate that the patient's immune system may have been impacted by the SARS-CoV-2 infection, resulting in a reduction in white blood cells and changes in electrolyte levels and these abnormalities can have profound effects on the nervous system (Figure-2).

Monocytes present in the bloodstream at the initial stage of SARS-CoV-2 infection are linked to persistent post-COVID-19 anosognosia. An initial monocyte proportion of 7.35% of the total leukocyte count at admission appeared to be indicative of the development of chronic anosognosia 6-9 months following infection. Anosognosia occurring after COVID-19 may be caused by immunological abnormalities during the acute phase of SARS-CoV-2 infection (Nuber-Champier et al., 2022).

The existence of systemic abnormalities is indicated by notable findings of low sodium, increased C-reactive protein, and aberrant plasma and urine osmolality. The test results showed a low sodium level of 123 mmol/l, an elevated C-reactive protein level of 44 mg/L, and plasma and urine osmolality levels of 252 and 291, respectively. The research proposes that coronavirus infections, such as SARS-CoV and COVID-19, might directly affect the central nervous system (CNS). The specific mechanism through which SARS-CoV enters the CNS is still unclear, although it could potentially include entry through the olfactory bulb and subsequent dissemination via retrograde trans-synaptic transmission. The patient received treatment with antibiotics, specifically levofloxacin, as well as intravenous administration of 0.9% normal saline (Butt et al., 2020).

4.1.8 Organ impairment:

SARS-CoV-2 infection can cause both direct harm to organs and an incorrect immune response, leading to viral sepsis. Respiratory samples have tested positive for the presence of SARS-CoV-2 virus particles, indicating the potential for widespread distribution of these particles and their effects on several organs including the central nervous system (CNS) (Figure-2). COVID-19 instances have shown severe lung damage, specifically diffuse alveolar destruction, which can lead to respiratory failure and death. The disease pathogenesis hypothesis suggests that the combination of viral replication and an inadequate immune response contributes to the emergence of severe COVID-19 (Ducloyer et al., 2020).

4.1.9 Cerebral Microangiopathy and Endothelial Cell Changes:

COVID-19-associated cerebral microangiopathy is characterised by alterations in the brain's endothelial cells surrounding blood vessels, where the spike protein of the SARS-CoV-2 virus, which plays a crucial role in virus replication, has been detected in the Golgi apparatus. The interruption in the virus's process of releasing waste products in the cells that line the blood vessels in the brain may clarify the restricted infection and distinctive cerebral microangiopathy lesions (Boluda et al., 2023).

4.1.10 Autoimmune Gastrointestinal Dysmotility and Psychiatric Manifestations:

Favourable therapeutic results were noted for autoimmune gastrointestinal dysmotility and mania accompanied by psychotic characteristics induced by SARS-CoV-2 infection. The patient's autoimmune gastrointestinal dysmotility (AGID) that occurred after SARS-CoV-2 infection was effectively managed using intravenous immunoglobulin therapy (Montalvo et al., 2022). Patients with mania accompanied by psychotic characteristics are administered lamotrigine and haloperidol for treatment (Russo et al., 2021).

4.1.11 Sensorineural Hearing Loss (SSNHL):

COVID-19 could contribute to the occurrence of sudden sensorineural hearing loss (SSNHL) (Figure-2). According to the study, out of the 53 cases of verified COVID-19 and one patient who received a COVID-19 vaccine and reported sudden sensorineural hearing loss (SSNHL), the majority of patients experienced severe hearing impairment (Elmoursy et al., 2023).

4.2 Expression of ACE2:

4.2.1 Expression of ACE2 on animal model:

During the study of the rat brain, it was discovered that ACE2 is ubiquitously present in brain vasculature, with the highest density of ACE2 expressing capillaries found in specific regions of the brain and ACE2 was also found in astrocytes, pericytes, and endothelial cells, which are important parts of the blood-brain barrier (Figure-3). The study successfully detected ACE2-expressing neurons in the rat brain, specifically within established functional circuits. This finding enables the prediction of potential neurological effects resulting from ACE2 dysregulation in the brain during and after COVID-19 infection (Hernández et al., 2021).

4.2.2 Expression of ACE2 on human:

ACE2 is expressed in human neurons, supporting the neuro-invasive potential of the COVID-19 virus (Xu & Lazartigues, 2022). The cellular expression profile of ACE2 was examined in cells of the neurovascular unit, particularly astrocytes and microglial cells, which express active receptors involved in SARS-CoV-2 infection (Figure-3). The virus's S1 protein modified the expression of tight junction proteins, while HIV-1 infection enhanced the expression of ACE2 and TMPRSS2. These findings provide useful knowledge for prospective treatments of COVID-19-related problems in the central nervous system (Torices et al., 2021).

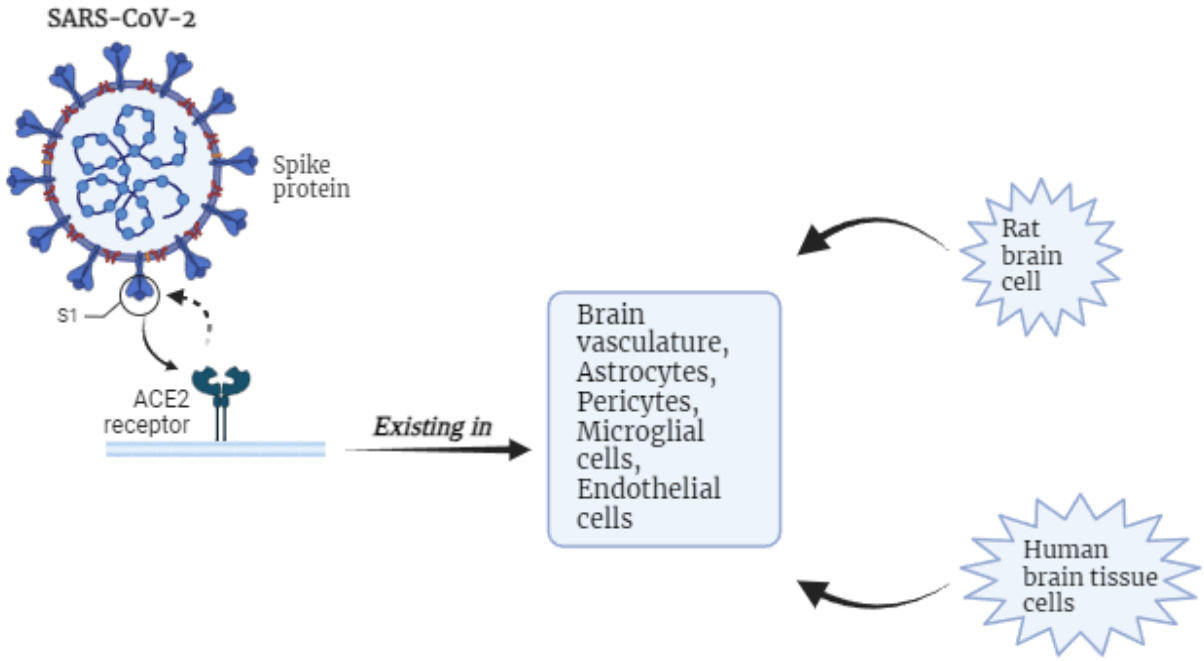

Figure 3: SAR-CoV-2-ace-2 receptor interaction and location

4.3 Therapeutic Insights:

While researching on animal model potent neutralising antibodies were discovered, protecting hamsters from lung pathology. The antibody CV07-209 was specifically selected for assessment in the hamster model of COVID-19. The results indicate that the administration of CV07-209 as a preventive or curative measure effectively shielded the hamsters from experiencing weight loss and lung damage resulting from SARS-CoV-2 infection (Kreye et al., 2020) (Figure-4). Multiple medications were discovered to interact with the spike protein, presenting possible therapeutic possibilities. The medication candidates Camostat, Favipiravir, Tenofovir, Raltegravir, and Stavudine exhibited notable interactions with the spike RBD of SARS-CoV-2, indicating their potential as choices for creating and advancing innovative combinations of therapies to treat COVID-19 (Toor et al., 2021). Melatonin, and its derivatives agomelatine and ramelteon, have the ability to inhibit the entry of SARS-CoV-2 into the brain (Figure-4). Additionally, they can mitigate the damage caused by the virus to small blood vessels in the brain, minimise the infiltration of immune cells, and alleviate brain

inflammation. It inhibits the entry of SARS-CoV-2 by attaching to a specific location on human angiotensin-converting enzyme 2 (ACE2), hence disrupting ACE2's role as a receptor for viral entry (Cecon et al., 2022). It is well established that cannabinoids reduce the release of pro-inflammatory cytokines, thereby having anti-inflammatory effects. In this study, we examined the effects of the cannabinoid agonist WIN 55,212-2 (WIN) on SARS-CoV-2-infected human iPSC-derived cardiomyocytes (hiPSC-CMs). WIN did not alter the levels of angiotensin-converting enzyme II protein, nor did it decrease viral infection and replication in hiPSC-CMs. However, WIN did decrease the levels of interleukins six, eight, 18, and tumour necrosis factor-alpha (TNF-a) that were released by infected cells. Additionally, WIN reduced cytotoxic damage as measured by the release of lactate dehydrogenase (LDH) (Figure-4). The observed effects on human cardiomyocytes infected with SARS-CoV-2 may be attributed to the anti-inflammatory characteristics of cannabis. The study revealed a reduction in the release of pro-inflammatory cytokines, which could be attributed to the negative modulation of cannabinoids on cytokine release (Aragão et al., 2021).

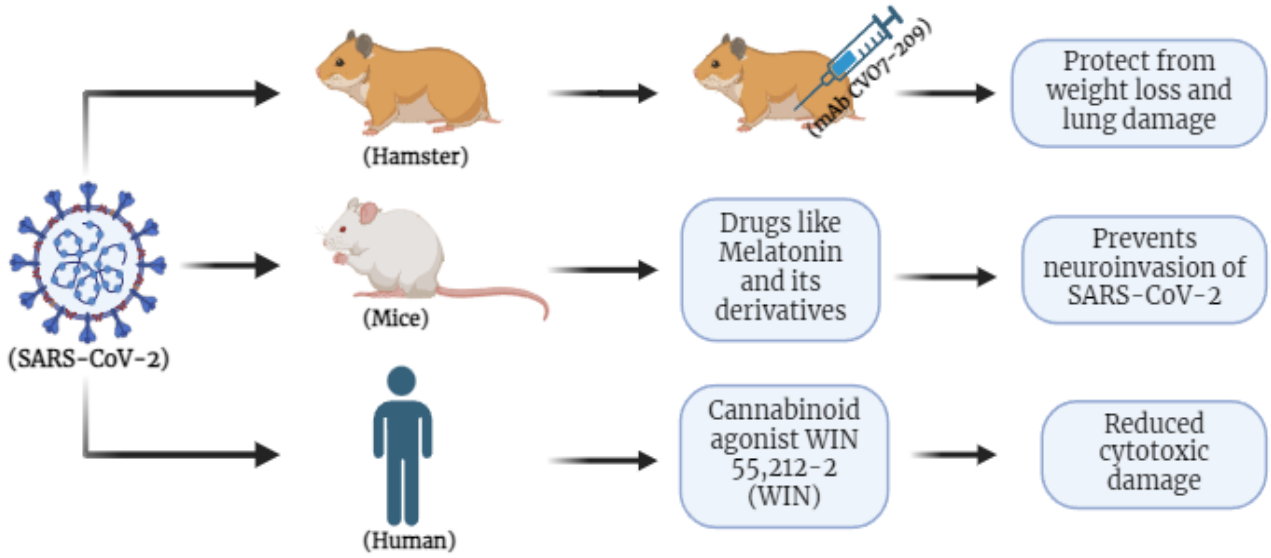

Figure 4: Therapeutic insights of SARS-CoV-2

Chapter 5

Conclusion

In conclusion, this paper explores the thorough examinations carried out on the long-term neurological effects of SARS-CoV-2, with a specific focus on research including biological samples. The COVID-19 pandemic, which was initially known for its impact on the respiratory system, has uncovered a wide range of neurological symptoms, including seizures, sleep difficulties, persisting post-COVID-19 syndrome, and neuroimmunological illnesses.

Cohort studies have shown multiple facets of the neurological consequences, establishing links between COVID-19 and disorders such as seizures, sleep disruptions, post-COVID-19 syndrome, and neurophysiological irregularities. Furthermore, inquiries have brought attention to the susceptibility of particular demographics, such as pediatric patients and individuals with pre-existing diseases such as multiple sclerosis. The virus has the ability to generate secondary autoimmune, making autoimmunity and neuroimmunological illnesses significant contributors. The presence of blood abnormalities and metabolic imbalance results, together with the occurrence of acute sensorineural hearing loss, contribute to the complex neurological effects. In animal models and people, ACE2 is found in the brain vasculature, neurons, astrocytes, and microglial cells, suggesting SARS-CoV-2 neuro-invasion. Therapy encompasses neutralizing antibodies like CV07-209 that protect the lungs and melatonin derivatives that reduce brain inflammation and viral entrance. The cannabinoid agonist WIN 55,212-2 reduces pro-inflammatory cytokine production and cytotoxic damage in SARS-CoV-2-infected human cardiomyocytes, suggesting it may treatment COVID-19.

Essentially, this thorough analysis highlights the crucial significance of comprehending the enduring neurological consequences of SARS-CoV-2. The findings together contribute to the ongoing discourse regarding COVID-19, providing guidance for future research, clinical practices, and public health actions.

Chapter 6

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