frontiers | Research Topics

The NeuroCOVID-19 syndrome: Cognitive and psychological profiles, physiopathology, and impact on neurologically vulnerable populations

Edited by
Ludivine Chamard-Witkowski, Caroline Jose and Thorsten Rudroff

Published in
Frontiers in Neurology

ISSN 1664-8714
ISBN 978-2-8325-5244-5
DOI 10.3389/978-2-8325-5244-5

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

The NeuroCOVID-19 syndrome: Cognitive and psychological profiles, physiopathology, and impact on neurologically vulnerable populations

Topic editors
Ludivine Chamard-Witkowski — Université de Sherbrooke, Canada
Caroline Jose — Vitalité Health Network, Canada
Thorsten Rudroff — The University of Iowa, United States

Citation
Chamard-Witkowski, L., Jose, C., Rudroff, T., eds. (2024). *The NeuroCOVID-19 syndrome: Cognitive and psychological profiles, physiopathology, and impact on neurologically vulnerable populations*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-5244-5

Prof. Ludivine Chamard-Witkowski acts as Principal Investigator in clinical trials funded by Cassava Sciences and Merck group. Dr. Caroline Jose is co-author on a patent on Local anesthetics and use thereof in cancer (European Patent N.13306023.6, 08/2013) and she is founder and owner of the translation services company AntonymeRedaction©. Prof. Thorsten Rudroff declares no competing interests with regard to the Research Topic subject.

Table of contents

frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 19 July 2024
DOI 10.3389/fneur.2024.1452895

OPEN ACCESS

EDITED AND REVIEWED BY
Christina M. Marra,
University of Washington, United States

*CORRESPONDENCE
Caroline Jose
caroline.jose@vitalitenb.ca

RECEIVED 21 June 2024
ACCEPTED 04 July 2024
PUBLISHED 19 July 2024

CITATION
Jose C, Rudroff T and Chamard-Witkowski L (2024) Editorial: The NeuroCOVID-19 syndrome: cognitive and psychological profiles, physiopathology, and impact on neurologically vulnerable populations. *Front. Neurol.* 15:1452895. doi: 10.3389/fneur.2024.1452895

Editorial: The NeuroCOVID-19 syndrome: cognitive and psychological profiles, physiopathology, and impact on neurologically vulnerable populations

Caroline Jose[1,2,3]*, Thorsten Rudroff[4] and Ludivine Chamard-Witkowski[1,2,5]

[1]Centre de Médecine de Précision, Centre Hospitalier Universitaire Georges-L.-Dumont, Réseau de Santé Vitalité, Moncton, NB, Canada, [2]Département de Médecine de Famille et de Médecine d'urgence, Faculté des Sciences de la Santé, Université de Sherbrooke, Sherbrooke, QC, Canada, [3]Département de Chimie et de Biochimie, Faculté des Sciences, Université de Moncton, Moncton, NB, Canada, [4]Department of Neurology, University of Iowa, Iowa City, IA, United States, [5]Centre de formation médicale du Nouveau-Brunswick, Moncton, NB, Canada

KEYWORDS

long COVID, sequelea, cognitive dysfunction, neurological involvement, NeuroCOVID, imaging, biomarkers, physiopathological mechanism

Editorial on the Research Topic
The NeuroCOVID-19 syndrome: cognitive and psychological profiles, physiopathology, and impact on neurologically vulnerable populations

1 Introduction—From COVID-19 to NeuroCOVID

The Coronavirus Disease 2019 (COVID-19) global pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has led to the identification of a broad range of post-acute COVID-19 neurological symptoms including cognitive impairments, executive dysfunctions, changes in sleep, emotional distress, pain and fatigue (1). Alarmingly, those post-acute sequelae of COVID-19 (PASC) can occur several weeks after infection, arise after severe, mild, or even asymptomatic SARS-CoV-2 infection, and are characterized by the persistence, worsening, or new onset of chronic and debilitating neurological symptoms, which have led to the use of NeuroCOVID syndrome terminology (2, 3).

Despite a global research effort in describing PASC, there are still many research challenges and many open questions, particularly relating to pathophysiology, specific biomarkers, effective treatments (3) and risk factors of cognitive deficits and other neurological manifestations (4).

The goal of this Research Topic was to consolidate and deepen our actual knowledge on cognitive and neuropsychological symptoms in NeuroCOVID syndrome. We highlight below the unique contributions to the Research Topic of 10 articles (seven reviews, one original article, and one case report), and discuss their findings in the broader context of the methodological pitfalls, knowledge gaps and future research needs in post-acute sequelae of COVID-19 (referred interchangeably to post-acute COVID-19 syndrome, PASC or NeuroCOVID in this editorial article).

2 Toward a comprehensive pathological understanding

Li et al. provide a broad perspective on the clinical and basic evidence of cognitive impairment following COVID-19 through an overview of the latest neuropsychological and neuroimaging findings. They then detail the five mechanisms by which COVID-19 may impair cognitive function and lead to memory loss, namely through (1) direct viral damage to the central nervous system (CNS), and indirect mechanisms such as (2) inflammation effects, (3) vascular and hypoxic changes, (4) metabolic impacts, and (5) immune response.

Interestingly, Bouhamdani et al. describe a unique case presentation of *Nocardia farcinica* cerebral abscess in a male patient with sudden immunodeficiency several months after mild COVID-19. This case strengthens the notion of immunomodulation after COVID-19 and well after the viral infection has cleared, and draws attention to the need for timely consideration of opportunistic infections for patients with a history of COVID-19.

Focusing on inflammation effects, Saucier et al. propose that disturbance of reactive microglia and astroglia potentially contribute to neurological impairment after COVID-19. They further illustrate an indirect pathway, where microglial activation and neuroinflammation are consequential repercussions of systemic inflammation induced by the SARS-CoV-2 virus infection and resulting in the blood-brain-barrier breakdown. They propose that the translocation of peripheral cytokines and immune cells to the CNS culminates in microglial activation and brain neurological damage.

Strikingly, in their original research article, Havdal et al. found no evidence of ongoing neuroinflammation, and neither brain injury biomarkers nor neurocognitive test results that were associated with subjective reported symptomatology. The discrepancy between subjective symptoms and objective findings adds to a growing body of evidence suggesting that PASC may be associated with functional CNS alterations and have origins more related to a combination of biological, psychological and social factors, rather than being solely biomedical in nature.

Even more surprising, they report that the SARS-CoV-2 infection status was not associated with PASC. Indeed, the percentage of PASC in the non-infected and in the infected groups were almost equal, at 47 and 48%, respectively, 6-month after the infection or baseline assessment. While some study limitations might partly explain these findings, Lavin et al. also discuss the possibility that the symptoms of PASC, notably pain, may arise independently of neuronal damage and/or interoceptive afferent signals, referring to published evidence of psychosocial factors as important predictors of persistent symptoms in PASC, at least in a subset of the patient population.

Therefore, it is still to be established whether the subjective experience of neurological and neuropsychological symptoms in PASC correspond with objectively measurable deficits.

3 The search for biomarkers

To determine the incidence of the common neurological abnormalities using magnetic resonance imaging (MRI) in patients with severe COVID-19, Boparai et al. conducted a meta-analysis including 32 studies. They report the incidence of any MRI abnormality to be 55%, with most injuries appearing to be of vascular origin. They note, however, that the presentation of brain injury was diverse among the studies with no substantial pattern of injury emerging. Moreover, their analysis of the association between MRI abnormalities and clinical findings further confirms that there are likely many mechanisms, both direct and indirect, by which brain injury occurs in COVID-19 patients.

Both Okrzeja et al. and Cull et al. reviewed findings obtained with several neuro-imaging modalities to identify NeuroCOVID-specific biomarkers. Okrzeja et al. reviewed neuroanatomical findings from three imaging modalities and their utility in differential diagnoses, namely, magnetic resonance imaging (MRI), positron emission tomography/computed tomography (PET/CT; and more specifically 18F-FDG-PET/CT), and computed tomography (CT). Notably, they highlighted the potential pathophysiological link between PASC and Guillain-Barré syndrome based on MRI findings that needs to be further explored. Cull et al. expanded their review to describe findings obtained with other advanced imaging techniques, such as SPECT imaging, 18F-Amyloid-PET/CT, structural MRI, functional MRI, diffusion MRI, and Susceptibility-weighted imaging.

Both studies highlight the potential of hypometabolism, as revealed by 18F-FDG-PET/CT in a subset of studies, as a quantitative marker of cerebral damage of post-COVID-19 syndrome. However, limitations and inconsistent findings highlighted by those two reviews led both teams to suggest combining different neuro-imaging modalities, from structural imaging to functional and metabolic imaging, to identify more specific and sensitive neurological markers of NeuroCOVID.

Overall, although numerous radiological findings have been reported in PASC patients, few studies have been able to link the brain lesions to the PACS symptoms. Comeau et al. reached similar conclusions from their review of studies using blood, plasma and/or cerebrospinal fluid biomarkers of neuronal injury and of inflammatory processes in PASC patients, stating that usefulness of the liquid biomarkers studied so far remains tenuous because of the heterogeneity of findings and of our insufficient state of knowledge on PASC.

4 The blurred line with neurodegenerative diseases

Complicating the understanding of NeuroCOVID pathophysiology is the symptoms' overlap with other neurological conditions (4).

The review published by Shajahan et al. explores the complex interrelationships between COVID-19 and Alzheimer's disease. They explain that Alzheimer's pathological terrain, such as increased proinflammatory cytokines, NLRP3 activation, and oxidative stress, even during its asymptomatic phase, could be a risk factor for severe neurological impact of SARS-CoV-2 infection. On the other hand, COVID-19 could trigger the onset of Alzheimer's disease by modulating pathological pathways in the brain that are common between both diseases through the direct or indirect mechanisms described by Li et al.

5 Summary and future directions

Through this Research Topic, we hoped to improve the knowledge of the risk factors and physiopathology of the NeuroCOVID cognitive deficits and other neurological manifestations. While there is still much more research that needs to be done to reach that goal, we believe that this Research Topic will initiate discussions on the psychosocial involvement as well as on the predictive value of objective neurological biomarkers in NeuroCOVID research and care.

From this Research Topic, we can draw three main conclusions:

- A complete and clear picture of the NeuroCOVID syndrome is hampered by the non-specific nature of the majority of clinical manifestations in the PASC spectrum, the lack of relevant control groups in most studies, and other methodological issues, such as small sample sizes or heterogeneous samples.
- The development and validation of biomarkers that can be employed for the prediction, diagnosis and prognosis of NeuroCOVID will stem from studies combining multimodal neuroimaging, liquid biomarkers investigation, and a thorough clinical assessment (including medical history, comorbidities and neuropsychological testing).
- The state of knowledge on NeuroCOVID lags behind the increasing care needs for patients experiencing PASC because of the varied factors impacting the clinical trajectories of both acute and long COVID-19 (clinical, Sociodemographic, genetic, psychosocial, environmental, ect.).

Large scale and multidisciplinary studies adequately designed to stratify the PASC population in subgroups of PASC symptoms profiles could help to better refine the risk factors associated with each of those different COVID-19 trajectories. Those subgrouping efforts could eventually guide the development of precision medicine and precision public health for the management of this post-COVID-19 clinical reality and of future pandemics.

Author contributions

CJ: Conceptualization, Writing – original draft, Writing – review & editing. TR: Writing – review & editing. LC-W: Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We acknowledge and are appreciative of the contributions of all authors that brought value and insightful perspectives to this Research Topic.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127

2. Helbok R, Chou SH, Beghi E, Mainali S, Frontera J, Robertson C, et al. NeuroCOVID: it's time to join forces globally. *Lancet Neurol.* (2020) 19:805–6. doi: 10.1016/S1474-4422(20)30322-7

3. Gheorghita R, Soldanescu I, Lobiuc A, Caliman Sturdza OA, Filip R, Constantinescu-Bercu A, et al. The knowns and unknowns of long COVID-19: from mechanisms to therapeutical approaches. *Front Immunol.* (2024) 15:1344086. doi: 10.3389/fimmu.2024.1344086

4. Jose C. Breaking through the noise: how to unveil the cognitive impact of long COVID on pre-existing conditions with executive dysfunctions? *Front Psychiatry.* (2024) 15:1390214. doi: 10.3389/fpsyt.2024.1390214

frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 09 February 2023
DOI 10.3389/fneur.2023.1136348

OPEN ACCESS

EDITED BY
Thorsten Rudroff,
The University of Iowa, United States

REVIEWED BY
Eric Guedj,
Aix-Marseille Université, France
Alexandra Fietsam,
The University of Iowa, United States

*CORRESPONDENCE
Jakub Okrzeja
jakubokrzeja086@gmail.com

SPECIALTY SECTION
This article was submitted to Neuroinfectious Diseases, a section of the journal Frontiers in Neurology

RECEIVED 03 January 2023
ACCEPTED 25 January 2023
PUBLISHED 09 February 2023

CITATION
Okrzeja J, Garkowski A, Kubas B and Moniuszko-Malinowska A (2023) Imaging and neuropathological findings in patients with Post COVID-19 Neurological Syndrome—A review. *Front. Neurol.* 14:1136348. doi: 10.3389/fneur.2023.1136348

Imaging and neuropathological findings in patients with Post COVID-19 Neurological Syndrome—A review

Jakub Okrzeja[1]*, Adam Garkowski[2], Bożena Kubas[2] and Anna Moniuszko-Malinowska[3]

[1]Medical University of Białystok, Białystok, Poland, [2]Department of Radiology, Medical University of Białystok, Białystok, Poland, [3]Department of Infectious Diseases and Neuroinfections, Medical University of Białystok, Białystok, Poland

Post COVID-19 syndrome is determined as signs and symptoms that appear during or after an infection consistent with SARS-CoV-2 disease, persist for more than 12 weeks and are not explained by an alternative diagnosis. This review presents the neuropathological findings and imaging findings in Post COVID-19 Neurological Syndrome: the focal point is on the manifestations of involvement evident on brain and spine imaging.

KEYWORDS

Post COVID-19 syndrome, Post COVID-19 Neurological Syndrome, COVID-19, imaging, magnetic resonance imaging, computed tomography, positron emission tomography

Introduction

The quickly developing coronavirus disease 2019 (COVID-19) pandemic was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Furthermore, the first cases of this illness were reported in Wuhan, Hubei Province, China (2). SARS-CoV-2 is typically connected with pulmonary infection which results in pneumonia, but recent studies indicate that other organs may be affected e.g., in the cardiovascular, immune, gastrointestinal and nervous systems (3).

Due to its strong affinity for the human angiotensin-converting enzyme 2 (ACE2) receptor, SARS-CoV-2 might infect the nervous system directly. This receptor is also present in neuronal and glial cells which might explain the observed neurological symptoms including: anosmia, peripheral neuropathy, and cerebrum disorders. In post-mortem studies, particles of SARS-CoV-2 were identified in the cerebrospinal fluid (CSF) and in the cytoplasm of hypothalamus and neocortex cells. Other findings in post-mortem studies were e.g., neuronal degeneration and death, oedema, cellular infiltration, and hyperplasia of the glial cells. An animal model research revealed that SARS-CoV-2 enters the central nervous system (CNS) *via* the olfactory bulb, expanding to nearby regions of the brain and causing significant perivascular inflammatory reaction and meningitis (4).

Case definitions

Post COVID-19 syndrome is defined by the World Health Organization (WHO) as "condition which occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis" (5).

Furthermore, it has been suggested that in treated individuals, coronavirus stays latent in the CNS for an extended period of time, capable of reactivating and causing neurological problems (4). Post COVID-19 Neurological Syndrome (PCNS) might comprise symptoms associated to residual inflammatory reaction, organ failure, and the influence on pre-existing diseases (6). Secondary hypoxia, cytokine-related dysfunction, and retrograde transit *via* the olfactory nerve and bulb are factors which could cause reactivation of SARS-CoV-2 (7).

Another point is that the pandemic numbers underline the importance of thorough and constant follow-up of all people with COVID-19, including those who are initially asymptomatic patients in the acute stage of the disease, with routine screening for possible long-term neurological effects. Such situations also need continuous contact between primary care physicians and neurologists in order to appropriately document and analyze them (8). A literature search was carried out in PubMed for this review to identify studies that included neuroimaging and neuropathological examinations of patients with PCNS. The keywords used to carry out this search were: (1) "COVID-19," "Post COVID-19," "Post COVID-19 syndrome," and "Post COVID-19 Neurological Syndrome" for the PCNS; (2) "neuropathology," "autopsy," "post-mortem," "neuropathological," "neuroimaging," "brain," "MRI," "magnetic resonance imaging," "PET," "positron emission tomography," "neuroradiology," and "vasculitis" for the neuroimaging/neuropathological findings. All article entries resulting from the initial search were screened to identify publications reporting original data, with no restrictions on the type of manuscript. The objective of this review is to describe radiological features which can be found in many cases of PCNS. It might be helpful for physicians and neurologists diagnosing PCNS.

Neuropathological findings after COVID-19

The most common neuropathologies of brain discovered in COVID-19 patients' autopsies are dispersed ischaemic/hypoxic damage, acute and subacute infarcts which could be big or slight—sometimes with a hemorrhagic constituent, vascular congestion that might be related to the hemodynamic lesions caused by the infection, and dispersed and focal microglial activation with destruction of neurons by phagocytic cells mainly localized in the lower part of brainstem (9, 10). It is not certain that all these lesions were caused by SARS-CoV-2, because some of the individuals were chronically ill and it is impossible to confirm whether all examined patients died of COVID-19 (9). Furthermore, neuronal injury and death in the lower part of brainstem might result in a variety of clinical manifestations, such as: abnormal cardiorespiratory regulation, lethargy, insomnia, and other clinical signs (9). Therefore, it is probable that associations between neurons and microglia were rather secondary to hypoxic/ischaemic damage, in the context of a systemic inflammatory response, than to a direct reaction to SARS-CoV-2 infection of nerve cells (9). Moreover, there was little T cell infiltration and no indication of acute vascular wall injury (9) (Figure 1).

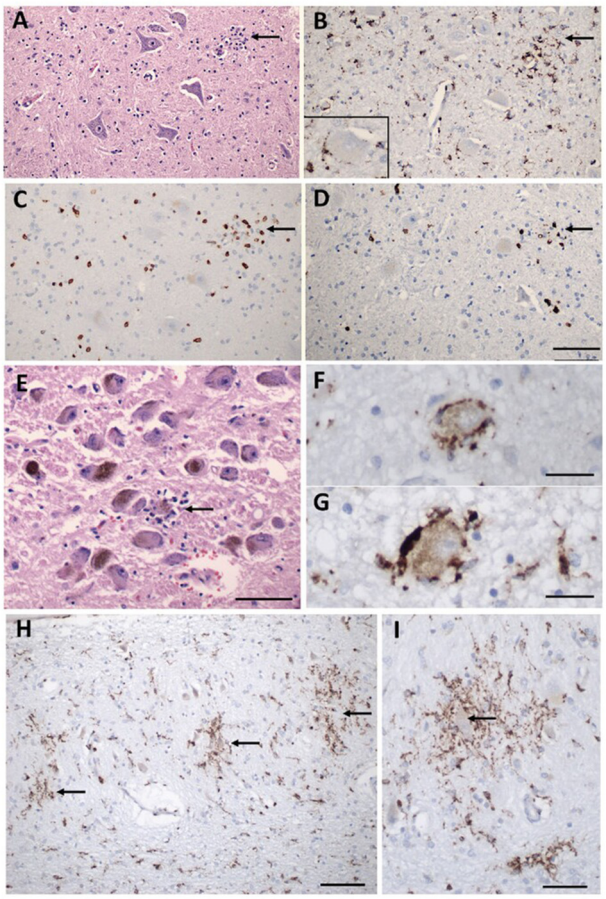


FIGURE 1
Inflammatory pathology in COVID-19 brains. **(A)** Section of the hypoglossal nucleus shows several motor neurons and a microglial module (*arrow*). **(B)** An adjacent section stained for CD68, showing clustered microglia in the nodule. Inset: Microglia in close apposition to a hypoglossal neuron (CD68). **(C)** An adjacent section stained for CD3, showing scattered T cells in the tissue and associated with the microglial nodule. **(D)** An adjacent section stained for CD8 showing that many of the T cells are CD8 +. **(E)** The locus coeruleus contains a microglial nodule with a degenerating neuron in the center, identified by its residual neuromelanin (*arrow*). **(F, G)** Neurons of the dorsal motor nucleus of the vagus surrounded by CD68 + microglia. **(H, I)** Microglial nodules in the dentate nucleus (*arrows in* **H**), neuron in the middle of a nodule (*arrow in* **I**), CD68. Scale bar in **(D)** = 200 μm for **(A–D)**; in **(E)** = 10 μm; **(F, G)** = 50 μm; **(H)** = 100 μm; **(I)** = 50 μm. Adapted from Thakur et al. (9) (License Number 5472500477340).

The ability of SARS-CoV-2 to infect and replicate within the human brain has been demonstrated beyond a shadow of a doubt by the detection of genomic RNA and subgenomic RNA through polymerase chain reaction (PCR), numerous imaging methods presenting SARS-CoV-2 RNA and protein within cells of the CNS, and sequencing in the CNS (10) but quantitative real time-PCR (RT-PCR) on multiple frozen cerebral samples from many cerebrums revealed low or undetectable amounts of RNA of SARS-CoV-2. While there is significant heterogeneity among brain regions, the comparatively low concentrations of viral RNA imply that SARS-CoV-2 has weak CNS tropism (9). Interestingly, studies have shown that SARS-CoV-2 can occur in most regions of the nervous system, including both hemispheres, brainstem, thalamus, sciatic nerves, except the dura mater (9, 10).

Neurological and neuropsychiatric manifestations of Post COVID-19 Neurological Syndrome

The impact of the acute phase of COVID-19 on the nervous system should be discussed to highlight the differences between acute phase of COVID-19 and PCNS. Even though some neurological consequences in COVID-19 patients have been found, the exact association between the infection and the nervous system diseases is unclear. In clinical studies conducted in Wuhan (China) 36.4% of the COVID-19 patients had CNS symptoms and 8.9% had peripheral nervous system (PNS) symptoms (11). Neurological symptoms may not usually indicate a direct infection of the CNS or PNS, but can be the result of a strong systemic response to a COVID-19 outside the CNS or PNS. Nevertheless, recently reported cases of meningitis and encephalitis, associated with the coronavirus illness, imply that SARS-CoV-2 can directly attack the neurological system (12). Acute COVID-19 manifestations such as pain in muscles, vertigo, headaches, and disorders of concentration may have a neurological cause and continue after the acute period (13, 14). Furthermore, small emboli in cerebrum (15, 16), blood-brain barrier (BBB) failure (17, 18), inflammatory reactions in CNS (19) resulting in coagulopathy, and hospital admission initiators (e.g., mechanical ventilation and sedatives) may all have a role in long-term neurological issues (19, 20).

Post COVID-19 syndrome includes psychiatric problems caused by social isolation, panic, and the loss of family members (20). The hospitalization and intensive care unit (ICU) stay, as well as the duration of critical disease, are likely to impact the occurrence of neuropsychiatric disorders after infection too (18). Moreover, chronic symptoms can be caused by a mix of physiological factors. Coronavirus RNA, for instance, might persist in cerebrum tissue for an extended period of time, exacerbating neurodegeneration (14, 21–23). Furthermore, innate immune cell infiltration associated with BBB failure may extend neuroinflammatory processes (21, 24). In addition, injury during acute illness, and chronic exhaustion are strongly linked to the development of neuropsychiatric disorders after infection (mainly sleep difficulties) (25).

The most common signs of neurological and neuropsychiatric Post COVID-19 syndrome are exhaustion, cognitive disorders such as brain fog, memory difficulties, difficulty concentrating, and sleep abnormalities which might be found in nearly one-third of individuals 12 weeks following the beginning of acute COVID-19 disease. Moreover, these symptoms remains and are much more prevalent in the short period (3–6 months) than in the long period of time (above half year after infection) (20, 26).

Furthermore, atrophy of the hippocampus and cortex (23, 27, 28), ischemic alterations (29), and small vessel disease (SVD) (30) have been demonstrated to develop as a result of inflammatory reactions and oxidative stress during COVID-19 (23, 31). The long-term effects of these processes might show as cognitive impairment e.g., brain fog, memory difficulties, difficulty concentrating.

Anosmia, i.e., loss of the sense of smell, dysgeusia, i.e., taste disturbance, and headaches are prevalent symptoms of acute COVID-19 disease, but they are not significant features of PCNS (suggesting that these particular manifestations often disappear). In a retrospective study, individuals who experienced anosmia or taste disturbance during acute coronavirus illness, 68% regained their sense of smell and above 70% regained taste after almost 2 months from the beginning of the symptoms (32).

Less common disorders in PCNS are: Guillain-Barré syndrome (GBS), polyneuropathy, myopathy, encephalopathy, post-infectious transverse myelitis, seizures, parkinsonism, orthostatic hypotension which is connected with vasovagal syncope, strokes and neuro-ophthalmology problems, i.e., post-infectious optic neuritis—these disorders have been found in some of the individuals at the 12 weeks follow-up (33).

GBS has been more common since the epidemic began. Some papers have been published showing the link between SARS-CoV-2 infection and GBS (34). The great majority of GBS patients with COVID-19 have been para infectious, whereas GBS after infection is rare (35). There were twelve GBS cases described after healing from COVID-19. In this context, there is increased interest in the connection between COVID-19 and the progression of GBS which typically occurs during the early stages of infection (36). Several hypotheses have been proposed to describe the genesis of GBS following COVID-19. The most likely mechanism is the production of antibodies against SARS-CoV-2 surface glycoproteins which might induce peripheral nerve damage due to similar native protein forms (34).

Consistent with previous studies, the chance of cerebrovascular episodes rose after COVID-19, with the frequency of ischemic stroke rising to roughly 1 in 10 (20). SARS-CoV-2 may cause stroke by a number of processes, such as: invasion of the vessel walls which results in coagulopathy due to endothelial inflammatory reactions, heart damage which results in clot formation, or destabilization of an atheroma plaques (37). Stroke has been observed in multiple studies about active COVID-19 disease, but stroke following COVID-19 without active illness has only been described in a few clinical studies (38).

According to analyses on SARS-CoV-1 and MERS, the majority of individuals return to full health after these viral diseases and might have many neurological sequelae even years later (39). Despite extensive studies on COVID-19 neurological symptoms and sequelae, only a few examples of neurological effects after full recovery from COVID-19 illness have been reported (40).

Which radiological features can we find in the imaging of the Post COVID-19 Neurological Syndrome?

Radiological examinations are one of the most important aspects of the diagnosis of many diseases. They are very often needed by doctors to confirm their current diagnostic hypotheses. PCNS is a relatively new neurological disorder, so only few studies describe the radiological imaging in the PCNS. This review brings together the radiology achievements of the PCNS imaging. The most useful types of imaging of the PCNS are magnetic resonance imaging (MRI), positron emission tomography/computed tomography (PET/CT) and computed tomography (CT).

The capacity to perform a whole-body examination, good individual compliance, and a high safety profile are benefits of PET/CT (41). The brain 18F-FDG-PET signal was taken as a direct indicator of neuronal activity (41). Local glucose metabolism and 18F-FDG brain uptake have been shown to be connected with the

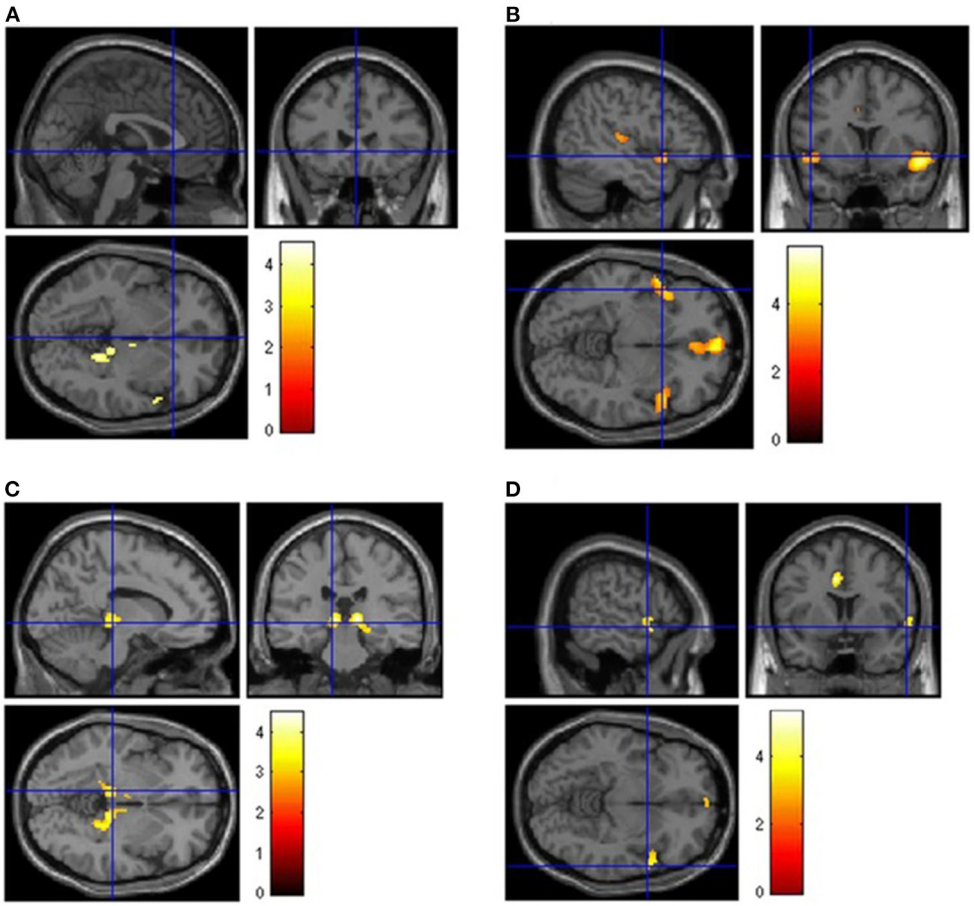


FIGURE 2
Brain [18F]FDG PET analysis. Regions of hypometabolism compared to controls in the 13 long COVID patients **(A)** and subgroups of patients showing persistence of anosmia **(B)**, fatigue **(C)**, or mild-to-moderate vessel [18F]FDG uptake **(D)**. Regions of significant difference are color-graded in terms of *Z*-values. Adapted from Sollini et al. (46) (License Number 5472490224310).

regional neuronal and synaptic activity due to neurotransmission and neurotransduction require a lot of energy (42). According to newer research, astrocytes also play a substantial role in the 18F-FDG-PET signal (43, 44).

According to certain studies, patients with Post COVID-19, who have chronic functional problems, have 18F-FDG-PET hypometabolism in several cerebrum areas (45–48). After analyzing the 18F-FDG cerebral PET of patients with PCNS, with a scientifically verified diagnosis of SARS-CoV-2 disease and chronic functional symptoms at least 3 weeks after the first infection, scientists discovered hypometabolism in: the bilateral orbital gyrus which contains the olfactory gyrus, the right parahippocampal gyrus, the right temporal lobe e.g., amygdala, hippocampus, and thalamus, the bilateral cerebellum and the bilateral pons/medulla brainstem (45–48) (Figures 2, 3). Furthermore, this hypometabolism was linked to the patients' problems e.g., memory and cognitive dysfunction, sleep disturbances and pain (45–47). Moreover, a new research with 18F-FDG-PET demonstrated the neurological long-term consequences of COVID-19 (49). The imaging revealed abnormal findings in more than 66% of the individuals, most of whom presented fronto-parietal hypometabolism (49). In conclusion, the 18F-FDG-PET data demonstrated above suggests that the frontal, temporal, and parietal lobes are sensitive to SARS-CoV-2 infection (45–49).

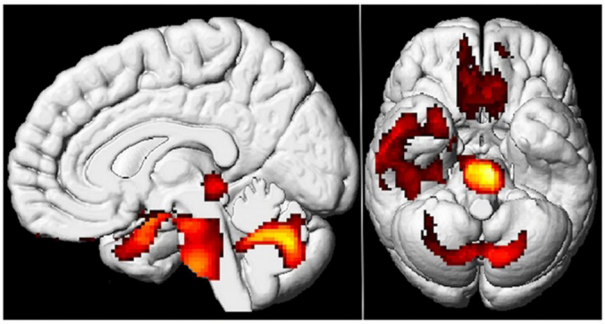


FIGURE 3
Brain 18F-FDG PET hypometabolism in patients with long COVID. In comparison to healthy subjects, the patients exhibit hypometabolism in the bilateral rectal/orbital gyrus, including the olfactory gyrus; the right temporal lobe, including the amygdala and the hippocampus, extending to the right thalamus; the bilateral pons/medulla brainstem; the bilateral cerebellum (p-voxel < 0.001 uncorrected, p-cluster < 0.05 FWE-corrected; SPM8 3D rendering). Adapted from Guedj et al. (45) (License Number 5474900644082).

Interestingly, Verger et al. reported not only 18F-FDG-PET hypometabolism in cerebrum of patients with PCNS but also

the demonstration of a brain impairment, and the differential diagnosis of PCNS in 18F-FDG-PET (47). The authors claims that an individual PET hypometabolism, suggesting network-based involvement, may indicate a real cerebrum impairment (47). Therefore, brain FDG PET could be a good type of imaging to objectify brain involvement in patients with PCNS—it might affect both a specific prognosis and treatment (47). Moreover, Verger et al. describe that PCNS should be differentiate from neurodegenerative diseases, encephalitis/encephalopathy, and psychiatric disorders in FDG PET (47). In addition, new PET radiotracers should be used in future studies to assess PCNS (47, 50, 51). For example, the translocator protein 18 kDa (TSPO) could be a good radiotracer for neuroinfammation PET targeting in PCNS because neuroinfammation is one of the primary hypotheses which explains cerebrum damage in patients with PCNS (47, 50, 51).

CT is one of the most frequently used imaging techniques in medicine due to: the short scan time, low cost and relatively high accuracy of an imaging examination in many disorders. In the case of PCNS imaging, CT is useful for detecting vascular alternations in the CNS (52–54).

Some cases in the literature of PCNS, in which CT was used, describe vascular changes in the brain. Patients with PCNS with lesions in CT imaging ranged from 53 to 85 years of age (52–54). The alternations in CT of CNS in most cases were not related to the clinical symptoms of PCNS (52–54). Typical manifestations of PCNS in CT imaging were: a moderate hypodensity in the frontal lobe (acute infarct), an insular area infarct, acute large parietal-occipital and cerebellar infarcts, acute infarcts of the middle cerebral arteries (MCAs), an occlusion and infarct of the posterior cerebral artery (PCA), a hemorrhagic stroke (48, 52–54). Moreover, CT angiography can make the changes visible such as: a thrombotic occlusion of a proximal M2 branch of the middle cerebral artery and an occlusion of the MCA (48, 52, 54). It should also be taken into account that some of these lesions may be related to age or chronic diseases of patients (52–54).

MRI is a non-invasive method that may give detailed, multi-parametric data on cerebrum structure, function, and metabolism (55). The lesions observed in MRI have a much wider scope of the PCNS imaging than PET/CT and CT (48, 56–58). They include, among others: vascular lesions in the CNS, changes in the brain, spinal cord and cranial nerves which confirm the diagnosis of GBS, neurodegeneration and gliosis (48, 56–58). Patients with PCNS with lesions in MR imaging ranged from 11 to 88 years of age (48, 56–58).

The cerebrovascular alternations in MRI of the CNS in most cases were not related to the neurological symptoms of PCNS (48, 56–58). There were some studies which describes patients with hyperintense subcortical images, as well as in occipital and frontal (bilaterally) white matter in T2-weighted and FLAIR sequences and hypointense lesions on T1-weighted images (48, 56–58). Typical vascular manifestations of PCNS in MR imaging were: an acute brain infarct in striatum, thalamus, pons, occipital lobes, temporal lobes and cerebellum, many small regions of restricted diffusion in the centrum semiovale which indicate a small acute infarction, an acute infarction near the frontal horn, blood vessels occlusion e.g., mild stenosis of the M1 segment, a thrombus in the basilar artery, bilateral P2 segment stenosis, intradural vertebral artery occlusion (48, 52, 53, 56–58). Interestingly, the occurrence of a cerebral vasculitis in the context of PCNS has also been described (48, 57, 58). Figure 4 shows exemplary hyperintensive foci and lesions in the form of engorgement of deep medullary veins and Figure 5 presents vasculitis changes in the form of thickening of the vessel wall, its irregularities and contrast enhancement (Figures 4, 5).

GBS has become increasingly frequent after the outbreak of pandemic (59–63). Several studies have shown a relationship between PCNS and GBS (59–63). Part of them describe lesions in the CNS observed in MRI (59–63). Alternations of the GBS in PCNS in the spinal cord demonstrated in MRI include an enhancement of the cauda equina nerve roots in T1-weighted images after gadolinium contrast (59–63). They are associated with the impairment in lower extremities (59–63). Furthermore, contrast-enhanced T1-weighted MR imaging of the head in GBS after COVID-19 revealed cranial nerves implication (more precisely enhancement of the bilateral facial nerves after contrast) (59–63). Approximately 18% patients have contrast-enhancement of the cranial nerves in GBS connected with the PCNS in MRI examination (59–63). Typically GBS after COVID-19 is associated with the: negative result of the examination for serum anti-glycolipid Ab (antibodies), a CSF test demonstrates albuminocytologic dissociation SARS-CoV-2 PCR in the CSF is negative (59).

It is worth mentioning that GBS has the chronic counterpart involving peripheral nerves which called chronic inflammatory demyelinating polyneuropathy (CIDP) (64). What is more, some individuals may show an acute presentation of CIDP that strongly resembles GBS that it is sometimes difficult to differentiate them (65). A large number of studies describe the connection between COVID-19 and GBS, but some of them show an association between COVID-19 and CIDP (66). Thickening and enhancement of peripheral nerves which sometimes resemble onion bulbs, brachial and lumbosacral plexus, and nerve roots are characteristic MRI findings of CIDP (64–66). Furthermore, a third of individuals have cranial nerve involvement (64) (Figure 6).

Many hyperintense focal regions in periventricular and subcortical white matter, as well as semioval centers, might be identified in the cerebrum MRI after intravenous gadolinium contrast administration in long TR scans, particularly in FLAIR (67). These MRI results are linked to symptoms including persistent tiredness, headache, anxiety episodes, and severe depression which may be manifestations of the PCNS (67). These changes in the cerebral tissue are quite comparable to those found in ∼40–45% of people experiencing migraine, systemic immunological disorders, and connective tissue inflammatory reactions (67). These disorders associated with the vasoconstriction, may cause microthrombosis which leads to neurodegeneration and gliosis (48, 67).

Furthermore, Douaud et al. investigated cerebrum lesions in MRI of patients with PCNS and discovered significant longitudinal effects (68). Many patients presented a reduction in gray matter thickness, in cerebrum size, and contrast of tissue in the orbitofrontal cortex and parahippocampal gyrus (68). Some of individuals demonstrated areas associated with the primary olfactory cortex in which changes in markers of tissue damage might be seen (68). These primarily brain imaging findings could be the features of a degenerative spread of the illness through olfactory pathways, of neurological inflammatory processes, or of the loss of sensory input (68). In addition, these examined patients with PCNS presented a cognitive decline (68).

Overall, PCNS should be considered a diagnosis of exclusion because there are currently no imaging findings considered to

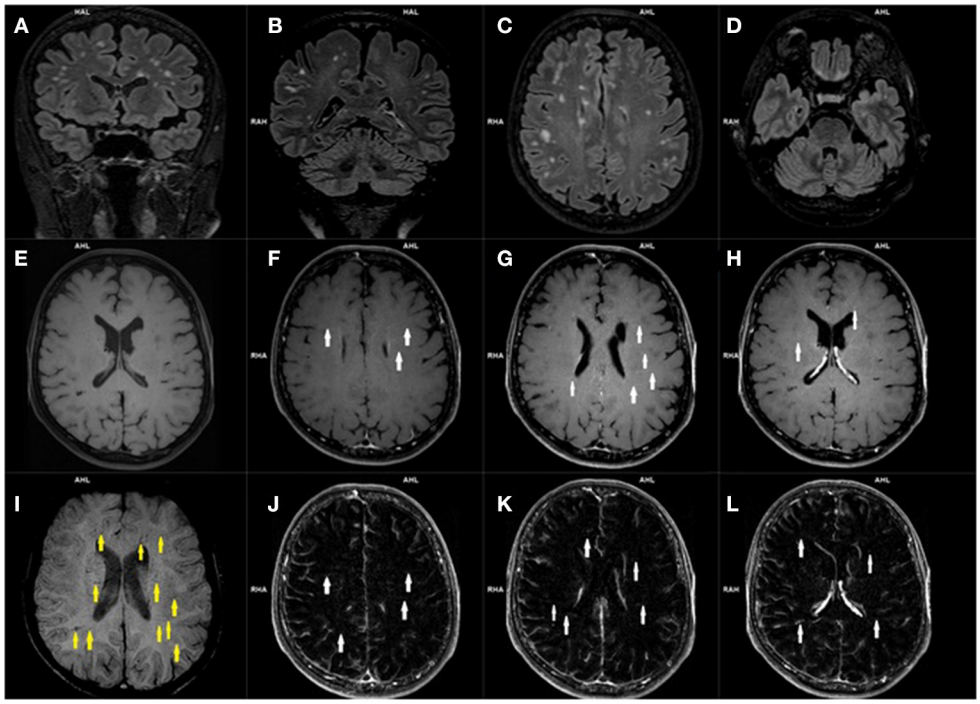


FIGURE 4
Magnetic resonance imaging of the brain of a patient with post COVID-19 symptoms. Coronal **(A, B)** and axial **(C, D)** 3D-FLAIR images demonstrate multiple hyperintensities located within subcortical and deep white matter. Axial precontrast T1-weighted image **(E)**, and contrast enhanced axial T1-weighted images **(E–H)** with axial T1-weighted subtraction maps **(J–L)** show subtle parenchymal enhancement along the course of deep located parenchymal veins (*white arrows*). Corresponding SWI image **(I)** demonstrates engorged some deep medullary veins (*yellow arrows*).

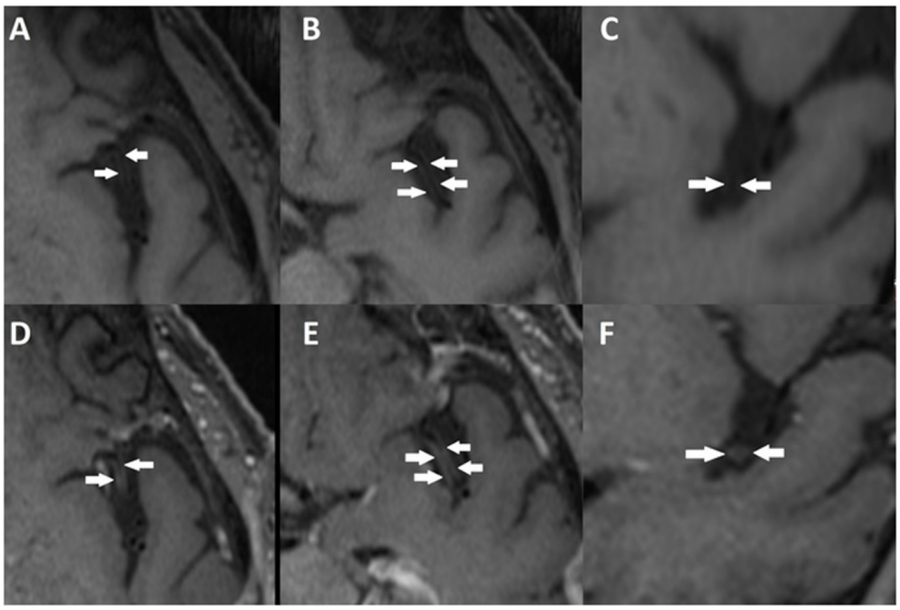


FIGURE 5
Vessel wall imaging (VWI-MR) of the brain of another patient who experienced post COVID-19 symptoms. Axial **(A, B)** and coronal **(C)** precontrast T1-weighted images, and contrast enhanced axial **(D, E)** and coronal **(F)** T1-weighted images, show segmental concentric wall thickening and enhancement of M2 left middle cerebral artery segments (*arrows*) consistent with cerebral vasculitis.

be specific for PCNS, and there is significant overlap with other neurologic illnesses (47, 69, 70). Therefore, clinical examination and EEG in conjunction with radiological examinations are also an important aspect to make a proper diagnosis of PCNS (47, 69, 70). The clinicians examining PCNS-like symptoms should remember about differential diagnoses e.g., stroke, cerebral vein thrombosis,

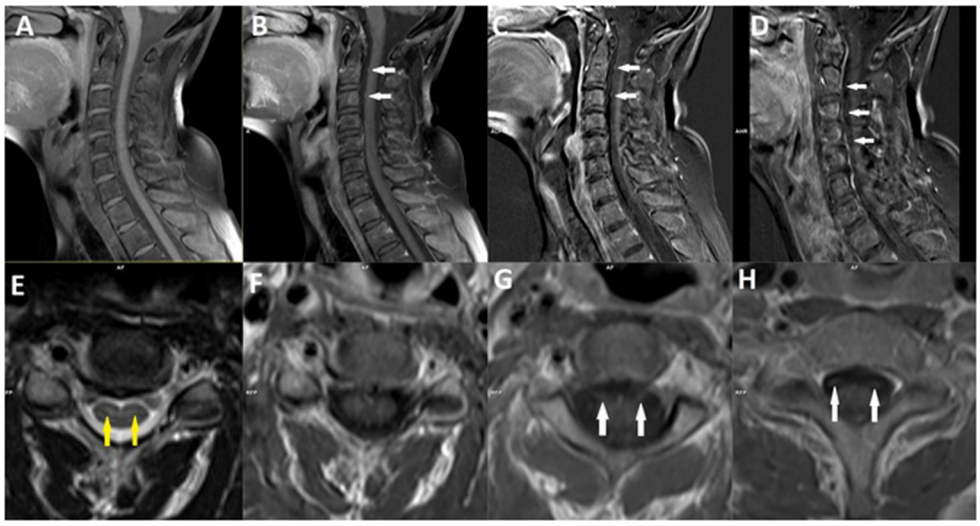


FIGURE 6
Magnetic resonance imaging of the cervical spine of a patient with chronic inflammatory demyelinating polyneuropathy (CIDP) after COVID-19 infection. Sagittal **(A)** and axial **(F)** precontrast T1-weighted images, and postcontrast sagittal **(B)** and axial **(G, H)** T1-weighted images with sagittal T1-weighted subtraction maps **(C, D)**, demonstrate bilateral enhancement of the ventral nerve roots (*white arrows*). Axial T2-weighted image **(E)** demonstrate discrete the hyperintensities in the anterior horns of gray matter (*yellow arrows*).

neurodegenerative diseases, encephalitis, encephalopathy, seizures, insomnia, anxiety, depression, Post Traumatic Stress Disorder (PTSD), and other mental disorders, in which imaging techniques such as PET/CT, CT and MRI might be very helpful (47, 69, 70).

Conclusions

In conclusion, PCNS is one of the most significant long-term worldwide public health problem that involves both hospitalized and non-hospitalized people. Age above 65, chronic pulmonary illness, heart diseases, high blood pressure, adiposity and diabetes are the most important risk agents for SARS-CoV-2 infection-related sequelae such as PCNS (71).

More studies are needed to define CNS neuroimaging in patients with PCNS. However, several imaging studies which describe lesions in PCNS may be of great clinical importance in the future. Several of them claim.

PET/CT

The 18F-FDG-PET signal in the cerebrum is used as an index of activity of neurons. Researchers observed hypometabolism in the bilateral orbital gyrus, right parahippocampal gyrus, frontal lobes, parietal lobes, right temporal lobe, bilateral cerebellum, and bilateral pons/medulla brainstem after assessing the 18F-FDG cerebral PET of PCNS patients. Moreover, this hypometabolism has been connected to the individuals' disorders e.g., memory and cognitive failure, sleep disorders, and pain. Furthermore, 18F-FDG-PET is considered as a good type of imaging to differentiate PCNS from neurodegenerative diseases, encephalitis/encephalopathy, and psychiatric disorders.

CT

CT is beneficial for identifying cerebrovascular lesions in the CNS in the PCNS imaging. In most patients, the changes in CT of the CNS were unrelated to the clinical manifestations of PCNS. An acute infarct of the frontal lobes, acute large parietal-occipital and cerebellar infarcts, acute infarcts of the MCA, an occlusion and infarct of the PCA, a hemorrhagic stroke, a blockage of a proximal M2 branch of the MCA, and an occlusion of the MCA were the most often manifestations of PCNS.

MRI

Magnetic resonance imaging has a significantly broader spectrum of the PCNS imaging than PET/CT and CT. In MRI, typical signs of PCNS included: infarcts in the striatum, thalamus, pons, occipital lobes, termporal lobes, and cerebellum, many minor areas of restricted diffusion in the centrum semiovale, blood vessel occlusion, cerebral vasculitis, and a reduction in gray matter thickness, in brain size, and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus. After contrast administration, several hyperintense focal areas in periventricular and subcortical white matter, and semioval centers, may be seen in cerebrum MRI in long TR scans. These MRI findings have been connected to manifestations that are similar to PCNS symptoms. Finally, changes in the GBS in the PCNS of the spinal cord shown in MRI include an enhancement of the cauda equina nerve roots in T1-weighted images with contrast. Additionally, contrast-enhanced T1-weighted MRI of the head in GBS, following COVID-19, demonstrated enhancement of the facial nerves. Furthermore, CIDP, as the chronic counterpart to GBS, associated with the Post COVID-19 condition presents thickening

and enhancement of peripheral nerves, brachial and lumbosacral plexus, nerve roots and demonstrates the hyperintensities in the gray matter.

CT, PET/CT, and MRI examinations of the cerebrum should be performed in each case of PCNS (broad availability examinations), in order to assessment any abnormalities of the brain to better identify PCNS. Frequent usage and documentation of these imaging methods could accelerate the development of imaging techniques in PCNS. In summary, our review demonstrated that despite healing from an acute disease, the epidemic underlines the importance of continued, extensive follow-up of all patients with COVID-19, because they may have complications later such as PCNS.

Author contributions

JO: material preparation, data collection, and writing-first draft of the manuscript. AG and BK: figures selection and description. AM-M: writing-first draft of the manuscript. All authors read and approved the final manuscript and agreed to be accountable for the content of the work.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* (2020) 382:727–33. doi: 10.1056/NEJMoa2001017

2. Xiang B, Li P, Yang X, Zhong S, Manyande A, Feng M. The impact of novel coronavirus SARS-CoV-2 among healthcare workers in hospitals: an aerial overview. *Am J Infect Control.* (2020) 48:915–7. doi: 10.1016/j.ajic.2020.05.020

3. Kakamad FH, Mahmood SO, Rahim HM, Abdulla BA, Abdullah HO, Othman S, et al. Post covid-19 invasive pulmonary Aspergillosis: a case report. *Int J Surg Case Rep.* (2021) 82:105865. doi: 10.1016/j.ijscr.2021.105865

4. Monroy-Gómez J, Torres-Fernández O. Effects of the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) on the nervous system. What can we expect from SARS-CoV-2? *Biomedica.* (2020) 40:173–9. doi: 10.7705/biomedica.5682

5. World Health Organization. *A Clinical Case Definition of Post COVID-19 Condition by a Delphi Consensus.* (2021). Available online at: https://www.https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1 (accessed January 10, 2023).

6. Moreno-Pérez O, Merino E, Leon-Ramirez JM, Andres M, Ramos JM, Arenas-Jiménez J, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: a Mediterranean cohort study. *J Infect.* (2021) 82:378–83. doi: 10.1016/j.jinf.2021.01.004

7. Kumar J, Makheja K, Rahul FN, Kumar S, Kumar M, Chand M, et al. Long-term neurological impact of COVID-19. *Cureus.* (2021) 13:18131. doi: 10.7759/cureus.18131

8. Wijeratne T, Crewther S. COVID-19 and long-term neurological problems: challenges ahead with post-COVID-19 neurological syndrome. *Aust J Gen Pract.* (2021) 50. doi: 10.31128/AJGP-COVID-43

9. Thakur KT, Miller EH, Glendinning MD, Al-Dalahmah O, Banu MA, Boehme AK, et al. COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. *Brain.* (2021) 144:2696–708. doi: 10.1093/brain/awab148

10. Stein SR, Ramelli SC, Grazioli A, Chung JY, Singh M, Yinda CK, et al. SARS-CoV-2 infection and persistence in the human body and brain at autopsy. *Nature.* (2022) 612:758–63. doi: 10.1038/s41586-022-05542-y

11. Collantes ME, Espiritu AI, Sy MC, Anlacan VM, Jamora RD. Neurological manifestations in COVID-19 infection: a systematic review and meta-analysis. *Can J Neurol Sci.* (2021) 48:66–76. doi: 10.1017/cjn.2020.146

12. Chen X, Laurent S, Onur OA, Kleineberg NN, Fink GR, Schweitzer F, et al. A systematic review of neurological symptoms and complications of COVID-19. *J Neurol.* (2020) 268:392–402. doi: 10.1007/s00415-020-10067-3

13. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. *Nat Med.* (2020) 26:1017–32. doi: 10.1038/s41591-020-0968-3

14. Singh KK, Chaubey G, Chen JY, Suravajhala P. Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. *Am J Phys Cell Phys.* (2020) 319:C258–67. doi: 10.1152/ajpcell.00224.2020

15. Dixon L, McNamara C, Gaur P, Mallon D, Coughlan C, Tona F, et al. Cerebral microhaemorrhage in COVID-19: a critical illness related phenomenon? *Stroke Vasc Neurol.* (2020) 5:315–22. doi: 10.1136/svn-2020-000652

16. Sawlani V, Scotton S, Nader K, Jen JP, Patel M, Gokani K, et al. COVID-19-related intracranial imaging findings: a large single-centre experience. *Clin Radiol.* (2021) 76:108–16. doi: 10.1016/j.crad.2020.09.002

17. Buzhdygan TP, DeOre BJ, Baldwin-Leclair A, Bullock TA, McGary HM, Khan JA, et al. The SARS-CoV-2 spike protein alters barrier function in 2D static and 3D microfluidic *in-vitro* models of the human blood–brain barrier. *Neurobiol Dis.* (2020) 146:105131. doi: 10.1016/j.nbd.2020.105131

18. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid—mechanisms, risk factors, and management. *BMJ.* (2021) 374:n1944. doi: 10.1136/bmj.n1648

19. Lee MH, Perl DP, Nair G, Li W, Maric D, Murray H, et al. Microvascular injury in the brains of patients with Covid-19. *N Engl J Med.* (2021) 384:481–3. doi: 10.1056/NEJMc2033369

20. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry.* (2021) 8:416–27. doi: 10.1016/S2215-0366(21)00084-5

21. Najjar S, Najjar A, Chong DJ, Pramanik BK, Kirsch C, Kuzniecky RI, et al. Central nervous system complications associated with SARS-CoV-2 infection: integrative concepts of pathophysiology and case reports. *J Neuroinflamm.* (2020) 17:231. doi: 10.1186/s12974-020-01896-0

22. Wu K, Zou J, Chang HY. RNA-GPS predicts SARS-CoV-2 RNA localization to host mitochondria and nucleolus. *Cell Systems.* (2020) 11:102–8. doi: 10.1016/j.cels.2020.06.008

23. Generoso JS, Barichello de Quevedo JL, Cattani M, Lodetti BF, Sousa L, Collodel A, et al. Neurobiology of COVID-19: how can the virus affect the brain? *Br J Psychiatr.* (2021) 43:650–64. doi: 10.1590/1516-4446-2020-1488

24. Theoharides TC, Cholevas C, Polyzoidis K, Politis A. Long-COVID syndrome-associated brain fog and chemofog: Luteolin to the rescue. *Biofactors.* (2021) 47:232–41. doi: 10.1002/biof.1726

25. Morin CM, Bjorvatn B, Chung F, Holzinger B, Partinen M, Penzel T, et al. Insomnia, anxiety, and depression during the COVID-19 pandemic: an international collaborative study. *Sleep Med.* (2021) 87:38–45. doi: 10.1016/j.sleep.2021.07.035

26. Estiri H, Strasser ZH, Brat GA, Semenov YR, Patel CJ, Murphy SN. Evolving phenotypes of non-hospitalized patients that indicate long covid. *BMC Med.* (2021) 19:249. doi: 10.1186/s12916-021-02115-0

27. Poloni TE, Medici V, Moretti M, Visonà SD, Cirrincione A, Carlos AF, et al. COVID-19-related neuropathology and microglial activation in elderly with and without dementia. *Brain Pathol.* (2021) 31:e12997. doi: 10.1111/bpa.12997

28. Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, et al. Neuropathological features of Covid-19. *N Engl J Med.* (2020) 383:989–92. doi: 10.1056/NEJMc2019373

29. Radnis C, Qiu S, Jhaveri M, Da Silva I, Szewka A, Koffman L. Radiographic and clinical neurologic manifestations of COVID-19 related hypoxemia. *J Neurol Sci.* (2020) 418:117119. doi: 10.1016/j.jns.2020.117119

30. Lowenstein CJ, Solomon SD. Severe COVID-19 is a microvascular disease. *Circulation.* (2020) 142:1609–11. doi: 10.1161/CIRCULATIONAHA.120.050354

31. Huth SF, Cho SM, Robba C, Highton D, Battaglini D, Bellapart J, et al. Neurological manifestations of Coronavirus disease 2019: a comprehensive review and meta-analysis of the First 6 months of pandemic reporting. *Front Neurol.* (2021) 12:664599. doi: 10.3389/fneur.2021.664599

32. Nguyen NN, Hoang VT, Lagier JC, Raoult D, Gautret P. Long-term persistence of olfactory and gustatory disorders in COVID-19 patients. *Clin Microbiol Infect.* (2021) 27:931–2. doi: 10.1016/j.cmi.2020.12.021

33. Rass V, Beer R, Schiefecker AJ, Kofler M, Lindner A, Mahlknecht P, et al. Neurological outcome and quality of life 3 months after COVID-19: a prospective observational cohort study. *Eur J Neurol.* (2021) 28:3348–59. doi: 10.1111/ene.14803

34. Gupta S, Chandra A, Ray BK, Pandit A. Treatment related fluctuation and response to intravenous immunoglobulin therapy in post COVID-19 Guillain-Barre syndrome. *Diabetes Metab Syndr.* (2021) 15:102246. doi: 10.1016/j.dsx.2021.102246

35. Maramattom BV, Zachariah AN, Meleth HA, Zachariah ZT, Mathew KM. Post Covid-19 guillain barre syndrome. *Ann Indian Acad Neurol.* (2021) 24:622. doi: 10.4103/aian.AIAN_853_20

36. Abolmaali M, Heidari M, Zeinali M, Moghaddam P, Ghamsari MR, Makiani MJ, et al. Guillain–Barré syndrome as a parainfectious manifestation of SARS-CoV-2 infection: a case series. *J Clin Neurosci.* (2021) 83:119–22. doi: 10.1016/j.jocn.2020.11.013

37. Fraiman P, Junior CG, Moro E, Cavallieri F, Zedde M. COVID-19 and cerebrovascular diseases: a systematic review and perspectives for stroke management. *Front Neurol.* (2020) 11:574694. doi: 10.3389/fneur.2020.574694

38. Ahmad SA, Kakamad FH, Mohamad HS, Salih BK, Mohammed SH, Abdulla BA, et al. Post COVID-19 cerebral venous sinus thrombosis; a case report. *Ann Med Surg.* (2021) 72:103031. doi: 10.1016/j.amsu.2021.103031

39. Fotuhi M, Mian A, Meysami S, Raji CA. Neurobiology of COVID-19. *J Alzheim Dis.* (2020) 76:3–19. doi: 10.3233/JAD-200581

40. Ahmad SA, Salih KH, Ahmed SF, Kakamad FH, Salh AM, Hassan MN, et al. Post COVID-19 transverse myelitis; a case report with review of literature. *Ann Med Surg.* (2021) 69:102749. doi: 10.1016/j.amsu.2021.102749

41. Mosconi L. Brain glucose metabolism in the early and specific diagnosis of Alzheimer's disease. FDG-PET studies in MCI and AD. *Eur J Nucl Med Mol Imaging.* (2005) 32:486–510. doi: 10.1007/s00259-005-1762-7

42. Berti V, Mosconi L, Pupi A. Brain: normal variations and benign findings in fluorodeoxyglucose-PET/computed tomography imaging. *PET Clin.* (2014) 9:129–40. doi: 10.1016/j.cpet.2013.10.006

43. Zimmer ER, Parent MJ, Souza DG, Leuzy A, Lecrux C, Kim HI, et al. [18F]FDG PET signal is driven by astroglial glutamate transport. *Nat Neurosci.* (2017) 20:393–5. doi: 10.1038/nn.4492

44. Carter SF, Herholz K, Rosa-Neto P, Pellerin L, Nordberg A, Zimmer ER. Astrocyte biomarkers in Alzheimer's disease. *Trends Mol Med.* (2019) 25:77–95. doi: 10.1016/j.molmed.2018.11.006

45. Guedj E, Campion JY, Dudouet P, Kaphan E, Bregeon F, Tisson-Dupont H, et al. 18F-FDG brain PET hypometabolism in patients with long COVID. *Eur J Nucl Med Mol Imaging.* (2021) 48:2823–33. doi: 10.1007/s00259-021-05215-4

46. Sollini M, Morbelli S, Ciccarelli M, Cecconi M, Aghemo A, Morelli P, et al. Long-Covid hallmarks on [^{18}F]FDG-PET/CT: a case control study. *Eur J Nucl Med Mol Imaging.* (2021) 48:3187–97. doi: 10.1007/s00259-021-05294-3

47. Verger A, Barthel H, Tolboom N, Fraioli F, Cecchin D, Albert NL, et al. 2-[18F]-FDG PET for imaging brain involvement in patients with long COVID: perspective of the EANM Neuroimaging Committee. *Eur J Nucl Med Mol Imaging.* (2022) 49:3599–606. doi: 10.1007/s00259-022-05913-7

48. Manca R, De Marco M, Ince PG, Venneri A. Heterogeneity in regional damage detected by neuroimaging and neuropathological studies in older adults with COVID-19: a cognitive-neuroscience systematic review to inform the long-term impact of the virus on neurocognitive trajectories. *Front Aging Neurosci.* (2021) 13:646908. doi: 10.3389/fnagi.2021.646908

49. Hosp JA, Dressing A, Blazhenets G, Bormann T, Rau A, Schwabenland M, et al. Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. *Brain.* (2021) 144:1263–76. doi: 10.1093/brain/awab009

50. Schurink B, Roos E, Radonic T, Barbe E, Bouman CSC, de Boer HH, et al. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *Lancet Microbe.* (2020) 1:e290–9. doi: 10.1016/S2666-5247(20)30144-0

51. Jain P, Chaney AM, Carlson ML, Jackson IM, Rao A, James ML. Neuroinfammation PET imaging: current opinion and future directions. *J Nucl Med.* (2020) 61:1107–12. doi: 10.2967/jnumed.119.229443

52. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry.* (2020) 91:889–91. doi: 10.1136/jnnp-2020-323586

53. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S. COVID-19 presenting as stroke. *Brain Behav Immun.* (2020) 87:115–9. doi: 10.1016/j.bbi.2020.04.077

54. Al Saiegh F, Ghosh R, Leibold A, Avery MB, Schmidt RF, Theofanis T. Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. *J Neurol Neurosurg Psychiatry.* (2020) 91:846–8. doi: 10.1136/jnnp-2020-323522

55. Yousaf T, Dervenoulas G, Politis M. Advances in MRI Methodology. *Int Rev Neurobiol.* (2018) 141:31–76. doi: 10.1016/bs.irn.2018.08.008

56. Giri P, Hong G, Lam H, Taheri AD. Covid encephalopathy in the setting of multiple bilateral acute cerebral vascular infarcts. *Chest.* (2020) 158:A890. doi: 10.1016/j.chest.2020.08.828

57. Ivanovic J, Stojanovic M, Ristic A, Sokic D, Vojvodic N. Post-acute COVID-19 syndrome presented as a cerebral and systemic vasculitis: a case report. *Acta Neurol Belg.* (2022) 122:1377–9. doi: 10.1007/s13760-022-01923-2

58. Lersy F, Anheim M, Willaume T, Chammas A, Brisset JC, Cotton F, et al. Cerebral vasculitis of medium-sized vessels as a possible mechanism of brain damage in COVID-19 patients. *J Neuroradiol.* (2021) 48:141–6. doi: 10.1016/j.neurad.2020.11.004

59. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. *J Neurol.* (2021) 268:1133–70. doi: 10.1007/s00415-020-10124-x

60. Bigaut K, Mallaret M, Baloglu S, Nemoz B, Morand P, Baicry F, et al. Guillain-Barré syndrome related to SARS-CoV-2 infection. *Neurol Neuroimmunol Neuroinflamm.* (2020) 7:e785. doi: 10.1212/NXI.0000000000000785

61. Chan JL, Ebadi H, Sarna JR. Guillain-Barré syndrome with facial diplegia related to SARS-CoV-2 infection. *Can J Neurol Sci.* (2020) 47:852–4. doi: 10.1017/cjn.2020.106

62. Hutchins KL, Jansen JH, Comer AD, Scheer RV, Zahn GS, Capps AE, et al. COVID-19-associated bifacial weakness with paresthesia subtype of Guillain-Barré syndrome. *Am J Neuroradiol.* (2020) 41:1707–11. doi: 10.3174/ajnr.A6654

63. Kakumoto T, Kobayashi S, Yuuki H, Kainaga M, Shirota Y, Hamada M, et al. Cranial nerve involvement and dysautonomia in post-COVID-19 Guillain-Barré Syndrome. *Intern Med.* (2021) 60:3477–80. doi: 10.2169/internalmedicine.7355-21

64. Rentzos M, Anyfanti C, Kaponi A, Pandis D, Ioannou M, Vassilopoulos D. Chronic inflammatory demyelinating polyneuropathy: a 6-year retrospective clinical study of a hospital-based population. *J Clin Neurosci.* (2007) 14:229–35. doi: 10.1016/j.jocn.2006.11.001

65. Li HF, Ji XJ. The diagnostic, prognostic, and differential value of enhanced MR imaging in Guillain-Barre syndrome. *Am J Neuroradiol.* (2011) 32:E140; author reply E141. doi: 10.3174/ajnr.A2620

66. Ruts L, Drenthen J, Jacobs BC, van Doorn PA. Distinguishing acute-onset CIDP from fluctuating Guillain-Barre syndrome: a prospective study. *Neurology.* (2010) 74:1680–6. doi: 10.1212/WNL.0b013e3181e07d14

67. Nuzzo D, Cambula G, Bacile I, Rizzo M, Galia M, Mangiapane P, et al. Long-term brain disorders in Post Covid-19 Neurological Syndrome (PCNS) Patient. *Brain Sci.* (2021) 11:454. doi: 10.3390/brainsci11040454

68. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature.* (2022) 604:697–707. doi: 10.1038/s41586-022-04569-5

69. Baig AM. Differential diagnosis and pathogenesis of the neurological signs and symptoms in COVID-19 and long-COVID syndrome. *CNS Neurosci Ther.* (2022) 28:1905–7. doi: 10.1111/cns.13957

70. StatPearls. *Post Acute Coronavirus (COVID-19) Syndrome.* (2022). Available online at: https://www.ncbi.nlm.nih.gov/books/NBK570608 (accessed January 14, 2023).

71. Nuzzo D, Vasto S, Scalisi L, Cottone S, Cambula G, Rizzo M, et al. Post-acute COVID-19 neurological syndrome: a new medical challenge. *J Clin Med.* (2021) 10:1947. doi: 10.3390/jcm10091947

frontiers | Frontiers in Neurology

TYPE Case Report
PUBLISHED 22 February 2023
DOI 10.3389/fneur.2023.1137024

OPEN ACCESS

EDITED BY
Thorsten Rudroff,
The University of Iowa, United States

REVIEWED BY
Carlo Contini,
University of Ferrara, Italy
Tohru Gonoi,
Chiba University, Japan

*CORRESPONDENCE
Nadia Bouhamdani
✉ nadia.bouhamdani@vitalitenb.ca

SPECIALTY SECTION
This article was submitted to Neuroinfectious Diseases, a section of the journal Frontiers in Neurology

RECEIVED 03 January 2023
ACCEPTED 02 February 2023
PUBLISHED 22 February 2023

CITATION
Bouhamdani N, Comeau D, Bourque C and Saulnier N (2023) Encephalic nocardiosis after mild COVID-19: A case report. *Front. Neurol.* 14:1137024. doi: 10.3389/fneur.2023.1137024

Encephalic nocardiosis after mild COVID-19: A case report

Nadia Bouhamdani[1,2,3]*, Dominique Comeau[1], Christine Bourque[1] and Nancy Saulnier[1]

[1]Vitalité Health Network, Dr. Georges-L.-Dumont University Hospital Center, Research Sector, Moncton, NB, Canada, [2]Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, QC, Canada, [3]Centre de Formation Médicale du Nouveau-Brunswick, Université de Moncton, Moncton, NB, Canada

The COVID-19 pandemic and the associated post-acute sequelae of COVID-19 (PASC) have led to the identification of a complex disease phenotype that is associated with important changes in the immune system. Herein, we describe a unique case of *Nocardia farcinica* cerebral abscess in an individual with sudden immunodeficiency several months after mild COVID-19. Intravenous Bactrim and Imipenem were prescribed for 6 weeks. After this, a 12-month course of Bactrim and Clavulin was prescribed to be taken orally, given the *N. farcinica* infection at the level of the central nervous system. This case report highlights the need for future research into the pathophysiology of COVID-19 and PASC immune dysregulation in convalescent individuals. It also draws attention to the need for timely consideration of opportunistic infections in patients with a history of COVID-19.

KEYWORDS

nocardiosis, *Nocardia farcinica*, coronavirus disease 2019 (COVID-19), post-acute sequelae of COVID-19 (PASC), brain abscess

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) is the causal agent of the coronavirus disease 2019 (COVID-19) global pandemic (1). Alarmingly, long COVID or post-acute sequelae of COVID-19 (PASC) can occur several weeks after infection in a subset of individuals and englobes a multitude of health problems (2, 3). This multisystem disease can arise after severe, mild, or even asymptomatic SARS-CoV2 infection (4, 5) and is characterized by the persistence or onset of new chronic symptoms lasting longer than what is ordinary in most cases of viral infection (6, 7). Indeed, this post-infectious syndrome draws a unique parallel with Ebola and SARS-CoV-1 (8, 9), wherein a long-lasting dysregulation of the immune system is observed long after the infection has cleared (10). Notably, flow cytometry analysis of COVID-19 convalescent individuals, both hospitalized and non-hospitalized, demonstrated that numerous adaptive and innate immune cells were decreased, and activation/exhaustion markers were elevated in T- and B-cell populations (11). Significant lymphopenia ($CD4^+$ and $CD8^+$ cells) in convalescent individuals were also identified by others (10, 12), and these changes in the peripheral immune system could potentially influence how individuals respond to other infections during this post-COVID-19 timeframe (10), potentially rendering some patients in a state of immunodeficiency.

Individuals may become immunocompromised secondary to underlying malignancies, cancer therapeutics, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), in situations of organ transplant, and after receiving a prolonged corticosteroid regimen (13, 14). Immunocompromised individuals are particularly vulnerable to infections, notably nocardiosis for which the causal agent is *Nocardia species*, a ubiquitous soil-dwelling Gram-positive bacteria. *Nocardia asteroids* are most associated with human disease (15); however, the less common *Nocardia farcinica* is associated with a higher risk of dissemination, drug resistance, and by extension, a higher mortality rate (16–18). The lungs are the primary site of *Nocardia* spp. infection and, when limited to the lung, can be treated with antibiotic treatment. This is however not the case when immunosuppression is prolonged, and secondary sites of infection are established (14); in such cases, bacteremia may later manifest as brain abscesses (19). Mortality rates in the central nervous system involvement range from 40 to 87%, despite therapeutic interventions (20, 21).

Herein, we describe a unique case of *N. farcinica* cerebral abscess in an individual with sudden immunodeficiency several months after mild COVID-19.

2. Case description

A male patient in his 50s with a history of high blood pressure, duodenal ulcer, dyslipidemia, and a history of smoking and alcoholism presented at the emergency with left-sided transient hemiparesis. Magnetic resonance imaging showed an enhancing lesion involving the high convexity on the right of the frontal lobe measuring ∼1.9 cm × 1.7 cm, associated with marked adjacent vasogenic edema (Figures 1A, B). A biopsy of the lesion highlighted brain parenchyma with reactive gliosis and no significant findings except the growth of *Propionibacterium acnes* in broth cultures. On repeat imaging a couple of weeks later, there was an increase in the size (2.9 cm) of the ring-enhancing posterior right frontal/anterior parietal lobe, as well as a new ring-enhancing posterior right frontal lobe lesion measuring 1.1 cm, superior to the lesion described earlier (Figure 1B). There was also central restricted diffusion. A neurosurgical biopsy showed gliotic brain tissue, necrotic debris, neutrophils, and macrophages within the abscess. Beaded, filamentous bacilli were detected and later confirmed on growth media by Public Health Laboratory to be *N. Farcinica* (Figures 2A, B). Susceptibility results confirmed amoxicillin/clavulanic acid, Imipenem, and trimethoprim–sulfamethoxazole as potentially efficacious against the harvested strain (Supplementary Figure 1).

At 1 month preceding *N. farcinica* cerebral abscess, the patient had contracted pneumonia (inferior right lobe) and was treated with amoxicillin/clavulanic acid, taken orally, twice daily for 10 days. Although the causal agent for the pneumonia was not confirmed to be *N. farcinica*, this route of dissemination (from the lungs to the brain) is very likely as 58% of central nervous system niches originate from the lungs (16). The patient had also contracted COVID-19 1 month before pneumonia, which was confirmed by bedside testing. The patient was fully immunized against COVID-19 (three doses of mRNA vaccine) before contracting the disease.

2.1. Investigations

The patient first presented to emergency services for temporary hemiparesis. Given the patient's cardiovascular history, temporary hemiparesis was initially suspected to be the result of an ischemic stroke. After this initial visit, the patient presented three additional times to emergency services over the course of 3 weeks (Figure 1A). Upon the second admission, an MRI was performed, which indicated a cerebral abscess rather than an ischemic stroke (Figures 1A, B). Upon the third admission, a neurological biopsy was negative for bacterial growth, and precautionary antibiotic treatment was prescribed. On the fourth and final visit to emergency services, neurological symptoms had progressed. The growth of the abscess prompted a second neurological biopsy and Public Health Laboratory testing, which revealed the presence of *N. farcinica* (Figure 1B). As cases of *N. farcinica* are mostly found in immunocompromised individuals, immunological flow cytometry analysis of peripheral blood was performed. Indeed, the patient had an immunodeficient profile, but immunosuppression was neither the result of corticosteroid use nor HIV/AIDS. More specifically, lymphopenia was documented in populations $CD3^+CD4^+$, $CD3^+CD8^+$, and $CD3^-CD16^+CD56^+$, albeit CD19-labeled cells (B lymphocytes) were increased (Table 1). Serum immunoglobulins were all reported to be within the reference range for IgG, IgA, and IgM. Flow cytometry was performed 15 weeks after the patient experienced mild COVID-19 (Table 1).

2.2. Treatment

Intravenous Bactrim and Imipenem were prescribed for 6 weeks. After this, a 12-month course of Bactrim and Clavulin was prescribed to be taken orally, given the *N. farcinica* infection at the level of the central nervous system, especially because of the immunosuppressive state.

2.3. Outcomes and follow-up

Antibiotic treatment was effective, and no other issues with infection were experienced afterward. The patient followed a 6-week rehabilitation plan for neurological sequelae and is doing well, despite some residual neuropathy of the left leg.

3. Discussion

Corticosteroids are often used in COVID-19-related pneumonia and may lead to an immunocompromised state (22–25) and opportunistic *N. farcinica* infection (26). However, in this case, the patient had not been prescribed any such treatment or other immunomodulators. The immunocompromised state was therefore presumed to have been SARS-CoV2-related. Furthermore, the occurrence of the ailment extended beyond the

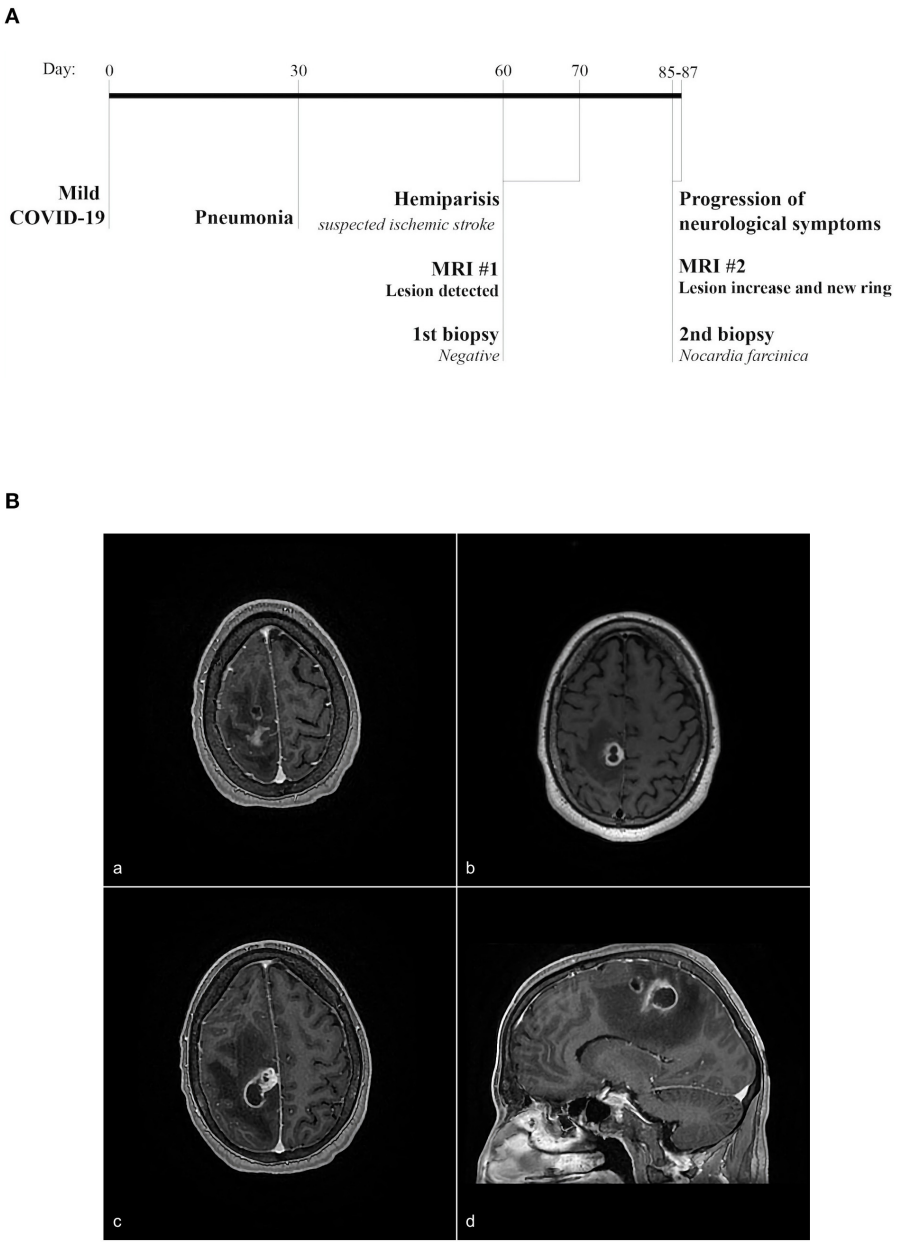


FIGURE 1
(A) Timeline of an episode of care. The patient contracted COVID-19 with mild symptomatology. Thirty days later, the patient was diagnosed with pneumonia and at day 60, presented with hemiparesis. MRI revealed a cerebral lesion. At day 85, the patient presented worsening neurological symptoms and a second MRI showed an additional lesion as well as an increased size of the primary cerebral lesion. At this time, a second biopsy confirmed *N. farcinica*. **(B)** MRI imaging showing an abscess involving the high convexity on the right of the frontal lobe measuring ~1.9 cm × 1.7 cm associated with marked adjacent vasogenic edema **(a, b)**. On repeat imaging, an increase in the size (2.9 cm) of the ring enhancing posterior right frontal/anterior parietal lobe is seen, as well as a new ring-enhancing posterior right frontal lobe lesion measuring 1.1 cm, superior to the lesion described prior **(c, d)**.

habitual course of infection and well into PASC territory. The immune response to SARS-CoV2 is believed to be responsible for the enduring symptoms in PASC, potentially through a persisting inflammatory process (27). In this case report, although the immunocompromised state was not typically so severe for opportunistic infection, we believe that the altered immune state in PASC indeed may have enabled *N. farcinica* infection. T-cell lymphopenia was documented, albeit with an accompanying rise in B lymphocytes, as previously documented (10–12). Therefore, we hypothesize that *N. farcinica* infection may potentially have been facilitated by an exhausted immune system; it is becoming increasingly apparent that COVID-19 may lead to an altered immune state and lymphopenia (27–32). Indeed, the immune response to *Nocardia* spp. is mediated by $CD8^+$ T cells, whereas B lymphocytes and humoral immunity do not appear to be as important (33), such that the immunocompromised host will be susceptible to such infections (34). Analogously, mucormycosis and links to abnormalities in immune cells after

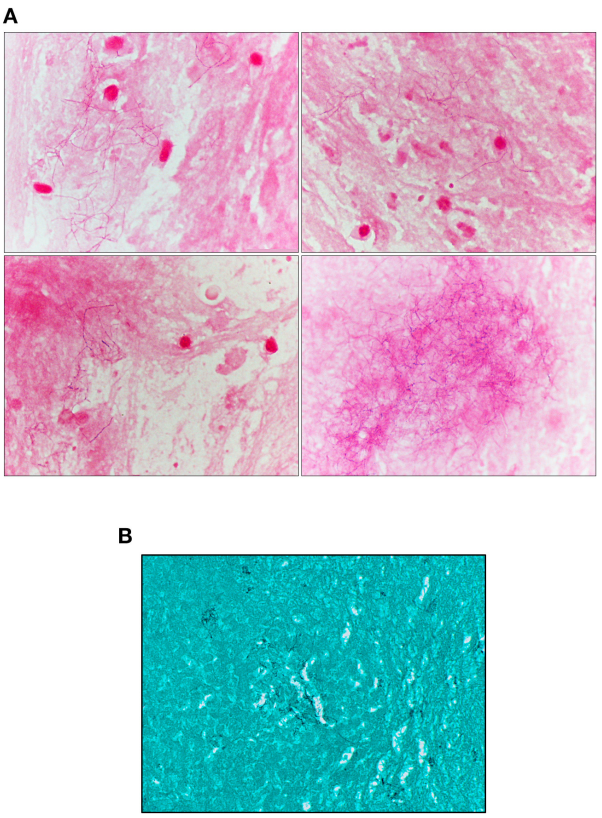


FIGURE 2
(A) Modified acid-fast staining on biopsy showing acid-fast rods. **(B)** Grocott staining.

TABLE 1 Immune assessment.

Test name	Result	Ref. range (units)
CD3 cells/100 cells	66.9	66.6–82.6 (%)
CD3 cells	547[a]	1,047–1,958 (Cell/μl)
$CD3^+CD4^+$ cells/100 cells	53.8	41.4–61.3 (%)
$CD3^+CD4^+$ cells	440[a]	701–1,352 (cell/μl)
$CD3^+CD8^+$ cells/100 cells	12.9[a]	13.4–29.6 (%)
$CD3^+$ $CD8^+$ cells	105[a]	215–667 (cell/μl)
CD19 cells/100 cells	29.5[a]	6.8–17.0 (%)
CD19 cells	242	105–386 (cell/μl)
$CD3^-CD16^+$ $CD56^+$ cells/100 cells	3.1[a]	6.8–19.3 (%)
$CD3^-CD16^+$ $CD56^+$ cells	25[a]	133–367 (cell/μl)
$CD3^+CD4^+$ cells/$CD3^+CD8^+$ cells	4.17	
IgA	1.56	0.85–3.85 (g/L)
IgM	1.40	0.53–3.75 (g/L)
IgG	5.90	5.60–17.70 (g/L)

[a]Abnormal.

a bout of asymptomatic COVID-19 have also been documented (31, 35). The patient in this study had not received corticosteroid treatments, was not HIV positive, and had similarly contracted COVID-19 but remained mildly symptomatic (31). Hence, it is possible that delayed recovery of T cells may lead to an increased risk of life-threatening infections. Little is currently known about T-cell modulation in mildly symptomatic and asymptomatic disease, as most studies have been carried out in more severe cases of COVID-19.

Furthermore, the considerable systemic inflammation during COVID-19 can lead to endothelitis and disruption of the blood–brain barrier (36, 37), which may have facilitated the entry of *N. farcinica* into the brain. Taken together, both the immunocompromised state and the potential disruption in the blood–brain barrier may have created a propitious environment for the growth and dissemination of the bacterium.

The patient underwent two neurological biopsies to detect bacterial growth. The first biopsy came with the growth of *P. acnes* in the broth only. The second biopsy was sent to a Public Health Laboratory, which identified the causal agent. *Nocardia farcinica* cultures are fastidious, and so, laboratory testing may be negative even in the event of nocardiosis (14); hence, failure to ensure proper growth conditions for an adequate amount of time may fail to reveal growth. Furthermore, if *N. farcinica* had originated from the lungs, the 10-day amoxicillin/clavulanic acid treatment during pneumonia was not sufficient to fully treat the infection as treatment is recommended to last several months (38). A limitation of this case report remains the absence of confirmation of the lungs being the primary site of *N. farcinica* infection. Another important limitation is the lack of understanding regarding the molecular and cellular mechanisms leading to PASC and susceptibility to opportunistic infections. This case emphasizes the importance of early consideration of opportunistic infection in patients with a known history of COVID-19.

This case report highlights the need for future research into the pathophysiology of COVID-19 and PASC immune dysregulation in convalescent individuals. It also draws attention to the need for timely consideration of opportunistic infections for patients with a history of COVID-19.

4. Conclusion

This unique case presentation strengthens the notion of immunomodulation after mild COVID-19 and well after the viral infection has cleared. Recognizing these features might prompt considering and testing for infection early on.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Vitalité Health Network Research Ethics Board. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained

from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NB prepared the ethical submission and paperwork to obtain patient consent. NB and DC wrote and corrected the manuscript. CB and NS coordinated the clinical investigations, patient management, and interpreted the clinical data. All authors reviewed, provided feedback, and approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1137024/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Antibiogram for *N. farcinica*.

References

1. Ramos-Casals M, Brito-Zerón P, Mariette X. Systemic and organ-specific immune-related manifestations of COVID-19. *Nat Rev Rheumatol.* (2021) 17:315–32. doi: 10.1038/s41584-021-00608-z

2. National Institute for Health and Care Excellence. *COVID-19 Rapid Guideline: Managing the Long-term Effects of COVID-19 NICE Guideline [NG188].* (2020). AVailale online at: https://www.nice.org.uk/guidance/ng188 (accessed July 12, 2022).

3. Rando HM, Bennett TD, Byrd JB, Bramante C, Callahan TJ, Chute CG, et al. Challenges in defining Long COVID: striking differences across literature, electronic health records, and patient-reported information. *medRxiv.* (2021). doi: 10.1101/2021.03.20.21253896

4. Greenhalgh T, Knight M. A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ.* (2020) 370:m3026. doi: 10.1136/bmj.m3026

5. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Persistent symptoms 15-6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. *Thorax.* (2021) 76:405–7. doi: 10.1136/thoraxjnl-2020-216377

6. Mahase E. Covid-19: what do we know about "long covid"? *BMJ.* (2020) 370:m2815. doi: 10.1136/bmj.m2815

7. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet.* (2021) 397:220–32. doi: 10.1016/S0140-6736(20)32656-8

8. Clark DV, Kibuuka H, Millard M, Wakabi S, Lukwago L, Taylor A, et al. Long-term sequelae after Ebola virus disease in Bundibugyo, Uganda: a retrospective cohort study. *Lancet Infect Dis.* (2015) 15:905–12. doi: 10.1016/S1473-3099(15)70152-0

9. Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology.* (2010) 15:543–50. doi: 10.1111/j.1440-1843.2010.01720.x

10. Ryan FJ, Hope CM, Masavuli MG, Lynn MA, Mekonnen ZA, Yeow AEL, et al. Long-term perturbation of the peripheral immune system months after SARS-CoV-2 infection. *BMC Med.* (2022) 20:26. doi: 10.1186/s12916-021-02228-6

11. Files JK, Boppana S, Perez MD, Sarkar S, Lowman KE, Qin K, et al. Sustained cellular immune dysregulation in individuals recovering from SARS-CoV-2 infection. *J Clin Invest.* (2021) 131:e140491. doi: 10.1172/JCI140491

12. Wen W, Su W, Tang H, Le W, Zhang X, Zheng Y, et al. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. *Cell Discov.* (2020) 6:31. doi: 10.1038/s41421-020-00187-5

13. Ambrosioni J, Lew D, Garbino J. Nocardiosis: updated clinical review and experience at a tertiary center. *Infection.* (2010) 38:89–97. doi: 10.1007/s15010-009-9193-9

14. Lederman ER, Crum NF. A case series and focused review of nocardiosis: clinical and microbiologic aspects. *Medicine.* (2004) 83:300–13. doi: 10.1097/01.md.0000141100.30871.39

15. Arabi Y, Fairfax MR, Szuba MJ, Crane L, Schuman P. Adrenal insufficiency, recurrent bacteremia, and disseminated abscesses caused by *Nocardia asteroides* in a patient with acquired immunodeficiency syndrome. *Diagn Microbiol Infect Dis.* (1996) 24:47–51. doi: 10.1016/0732-8893(95)00249-9

16. Torres OH, Domingo P, Pericas R, Boiron P, Montiel JA, Vázquez G. Infection caused by *Nocardia farcinica*: case report and review. *Eur J Clin Microbiol Infect Dis.* (2000) 19:205–12. doi: 10.1007/s100960050460

17. Wallace RJ, Tsukamura M, Brown BA, Brown J, Steingrube VA, Zhang YS, et al. Cefotaxime-resistant *Nocardia asteroides* strains are isolates of the controversial species *Nocardia farcinica*. *J Clin Microbiol.* (1990) 28:2726–32. doi: 10.1128/jcm.28.12.2726-2732.1990

18. Wenger PN, Brown JM, McNeil MM, Jarvis WR. *Nocardia farcinica* sternotomy site infections in patients following open heart surgery. *J Infect Dis.* (1998) 178:1539–43. doi: 10.1086/314450

19. Peters BR, Saubolle MA, Costantino JM. Disseminated and cerebral infection due to *Nocardia farcinica*: diagnosis by blood culture and cure with antibiotics alone. *Clin Infect Dis.* (1996) 23:1165–7. doi: 10.1093/clinids/23.5.1165

20. Hoeprich PD, Brandt D, Parker RH. Nocardial brain abscess cured with cycloserine and sulfonamides. *Am J Med Sci.* (1968) 255:208–16. doi: 10.1097/00000441-196803000-00008

21. Smego RA, Moeller MB, Gallis HA. Trimethoprim-sulfamethoxazole therapy for Nocardia infections. *Arch Intern Med.* (1983) 143:711–8. doi: 10.1001/archinte.143.4.711

22. Ross SH, Cantrell DA. Signaling and function of interleukin-2 in T lymphocytes. *Annu Rev Immunol.* (2018) 36:411–33. doi: 10.1146/annurev-immunol-042617-053352

23. Lanza L, Scudeletti M, Puppo F, Bosco O, Peirano L, Filaci G, et al. Prednisone increases apoptosis in in vitro activated human peripheral blood T lymphocytes. *Clin Exp Immunol.* (1996) 103:482–90. doi: 10.1111/j.1365-2249.1996.tb08306.x

24. Fauci AS, Dale DC, Balow JE. Glucocorticosteroid therapy: mechanisms of action and clinical considerations. *Ann Intern Med.* (1976) 84:304–15. doi: 10.7326/0003-4819-84-3-304

25. Paliogianni F, Ahuja SS, Balow JP, Balow JE, Boumpas DT. Novel mechanism for inhibition of human T cells by glucocorticoids. Glucocorticoids inhibit signal transduction through IL-2 receptor. *J Immunol.* (1993) 151:4081–9. doi: 10.4049/jimmunol.151.8.4081

26. DiMeglio M, Shaikh H, Newman J, Vazsquez-Rubio G. Nocardiosis of the central nervous system: a rare complication of COVID management? *IDCases.* (2022) 29:e01599. doi: 10.1016/j.idcr.2022.e01599

27. Ramakrishnan RK, Kashour T, Hamid Q, Halwani R, Tleyjeh IM. Unraveling the mystery surrounding post-acute sequelae of COVID-19. *Front Immunol.* (2021) 12:686029. doi: 10.3389/fimmu.2021.686029

28. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. *BMJ.* (2020) 369:m1328.

29. Mahmoodpoor A, Hosseini M, Soltani-Zangbar S, Sanaie S, Aghebati-Maleki L, Saghaleini SH, et al. Reduction and exhausted features of T lymphocytes under

serological changes, and prognostic factors in COVID-19 progression. *Mol Immunol.* (2021) 138:121–7. doi: 10.1016/j.molimm.2021.06.001

30. De Biasi S, Meschiari M, Gibellini L, Bellinazzi C, Borella R, Fidanza L, et al. Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia. *Nat Commun.* (2020) 11:3434. doi: 10.1038/s41467-020-17292-4

31. Mandke C, Divekar R, Pradhan V, Arora S. Quantitative B and T cell abnormalities in four patients presenting with mucormycosis and prior asymptomatic COVID-19 infection. *BMJ Case Rep*. (2022) 15:e247893. doi: 10.1136/bcr-2021-247893

32. Hanna SJ, Codd AS, Gea-Mallorqui E, Scourfield DO, Richter FC, Ladell K, et al. T cell phenotypes in COVID-19 - a living review. *Oxf Open Immunol*. (2021) 2:iqaa007. doi: 10.1093/oxfimm/iqaa007

33. Rico G, Ochoa R, Oliva A, Gonzalez-Mendoza A, Walker SM, Ortiz-Ortiz L. Enhanced resistance to *Nocardia brasiliensis* infection in mice depleted of antigen-specific B cells. *J Immunol.* (1982) 129:1688–93. doi: 10.4049/jimmunol.129.4.1688

34. Beaman BL, Beaman L. Nocardia species: host-parasite relationships. *Clin Microbiol Rev.* (1994) 7:213–64. doi: 10.1128/CMR.7.2.213

35. Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, et al. Multicenter epidemiologic study of coronavirus disease-associated mucormycosis, India. *Emerg Infect Dis.* (2021) 27:2349–59. doi: 10.3201/eid2709.210934

36. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5

37. Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. *Eur Heart J.* (2020) 41:3038–44. doi: 10.1093/eurheartj/ehaa623

38. Wilson JW. Nocardiosis: updates and clinical overview. *Mayo Clin Proc.* (2012) 87:403–7. doi: 10.1016/j.mayocp.2011.11.016

frontiers | Frontiers in Neurology

TYPE Mini Review
PUBLISHED 21 July 2023
DOI 10.3389/fneur.2023.1233192

OPEN ACCESS

EDITED BY
Pankaj Seth,
National Brain Research Centre (NBRC), India

REVIEWED BY
Jolanta B. Zawilska,
Medical University of Lodz, Poland

*CORRESPONDENCE
Ludivine Chamard-Witkowski
✉ Ludivine.witkowski@vitalitenb.ca

†These authors have contributed equally to this work

RECEIVED 01 June 2023
ACCEPTED 10 July 2023
PUBLISHED 21 July 2023

CITATION
Comeau D, Martin M, Robichaud GA and Chamard-Witkowski L (2023) Neurological manifestations of post-acute sequelae of COVID-19: which liquid biomarker should we use?.
Front. Neurol. 14:1233192.
doi: 10.3389/fneur.2023.1233192

Neurological manifestations of post-acute sequelae of COVID-19: which liquid biomarker should we use?

Dominique Comeau[1†], Mykella Martin[2†], Gilles A. Robichaud[3,4,5] and Ludivine Chamard-Witkowski[2,6*]

[1]Dr. Georges-L. Dumont University Hospital Centre, Clinical Research Sector, Vitalité Health Network, Moncton, NB, Canada, [2]Centre de Formation médicale du Nouveau-Brunswick, Université de Sherbrooke, Moncton, NB, Canada, [3]Department of Chemistry and Biochemistry, Université de Moncton, Moncton, NB, Canada, [4]The New Brunswick Center for Precision Medicine, Moncton, NB, Canada, [5]The Atlantic Cancer Research Institute, Moncton, NB, Canada, [6]Department of Neurology, Dr. Georges-L. Dumont University Hospital Centre, Moncton, NB, Canada

Long COVID syndrome, also known as post-acute sequelae of COVID-19 (PASC), is characterized by persistent symptoms lasting 3–12 weeks post SARS-CoV-2 infection. Patients suffering from PASC can display a myriad of symptoms that greatly diminish quality of life, the most frequent being neuropsychiatric. Thus, there is an eminent need to diagnose and treat PASC related neuropsychiatric manifestation (neuro-PASC). Evidence suggests that liquid biomarkers could potentially be used in the diagnosis and monitoring of patients. Undoubtedly, such biomarkers would greatly benefit clinicians in the management of patients; however, it remains unclear if these can be reliably used in this context. In this mini review, we highlight promising liquid (blood and cerebrospinal fluid) biomarkers, namely, neuronal injury biomarkers NfL, GFAP, and tau proteins as well as neuroinflammatory biomarkers IL-6, IL-10, TNF-α, and CPR associated with neuro-PASC and discuss their limitations in clinical applicability.

KEYWORDS

neuro-PASC, biomarkers, NfL, GFAP, IL-6, IL-10, TNF-α, CPR

1. Introduction

Persistent neurological and psychiatric symptoms associated with coronavirus disease 2019 (COVID-19), referred to as neurological symptoms of Post-Acute Sequelae of COVID-19 (neuro-PASC), has garnered much attention since the beginning of the pandemic (1–4). Symptoms persisting 3–12 weeks after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) include fatigue, cognitive dysfunction, sleep disorders, anxiety disorders and dementia, among others (1, 4–7). Neurological symptoms represent some of the most debilitating symptoms of PASC (1). Furthermore, the commonality of these symptoms signals an urgent need for clinically relevant tools for the diagnosis and management of the illness (1, 5, 6, 8, 9). Opportune and accurate diagnosis of neurological disease in clinical practice is of great importance; in this context, biomarkers may represent a potentially viable diagnostic tool. Biomarkers could be used in guiding clinical diagnosis, prognosis, evaluating disease stage and monitoring disease progression or disease-modifying therapies. Furthermore, identifying reliable biomarkers in neuro-PASC could avoid misdiagnosis which can lead to suboptimal care and avoid unnecessary care-seeking and costly investigations due to diagnostic uncertainty (7).

Liquid biomarkers have proven to be extremely useful in the assessment of neurological disease (10) and as indicators of general neurodegeneration and glial activation (11). More specifically, liquid biomarkers from the blood or cerebrospinal fluid (CSF) are particularly practical as they are cost-affective, highly specific and sampling is minimally invasive (12). The aim of this review is to summarize the current knowledge about clinically relevant biomarkers in neuro-PASC and their potential applicability and limitations. We focused our mini-review on the biomarkers that had been the most described and reported in the literature. These biomarkers include neuronal injury biomarkers neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP) and tau proteins as well as inflammatory markers Interleukin (IL)-6, IL-10, tumor necrosis factor alpha (TNF-α) and C-Reactive Protein (CRP).

2. Potential neuro-PASC biomarkers

2.1. Neuronal injury biomarkers

2.1.1. NfL and GFAP

Plasma NfL and GFAP are well established biomarkers of central nervous system disease diagnosis and progression (13, 14). NfL is a major structural protein only expressed in neurons and an indicator of axonal degeneration and injury used as a blood and CSF biomarker in the assessment of neurodegenerative diseases including frontotemporal lobal degeneration, amyotrophic lateral sclerosis, Alzheimer's disease (AD), Multiple Sclerosis and primary tauopathies (15–17). Levels of NfL are associated with the intensity of on-going neurodegeneration (17–19) as well as the clinical effectiveness of treatment modalities (20, 21), making it an invaluable clinical tool. GFAP is also an important blood and CSF biomarker. GFAP is an astrocytic intermediate filament which signals astrocytic damage or activation, the presence of which is found in neurodegenerative diseases (22–25) and neuroinflammatory conditions (26, 27).

NfL and GFAP have been found to be elevated in the blood and CSF of patients with COVID-19 as well as in patients with COVID-19 related neurological symptoms (neuro-COVID-19) (28–43). An association between these biomarkers and COVID-19 has been demonstrated during the acute phase of the disease; levels are notably increased in severe cases with neurological involvement and unfavorable outcome (30, 35, 39, 44, 45). Demonstrably, NfL and GFAP were found to be elevated in deceased hospitalized COVID-19 patients (32, 36) and were higher in this cohort when compared to convalescent patients (32). A longitudinal study measuring the trajectories of GFAP and NfL found that patients with severe disease presented an early peak of GFAP during the acute phase which quickly resolved within the first 21 days, and NfL levels were maintained past the 3-week mark (39). Unfortunately, given the severity of the illness, a full neurological and cognitive evaluation was not feasible in this cohort, nor was long-term follow up to evaluate the presence of neuro-PASC in these individuals. In patients with self-reported neuro-PASC (mostly trouble concentrating, headache and dizziness) approximately 4 months after initial infection, plasma NfL and GFAP were measured at early (< 90 days) and late (> 90 days) recovery and compared to levels in patients who did not go on to report neuro-PASC (46). At early recovery, those reporting neuro-PASC symptoms had elevated GFAP but no changes in NfL, and during late recovery neither GFAP nor NfL levels were elevated. Furthermore, there were no significant difference between the two groups at either time point when considering the presence of neurological symptoms during acute infection. Taken together, this may support the possibility of early CNS injury without ongoing neurologic injury even though clinical symptoms persist (46). Irrespective of disease severity, levels of NfL and GFAP were also found to steadily decrease over time and normalize around the 6-month mark (40). In a subset of patients, although levels returned to normal, neurological symptoms persisted, namely, fatigue, brain-fog, and changes in cognition (memory loss and lack of concentration) (40); furthermore, these persistent symptoms were also not correlated to biomarker concentration during the acute phase of the disease. Evidently, trajectories and timing for these biomarkers remains inconsistent between studies (39–41, 44, 46, 47).

Levels of NfL and GFAP were also found increased in mild-to-moderate COVID-19 without evidence of neurological symptoms (29, 44). And, although associated with disease severity, an increase in GFAP in COVID-19 patients was also not associated to neurological symptoms (38). Similarly, NfL was also elevated in the serum of patients without overt neurological manifestations (35, 42). Indeed, in another study, patients with elevated NfL and GFAP did not report persistent neurological disorders (32). In a long-term follow up study (6 months), decreased levels of serum NfL also did not correlate with persistent neurological symptoms or lack thereof (48). Plasma NfL and GFAP was also assessed in hospitalized and non-hospitalized COVID-19 patients with neuro-PASC (41). In this population, both previously hospitalized and non-hospitalized patients experienced decreased quality of life measures (PROMIS) and cognitive dysfunction (NIH Toolbox T scores). Notably, a higher neuroglial score (GFAP/NfL ratio) correlated with increased patient reported anxiety/depression and data suggested that neuro-PASC patients have decreased quality of life irrespective of disease severity. An important caveat to this study was the lack of a control population, namely, patients with COVID-19 but with no neurological symptoms (41). Boni et al. found that in a subgroup of neuro-PASC patients, persistent headaches were not associated to increased NfL and GFAP levels, potentially indicating that this symptom may not be a sign of underlying neuronal damage or neuroinflammation (49). Taken together, the literature is to some extent limited and at variance for the use of these biomarkers in neuro-PASC.

2.1.2. Tau proteins

Tau is a microtubule-associated protein involved in microtubule assembly and stability in CNS axons. Neuronal neurofibrillary tangles and neuropil threads containing hyperphosphorylated tau are pathological features of AD (50). Soluble tau found in CSF, namely, total tau (T-tau) and phosphorylated tau at threonine 181 (p-tau181) have been widely studied in AD (51). Phosphorylated tau has also been reliably detected in blood (52–55). These biomarkers have also been found in neuro-COVID-19 patients (33, 36, 37, 43, 56). COVID-19 patients with new neurological events during hospitalization or presenting with encephalopathy had elevated plasma T-tau and p-tau181 in comparison to patients without these clinical entities. A rise in T-tau and p-tau181 also correlated with symptom severity (36). It was shown that Tau protein levels at admission may also accurately predict fatal outcome (33) although it was not related to ICU transfers (33). A significant correlation between p-tau181, NfL, GFAP levels at admission was also identified; this was however not observed with other inflammatory biomarkers, namely,

IL-6, CRP, or ferritin (36). Furthermore, elevated p-tau181 was associated to increased admission, and elevated T-tau was associated with a lower rate of discharge home (36) and in hospital death (36). Conversely, CSF T-tau has been shown to be increased in neuro-COVID-19 patients but not associated to clinical outcomes (45). Paterson et al. found that T-tau and p-tau were also not significantly elevated in the CSF of neuro-COVID-19 patients when compared to non-COVID-19 controls (47). Increased levels of T-tau and p-tau181 have however been correlated with NfL levels (37, 56), notably in patients that report neurological sequelae (56). To date, there are no studies evaluating these biomarkers in neuro-PASC, specifically.

2.2. Inflammatory biomarkers

2.2.1. IL-6, IL-10, TNF-α, and CPR

Although the pathophysiologic processes of PASC are not fully understood, immune activation has been proposed to play an important role in the biology of the disease (57, 58); notably, inflammatory biomarkers have been associated with persisting symptoms (57, 59), and major contributing factors in neuropathological processes (60). Namely, IL-6, IL-10, TNF-α and CRP (61, 62) were found to be elevated in the serum of patients with COVID-19 (46, 61, 63–66) and IL-6, IL-10, and CRP have been found to correlate with symptom severity (61, 67). Deceased COVID-19 patients were shown to have higher levels of IL-6 and CRP and were associated to poor clinical outcome and severe organ failure (63). Furthermore, patients with neurological symptoms had increased levels of IL-10 (68) and IL-6 (46). Encephalopathy and inflammatory neurological diseases such as encephalitis, meningitis, acute myelitis was associated with an increase in CSF IL-6 levels (64). It is to be noted that patients only presenting headache as a persistent symptom did not reveal increased inflammatory biomarkers (64). This may suggest that more severe neurological conditions may be correlated with inflammatory process and biomarker expression. TNF-α levels were higher in neuro-PASC patients (46), but when compared to ICU patients, levels did not differ (68) suggesting that ICU patients may had an underlying inflammatory process that could not be discriminated from COVID-19 neurological sequalae. In a study examining neuronal-enriched extracellular vesicles in the plasma of COVID-19 patients 21 days after illness onset, no difference was observed in TNF-α between patients with and without neurological symptoms, which were primarily related to cognitive impairment (56). In contrast, IL-6 tended to be higher (56). In patients with self-reported neuro-PASC, plasma IL-6 and TNF-α measured at late (> 90 days) recovery were significantly higher compared to levels in patients who did not go on to report neuro-PASC symptoms (46). This suggest that inflammation is still present even after infection resolution and may be related to persistent immune response (46). IL-10, TNF-α, CRP and IL-6 have potential diagnostic value for COVID-19 (65); however, evidence supporting their utility in neuro-PASC is presently sparse.

3. Limitations

The definition of the timeline for PASC is not unanimous (6). The World Health Organization suggested that post-COVID-19 occurs in individuals after SARS-CoV-2 infection, usually 3 months from onset of COVID-19 with symptoms that last for at least 2 months that cannot be explained by another clinical entity (8). Several limitations exist in terms of definitions for PASC especially due to the lack of systematic description (6) making it difficult to truly characterize patients presenting this syndrome. Since neurological manifestations are not specifically defined, it is difficult to stratify the study population. Furthermore, a potential confounding factor could be the influence of vaccination on physiological variation of biomarkers in COVID-19 patients, including neuro-PASC patients. To our knowledge, none of the studies have considered the effects of vaccination on the study population. In fact, a few studies specified that recruitment of their study participants was made before the availability of COVID-19 vaccines (41, 46, 68). Therefore, more studies need to be conducted to assess the influence of biomarkers in vaccinated and non-vaccinated population presenting neurological sequalae. Additionally, since GFAP, NfL and tau proteins are presently being used as biomarkers in neurodegenerative diseases, there is also a need to distinguish neuro-PASC from early neurodegenerative processes (69). Furthermore, although there are established relationships between blood and CSF measurements for these markers in other diseases, this has not been thoroughly established for COVID-19 (47).

An important limitation is also the small size of participants in studies (32, 38, 39, 41, 48), which may not accurately reflect the potential future applicability of these biomarkers in a clinical setting. Replication of findings in a larger and more diverse cohorts with distinct phenotypic clusters of symptoms (subgroups) may be a first step toward identifying reliable biomarkers. This could also give some much needed insight into the pathobiology of neuro-PASC, as nervous system affection in COVID-19 and neuro-PASC remains elusive (70). Acute neurological dysfunctions may be caused by direct viral invasion, para-infectious complications, secondary neurological manifestations of systemic disease, or coincident neurological dysfunction in the context of high SARS-CoV-2 prevalence (71). A deeper understanding of the molecular underpinning of the disease will be a linchpin in the discovery of clinically relevant biomarkers. Future large-scale studies should also look to delineate whether SARS-CoV-2 infection affects the levels of biomarkers in the absence of neurologic sequelae (41) to ensure their specificity. Furthermore, a full neurological, psychiatric, and cognitive evaluation as well as neuroimaging data would be ideal; something that was not available or feasible in many studies (32, 36, 38, 48). Studies that include such objective measurements are likely to be more informative and are urgently needed. Ultimately, more research is needed to evaluate the usefulness of these biomarkers in neuro-PASC (72). Moreover, the highlighted biomarkers herein are not the only prospective biomarkers; others have been identified and should be considered in studies looking to identify or validate potential biomarkers (73).

4. Conclusion

A handful of studies have explored the measurement of biomarkers NfL, GFAP, tau proteins, IL-6, IL-10, TNF-α, and CPR during acute COVID-19 and PASC. In some cases, higher levels were identified in patients with neurologic symptoms; however, other studies have not corroborated these findings. Ultimately, more research is needed to evaluate the usefulness of these biomarkers in neuro-PASC. Longitudinal clinical, biological, and neuropathological studies are required to better understand the long-term consequences

of SARS-CoV-2 infection on the brain and the identification of clinically relevant biomarker in neuro-PASC. Presently, the use of these biomarkers in diagnosing and prognostication neuro-PASC remains tenuous.

Author contributions

DC and MM drafted the manuscript under the supervision of LC-W. GAR and LC-W contributed to writing and editing the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by grants from: the New Brunswick (NB) Health Research Foundation (NBHRF) and the Centre de Formation Médicale du NB (DUO research grant # DUO2023). GAR is supported by the Canadian Cancer Society (Grant # CHA-22).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*. (2021) 8:416–27. doi: 10.1016/S2215-0366(21)00084-5

2. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127

3. Boldrini M, Canoll PD, Klein RS. How COVID-19 affects the brain. *JAMA Psychiat*. (2021) 78:682–3. doi: 10.1001/jamapsychiatry.2021.0500

4. Pilotto A, Cristillo V, Cotti Piccinelli S, Zoppi N, Bonzi G, Sattin D, et al. Long-term neurological manifestations of COVID-19: prevalence and predictive factors. *Neurol Sci*. (2021) 42:4903–7. doi: 10.1007/s10072-021-05586-4

5. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*. (2021) 38:101019. doi: 10.1016/j.eclinm.2021.101019

6. Badenoch JB, Rengasamy ER, Watson C, Jansen K, Chakraborty S, Sundaram RD, et al. Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. *Brain Commun*. (2022) 4:fcab297. doi: 10.1093/braincomms/fcab297

7. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ*. (2020) 370:m3026. doi: 10.1136/bmj.m3026

8. Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, et al. Fatigue and cognitive impairment in post-COVID-19 syndrome: a systematic review and meta-analysis. *Brain Behav Immun*. (2022) 101:93–135. doi: 10.1016/j.bbi.2021.12.020

9. Miskowiak KW, Fugledalen L, Jespersen AE, Sattler SM, Podlekareva D, Rungby J, et al. Trajectory of cognitive impairments over 1 year after COVID-19 hospitalisation: pattern, severity, and functional implications. *Eur Neuropsychopharmacol*. (2022) 59:82–92. doi: 10.1016/j.euroneuro.2022.04.004

10. Lleó A. Biomarkers in neurological disorders: a fast-growing market. *Brain Commun*. (2021) 3:fcab086. doi: 10.1093/braincomms/fcab086

11. Hansson O. Biomarkers for neurodegenerative diseases. *Nat Med*. (2021) 27:954–63. doi: 10.1038/s41591-021-01382-x

12. Balogun WG, Zetterberg H, Blennow K, Karikari TK. Plasma biomarkers for neurodegenerative disorders: ready for prime time? *Curr Opin Psychiatry*. (2023) 36:112–8. doi: 10.1097/YCO.0000000000000851

13. McMahon PJ, Panczykowski DM, Yue JK, Puccio AM, Inoue T, Sorani MD, et al. Measurement of the glial fibrillary acidic protein and its breakdown products GFAP-BDP biomarker for the detection of traumatic brain injury compared to computed tomography and magnetic resonance imaging. *J Neurotrauma*. (2015) 32:527–33. doi: 10.1089/neu.2014.3635

14. Zetterberg H, Blennow K. Fluid biomarkers for mild traumatic brain injury and related conditions. *Nat Rev Neurol*. (2016) 12:563–74. doi: 10.1038/nrneurol.2016.127

15. Ashton NJ, Janelidze S, al Khleifat A, Leuzy A, van der Ende EL, Karikari TK, et al. A multicentre validation study of the diagnostic value of plasma neurofilament light. *Nat Commun*. (2021) 12:3400. doi: 10.1038/s41467-021-23620-z

16. Ashton NJ, Hye A, Rajkumar AP, Leuzy A, Snowden S, Suárez-Calvet M, et al. An update on blood-based biomarkers for non-Alzheimer neurodegenerative disorders. *Nat Rev Neurol*. (2020) 16:265–84. doi: 10.1038/s41582-020-0348-0

17. Khalil M, Teunissen CE, Otto M, Piehl F, Sormani MP, Gattringer T, et al. Neurofilaments as biomarkers in neurological disorders. *Nat Rev Neurol*. (2018) 14:577–89. doi: 10.1038/s41582-018-0058-z

18. Preische O, Schultz SA, Apel A, Kuhle J, Kaeser SA, Barro C, et al. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. *Nat Med*. (2019) 25:277–83. doi: 10.1038/s41591-018-0304-3

19. Johnson SC, Suárez-Calvet M, Suridjan I, Minguillón C, Gispert JD, Jonaitis E, et al. Identifying clinically useful biomarkers in neurodegenerative disease through a collaborative approach: the NeuroToolKit. *Alzheimers Res Ther*. (2023) 15:25. doi: 10.1186/s13195-023-01168-y

20. Delcoigne B, Manouchehrinia A, Barro C, Benkert P, Michalak Z, Kappos L, et al. Blood neurofilament light levels segregate treatment effects in multiple sclerosis. *Neurology*. (2020) 94:e1201–12. doi: 10.1212/WNL.0000000000009097

21. Olsson B, Alberg L, Cullen NC, Michael E, Wahlgren L, Kroksmark AK, et al. NFL is a marker of treatment response in children with SMA treated with nusinersen. *J Neurol*. (2019) 266:2129–36. doi: 10.1007/s00415-019-09389-8

22. Chatterjee P, Pedrini S, Stoops E, Goozee K, Villemagne VL, Asih PR, et al. Plasma glial fibrillary acidic protein is elevated in cognitively normal older adults at risk of Alzheimer's disease. *Transl Psychiatry*. (2021) 11:27. doi: 10.1038/s41398-020-01137-1

23. Ferrari-Souza JP, Ferreira PCL, Bellaver B, Tissot C, Wang YT, Leffa DT, et al. Astrocyte biomarker signatures of amyloid-β and tau pathologies in Alzheimer's disease. *Mol Psychiatry*. (2022) 27:4781–9. doi: 10.1038/s41380-022-01716-2

24. Benussi A, Ashton NJ, Karikari TK, Gazzina S, Premi E, Benussi L, et al. Serum glial fibrillary acidic protein (GFAP) is a marker of disease severity in frontotemporal lobar degeneration. *J Alzheimers Dis*. (2020) 77:1129–41. doi: 10.3233/JAD-200608

25. Katisko K, Cajanus A, Huber N, Jääskeläinen O, Kokkola T, Kärkkäinen V, et al. GFAP as a biomarker in frontotemporal dementia and primary psychiatric disorders: diagnostic and prognostic performance. *J Neurol Neurosurg Psychiatry*. (2021) 92:1305–12. doi: 10.1136/jnnp-2021-326487

26. Abdelhak A, Huss A, Kassubek J, Tumani H, Otto M. Serum GFAP as a biomarker for disease severity in multiple sclerosis. *Sci Rep*. (2018) 8:14798. doi: 10.1038/s41598-018-33158-8

27. Barro C, Healy BC, Liu Y, Saxena S, Paul A, Polgar-Turcsanyi M, et al. Serum GFAP and NfL levels differentiate subsequent progression and disease activity in patients with progressive multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. (2023) 10:e200052. doi: 10.1212/NXI.0000000000200052

28. Garcia MA, Barreras PV, Lewis A, Pinilla G, Sokoll LJ, Kickler T, et al. Cerebrospinal fluid in COVID-19 neurological complications: Neuroaxonal damage, anti-SARS-Cov2 antibodies but no evidence of cytokine storm. *J Neurol Sci*. (2021) 427:117517. doi: 10.1016/j.jns.2021.117517

29. Ameres M, Brandstetter S, Toncheva AA, Kabesch M, Leppert D, Kuhle J, et al. Association of neuronal injury blood marker neurofilament light chain with mild-to-moderate COVID-19. *J Neurol*. (2020) 267:3476. doi: 10.1007/s00415-020-10050-y

30. Sutter R, Hert L, de Marchis GM, Twerenbold R, Kappos L, Naegelin Y, et al. Serum Neurofilament light chain levels in the intensive care unit: comparison between severely ill patients with and without coronavirus disease 2019. *Ann Neurol*. (2021) 89:610–6. doi: 10.1002/ana.26004

31. Cooper J, Stukas S, Hoiland RL, Fergusson NA, Thiara S, Foster D, et al. Quantification of neurological blood-based biomarkers in critically ill patients with coronavirus disease 2019. *Crit Care Explor*. (2020) 2:e0238. doi: 10.1097/CCE.0000000000000238

32. Aamodt AH, Høgestøl EA, Popperud TH, Holter JC, Dyrhol-Riise AM, Tonby K, et al. Blood neurofilament light concentration at admittance: a potential prognostic marker in COVID-19. *J Neurol*. (2021) 268:3574–83. doi: 10.1007/s00415-021-10517-6

33. De Lorenzo R, Loré NI, Finardi A, Mandelli A, Cirillo DM, Tresoldi C, et al. Blood neurofilament light chain and total tau levels at admission predict death in COVID-19 patients. *J Neurol*. (2021) 268:4436–42. doi: 10.1007/s00415-021-10595-6

34. Frithiof R, Rostami E, Kumlien E, Virhammar J, Fällmar D, Hultström M, et al. Critical illness polyneuropathy, myopathy and neuronal biomarkers in COVID-19 patients: a prospective study. *Clin Neurophysiol*. (2021) 132:1733–40. doi: 10.1016/j.clinph.2021.03.016

35. Prudencio M, Erben Y, Marquez CP, Jansen-West KR, Franco-Mesa C, Heckman MG, et al. Serum neurofilament light protein correlates with unfavorable clinical outcomes in hospitalized patients with COVID-19. *Sci Transl Med*. (2021) 13:abi7643. doi: 10.1126/scitranslmed.abi7643

36. Frontera JA, Boutajangout A, Masurkar AV, Betensky RA, Ge Y, Vedvyas A, et al. Comparison of serum neurodegenerative biomarkers among hospitalized COVID-19 patients versus non-COVID subjects with normal cognition, mild cognitive impairment, or Alzheimer's dementia. *Alzheimers Dement*. (2022) 18:899–910. doi: 10.1002/alz.12556

37. Chaumont H, Kaczorowski F, San-Galli A, Michel PP, Tressières B, Roze E, et al. Cerebrospinal fluid biomarkers in SARS-CoV-2 patients with acute neurological syndromes. *Rev Neurol (Paris)*. (2023) 179:208–17. doi: 10.1016/j.neurol.2022.11.002

38. Sahin BE, Celikbilek A, Kocak Y, Saltoglu GT, Konar NM, Hizmali L. Plasma biomarkers of brain injury in COVID-19 patients with neurological symptoms. *J Neurol Sci*. (2022) 439:120324. doi: 10.1016/j.jns.2022.120324

39. Kanberg N, Ashton NJ, Andersson LM, Yilmaz A, Lindh M, Nilsson S, et al. Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. *Neurology*. (2020) 95:e1754–9. doi: 10.1212/WNL.0000000000010111

40. Kanberg N, Simrén J, Edén A, Andersson LM, Nilsson S, Ashton NJ, et al. Neurochemical signs of astrocytic and neuronal injury in acute COVID-19 normalizes during long-term follow-up. *EBioMedicine*. (2021) 70:103512. doi: 10.1016/j.ebiom.2021.103512

41. Hanson BA, Visvabharathy L, Ali ST, Kang AK, Patel TR, Clark JR, et al. Plasma biomarkers of Neuropathogenesis in hospitalized patients with COVID-19 and those with Postacute sequelae of SARS-CoV-2 infection. *Neurol Neuroimmunol Neuroinflamm*. (2022) 9:e1151. doi: 10.1212/NXI.0000000000001151

42. Verde F, Milone I, Bulgarelli I, Peverelli S, Colombrita C, Maranzano A, et al. Serum neurofilament light chain levels in Covid-19 patients without major neurological manifestations. *J Neurol*. (2022) 269:5691–701. doi: 10.1007/s00415-022-11233-5

43. Espíndola OM, Brandão CO, Gomes YCP, Siqueira M, Soares CN, Lima MASD, et al. Cerebrospinal fluid findings in neurological diseases associated with COVID-19 and insights into mechanisms of disease development. *Int J Infect Dis*. (2021) 102:155–62. doi: 10.1016/j.ijid.2020.10.044

44. Mariotto S, Savoldi A, Donadello K, Zanzoni S, Bozzetti S, Carta S, et al. Nervous system: subclinical target of SARS-CoV-2 infection. *J Neurol Neurosurg Psychiatry*. (2020) 91:1010–2. doi: 10.1136/jnnp-2020-323881

45. Virhammar J, Nääs A, Fällmar D, Cunningham JL, Klang A, Ashton NJ, et al. Biomarkers for central nervous system injury in cerebrospinal fluid are elevated in COVID-19 and associated with neurological symptoms and disease severity. *Eur J Neurol*. (2021) 28:3324–31. doi: 10.1111/ene.14703

46. Peluso MJ, Sans HM, Forman CA, Nylander AN, Ho HE, Lu S, et al. Plasma markers of neurologic injury and inflammation in people with self-reported neurologic Postacute sequelae of SARS-CoV-2 infection. *Neurol Neuroimmunol Neuroinflamm*. (2022) 9:e200003. doi: 10.1212/NXI.0000000000200003

47. Paterson RW, Benjamin LA, Mehta PR, Brown RL, Athauda D, Ashton NJ, et al. Serum and cerebrospinal fluid biomarker profiles in acute SARS-CoV-2-associated neurological syndromes. *Brain Commun*. (2021) 3:fcab099. doi: 10.1093/braincomms/fcab099

48. Bozzetti S, Ferrari S, Zanzoni S, Alberti D, Braggio M, Carta S, et al. Neurological symptoms and axonal damage in COVID-19 survivors: are there sequelae? *Immunol Res*. (2021) 69:553–7. doi: 10.1007/s12026-021-09220-5

49. de Boni L, Odainic A, Gancarczyk N, Kaluza L, Strassburg CP, Kersting XAK, et al. No serological evidence for neuronal damage or reactive gliosis in neuro-COVID-19 patients with long-term persistent headache. *Neurol Res Pract*. (2022) 4:53. doi: 10.1186/s42466-022-00217-5

50. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegener*. (2019) 14:32. doi: 10.1186/s13024-019-0333-5

51. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. *J Intern Med*. (2018) 284:643–63. doi: 10.1111/joim.12816

52. Janelidze S, Mattsson N, Palmqvist S, Smith R, Beach TG, Serrano GE, et al. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. *Nat Med*. (2020) 26:379–86. doi: 10.1038/s41591-020-0755-1

53. Lantero Rodriguez J, Karikari TK, Suárez-Calvet M, Troakes C, King A, Emersic A, et al. Plasma p-tau181 accurately predicts Alzheimer's disease pathology at least 8 years prior to post-mortem and improves the clinical characterisation of cognitive decline. *Acta Neuropathol*. (2020) 140:267–78. doi: 10.1007/s00401-020-02195-x

54. Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, et al. Discriminative accuracy of plasma Phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. *JAMA*. (2020) 324:772–81. doi: 10.1001/jama.2020.12134

55. Thijssen EH, La Joie R, Wolf A, Strom A, Wang P, Iaccarino L, et al. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. *Nat Med*. (2020) 26:387–97. doi: 10.1038/s41591-020-0762-2

56. Sun B, Tang N, Peluso MJ, Iyer NS, Torres L, Donatelli JL, et al. Characterization and biomarker analyses of post-COVID-19 complications and neurological manifestations. *Cells*. (2021) 10:20386. doi: 10.3390/cells10020386

57. Peluso MJ, Lu S, Tang AF, Durstenfeld MS, Ho HE, Goldberg SA, et al. Markers of immune activation and inflammation in individuals with Postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection. *J Infect Dis*. (2021) 224:1839–48. doi: 10.1093/infdis/jiab490

58. Ong SWX, Fong SW, Young BE, Chan YH, Lee B, Amrun SN, et al. Persistent symptoms and association with inflammatory cytokine signatures in recovered coronavirus disease 2019 patients. Open forum. *Infect Dis*. (2021) 8:ofab156. doi: 10.1093/ofid/ofab156

59. Kappelmann N, Dantzer R, Khandaker GM. Interleukin-6 as potential mediator of long-term neuropsychiatric symptoms of COVID-19. *Psychoneuroendocrinology*. (2021) 131:105295. doi: 10.1016/j.psyneuen.2021.105295

60. Wang WY, Tan MS, Yu JT, Tan L. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. *Ann Transl Med*. (2015) 3:136. doi: 10.3978/j.issn.2305-5839.2015.03.49

61. Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, et al. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerg Microbes Infect*. (2020) 9:1123–30. doi: 10.1080/22221751.2020.1770129

62. Wang G, Wu C, Zhang Q, Wu F, Yu B, Lv J, et al. C-reactive protein level may predict the risk of COVID-19 aggravation. Open forum. *Infect Dis*. (2020) 7:ofaa153. doi: 10.1093/ofid/ofaa153

63. Lavillegrand JR, Garnier M, Spaeth A, Mario N, Hariri G, Pilon A, et al. Elevated plasma IL-6 and CRP levels are associated with adverse clinical outcomes and death in critically ill SARS-CoV-2 patients: inflammatory response of SARS-CoV-2 patients. *Ann Intensive Care*. (2021) 11:9. doi: 10.1186/s13613-020-00798-x

64. Espíndola OM, Gomes YCP, Brandão CO, Torres RC, Siqueira M, Soares CN, et al. Inflammatory cytokine patterns associated with neurological diseases in coronavirus disease 2019. *Ann Neurol*. (2021) 89:1041–5. doi: 10.1002/ana.26041

65. Lu Q, Zhu Z, Tan C, Zhou H, Hu Y, Shen G, et al. Changes of serum IL-10, IL-1β, IL-6, MCP-1, TNF-α, IP-10 and IL-4 in COVID-19 patients. *Int J Clin Pract*. (2021) 75:e14462. doi: 10.1111/ijcp.14462

66. Frontera JA, Sabadia S, Lalchan R, Fang T, Flusty B, Millar-Vernetti P, et al. A prospective study of neurologic disorders in hospitalized patients with COVID-19 in new York City. *Neurology*. (2021) 96:e575–86. doi: 10.1212/WNL.0000000000010979

67. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *J Med Virol*. (2020) 92:856–62. doi: 10.1002/jmv.25871

68. Bonetto V, Pasetto L, Lisi I, Carbonara M, Zangari R, Ferrari E, et al. Markers of blood-brain barrier disruption increase early and persistently in COVID-19 patients with neurological manifestations. *Front Immunol*. (2022) 13:1070379. doi: 10.3389/fimmu.2022.1070379

69. Spudich S, Nath A. Nervous system consequences of COVID-19. *Science*. (2022) 375:267–9. doi: 10.1126/science.abm2052

70. Boldrini M, Canoll PD, Klein RS. How does COVID-19 affect the brain? *Tidsskr Nor Laegeforen*. (2020) 140:444. doi: 10.4045/tidsskr.20.0444

71. Needham EJ, Chou SHY, Coles AJ, Menon DK. Neurological implications of COVID-19 infection. *Neurocrit Care*. (2020) 32:667–71. doi: 10.1007/s12028-020-00978-4

72. Frontera J, Mainali S, Fink EL, Robertson CL, Schober M, Ziai W, et al. Global consortium study of neurological dysfunction in COVID-19 (GCS-NeuroCOVID): study design and rationale. *Neurocrit Care*. (2020) 33:25–34. doi: 10.1007/s12028-020-00995-3

73. Lai YJ, Liu SH, Manachevakul S, Lee TA, Kuo CT, Bello D. Biomarkers in long COVID-19: a systematic review. *Front Med (Lausanne)*. (2023) 10:1085988. doi: 10.3389/fmed.2023.1085988

frontiers | Frontiers in Neurology

TYPE Perspective
PUBLISHED 31 July 2023
DOI 10.3389/fneur.2023.1239182

OPEN ACCESS

EDITED BY
Thorsten Rudroff,
The University of Iowa, United States

REVIEWED BY
Maria Aparecida Bicalho,
Federal University of Minas Gerais, Brazil

*CORRESPONDENCE
Hao Li
✉ xyhplihao@126.com
Zhiyong Wang
✉ wzyl00@126.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 13 June 2023
ACCEPTED 12 July 2023
PUBLISHED 31 July 2023

CITATION
Li Z, Zhang Z, Zhang Z, Wang Z and Li H (2023) Cognitive impairment after long COVID-19: current evidence and perspectives. *Front. Neurol.* 14:1239182. doi: 10.3389/fneur.2023.1239182

Cognitive impairment after long COVID-19: current evidence and perspectives

Zhitao Li[1,2†], Zhen Zhang[3†], Zhuoya Zhang[4†], Zhiyong Wang[3*] and Hao Li[1*]

[1]Wangjing Hospital of China Academy of Chinese Medical Sciences, Beijing, China, [2]The Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, China, [3]Xiyuan Hospital of China Academy of Chinese Medical Sciences, Beijing, China, [4]Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China

COVID-19, caused by the SARS-CoV-2 virus, is a respiratory infectious disease. While most patients recover after treatment, there is growing evidence that COVID-19 may result in cognitive impairment. Recent studies reveal that some individuals experience cognitive deficits, such as diminished memory and attention, as well as sleep disturbances, suggesting that COVID-19 could have long-term effects on cognitive function. Research indicates that COVID-19 may contribute to cognitive decline by damaging crucial brain regions, including the hippocampus and anterior cingulate cortex. Additionally, studies have identified active neuroinflammation, mitochondrial dysfunction, and microglial activation in COVID-19 patients, implying that these factors may be potential mechanisms leading to cognitive impairment. Given these findings, the possibility of cognitive impairment following COVID-19 treatment warrants careful consideration. Large-scale follow-up studies are needed to investigate the impact of COVID-19 on cognitive function and offer evidence to support clinical treatment and rehabilitation practices. In-depth neuropathological and biological studies can elucidate precise mechanisms and provide a theoretical basis for prevention, treatment, and intervention research. Considering the risks of the long-term effects of COVID-19 and the possibility of reinfection, it is imperative to integrate basic and clinical research data to optimize the preservation of patients' cognitive function and quality of life. This integration will also offer valuable insights for responding to similar public health events in the future. This perspective article synthesizes clinical and basic evidence of cognitive impairment following COVID-19, discussing potential mechanisms and outlining future research directions.

KEYWORDS

SARS-CoV-2, post-COVID cognitive impairment, neuroinflammation, mitochondrial dysfunction, neurodegeneration

Introduction

COVID-19 is an acute infectious disease caused by the novel coronavirus (SARS-CoV-2) that can manifest as asymptomatic or severe pneumonia and multiple organ failure (1). Severe cases may present with high fever, dry cough, dyspnea, acute respiratory failure, septic shock, myocardial injury, and other complications (2). The global case fatality rate of COVID-19 is currently ~3.5%, but it can reach 15% or higher for high-risk groups, particularly older adults with underlying diseases (3, 4). Viral pneumonia, such as SARS and MERS, has been shown to cause cognitive impairment, especially in older individuals

(5, 6). The mechanism may be related to direct viral infection of the CNS, extensive inflammatory response resulting from cytokine release and neurotoxicity, tissue hypoxia, and microangiopathy (7, 8). COVID-19 infection may also cause cognitive dysfunction. Some patients experience headaches, dizziness, and fatigue during the acute phase, and case reports have shown abnormal brain imaging findings (9, 10).

Patients recovering from COVID-19 have reported cognitive problems such as decreased memory and attention and sleep disorder. Studies have shown that some patients had abnormal results in neuropsychological tests, exhibiting declined working memory, language expression, and executive function (11–13). Given that the COVID-19 virus can invade the central nervous system by crossing the blood–brain barrier and nasal mucosa and infect neural cells, such as neurons, astrocytes, and microglia, that assist in their transport, it may directly damage the structure and function of the brain, leading to cognitive impairment (14, 15). In addition to the direct infection, COVID-19 may affect cognition through other mechanisms. First, the cytokine storm and widespread neuroinflammation triggered by the COVID-19 virus may disrupt neural circuits and connections, leading to neurotransmitter changes (16, 17). Second, sustained activation of the sympathetic nervous system and metabolic abnormalities can also damage the brain's vulnerable cognitive-related areas (18). Third, persistent hypoxemia caused by the disease can damage the brain tissue and affect neural activity (19). Finally, thrombus formation and microangiopathy caused by COVID-19 may also reduce cerebral blood flow, impairing cognitive function (20). Although most patients recovering from COVID-19 experience spontaneous recovery of cognitive function over time, some individuals, especially older adults and those with underlying diseases, may face long-term cognitive impairment (21, 22). Especially under the current situation of long COVID infections globally, it is necessary to strengthen the assessment of cognitive function in recovering individuals, paying particular attention to those with more severe conditions and longer hospital stays. Once abnormalities are detected, early identification and customized intervention should be provided. At the same time, accelerating the exploration of relevant mechanisms will help guide treatment and follow-up, thereby minimizing the impact of this complication and protecting the cognitive health of COVID-19 recoverers.

Evidence of post-COVID cognitive impairment: neuropsychological and neuroimaging findings

After recovering from COVID-19, some patients have shown cognitive abnormalities, such as a decline in working memory, language expression, and executive function, as revealed by neuropsychological tests conducted after discharge. These findings suggest that COVID-19 may impair specific cognitive domains, such as executive control and working memory. In a survey of 969 people with SARS-CoV-2 infection 6–11 months ago, 26% of patients had mild cognitive impairment (23). A meta-analysis involving 2,049 people (24) suggested that COVID-19 patients had different MoCA scores than controls. COVID-19 recoverers showed lower general cognitive ability up to 7 months after infection. This was mainly reflected in visuospatial and executive function, while language and calculation abilities were relatively preserved (25). In executive function tests, some patients showed impaired executive control function, increased interference effects, and prolonged reaction times (26). This suggests that COVID-19 may damage the prefrontal cortex and executive control network, leading to attention-shifting and behavioral inhibition disorders. Baseler HA et al.'s study (27) found that in the working memory quiz, COVID-19 patients were significantly lower than non-COVID-19 patients. Some COVID-19 patients had retroactive interference disorders, making recalling and repeating the digit sequences they had just heard difficult. This suggests that COVID-19 may damage the hippocampus and related brain regions, affecting working memory's encoding and retrieval processes. In addition, a few studies have also found that COVID-19 patients have decreased language expressiveness and vocabulary. For example, in language fluency tests, the number of words generated by patients was lower than that in the healthy control group (28, 29). This may be due to the damage to brain regions closely related to language functions, leading to disorders of language fluency and vocabulary retrieval.

Brain imaging studies have found mild abnormalities in the brain structure and function of COVID-19 patients, possibly related to cognitive decline (30). Studies using structural magnetic resonance imaging (MRI) found that a few patients had mild atrophy of the hippocampus, gray matter, and mild ventriculomegaly (31). This suggests that COVID-19 may indirectly lead to brain tissue atrophy and ventriculomegaly by damaging neurons and synapses around the ventricles. These changes occur in brain regions with dense memory and cognitive networks, possibly related to decreased working memory and executive function. Positron emission tomography (PET) studies also found that glucose metabolism decreased in some patients' hippocampus, prefrontal cortex, and posterior cingulate cortex (32). This implies that these brain regions may have functional impairments after COVID-19 as glucose is the main energy source for these brain regions and is closely related to their activity. This could lead to decreased cognitive functions such as executive control, attention, and memory.

Another study compared the functional connectivity of the default network in 22 COVID-19 patients and healthy controls using resting-state fMRI. The results showed that the connectivity strength of the default network was weakened in the former group. The connectivity of the executive control network and emotional regulation network also changed (33). This suggests that COVID-19 can remodel brain functional networks and affect brain functional connectivity closely related to cognitive function.

In addition, relevant studies have also reported persistent cognitive impairments in COVID-19 patients. For example, a survey of 292 COVID-19 recoverers found that patients generally had physical damage, and these injuries were associated with more cognitive impairments (34). A 1-year prospective cohort study (35) investigated 1,438 COVID-19 survivors and 438 uninfected elderly individuals (all $\geq$60 years old) in China. By conducting cognitive tests at 6 and 12 months, respectively, changes in

cognitive ability between the two groups were compared. The study excluded those with pre-existing cognitive impairment, a family history of dementia, or severe chronic diseases. Compared with the uninfected group, the cognitive decline rate in the infected group was significantly higher, especially in severe COVID-19 survivors. In these participants, the risk of mild cognitive decline was 4.87 times that of the uninfected group, and the risk of severe cognitive decline was 19 times that of the uninfected group. Non-severe COVID-19 was associated with a 1.71-fold increased risk (1.30–2.27) of early cognitive decline. Although the sample size was limited, these studies preliminarily show that a small proportion of COVID-19 patients may continue to suffer from cognitive impairments after recovery. Similarly, an Italian follow-up study of 50 recovered patients found that nearly one-fourth of patients had mild cognitive impairment 60 days after discharge, mainly manifested as decreased executive function and attention (12). A preliminary study of 100 patients by British scholars (36) also found that ∼81% of COVID-19 patients who were not hospitalized had significant and persistent "brain fog" and fatigue symptoms after discharge, affecting their cognition and quality of life. This further confirms the risk of longer-term cognitive abnormalities in COVID-19 recoverers.

Multiple clinical study results support that memory and concentration may decrease persistently after COVID-19 infection. Some patients' neuropsychological tests and brain imaging performances suggest mild cognitive impairment. However, due to the limited sample size and lack of long-term follow-up in existing studies, we lack an in-depth understanding of the impact and incidence of this complication. Large-scale, long-term follow-up studies are needed to comprehensively assess changes in cognitive function after COVID-19 and provide evidence for early intervention.

Potential mechanisms underlying post-COVID cognitive impairment

After recovery from COVID-19, some patients experience subjective memory loss, decreased concentration, and other cognitive problems. This may be related to the following mechanisms.

The COVID-19 virus can directly infect the central nervous system and damage the brain tissue and neurons, which may be an important mechanism leading to cognitive impairment. COVID-19 viral RNA and antigens have been detected in the cerebrospinal fluid and the brain tissue, indicating that the virus can cross the blood–brain barrier to invade the central nervous system (37). Viral surface proteins may promote the spread of protein aggregates in neurodegenerative diseases. The SARS-CoV-2 spike protein promotes the transmission of pathogenic seeds between cells *via* extracellular vesicles and direct intercellular transmission (38). The direct membrane contact mechanism spreads pathogenic seeds, and viral infection may accelerate the spread. Studies have found (39) that the spike protein is associated with memory loss after COVID-19. The SARS-CoV-2 spike protein activates the TLR4 receptor, causing neuroinflammation and microglial phagocytosis of synaptic proteins, leading to memory impairment. SARS-CoV-2-infected patients carrying TLR4-related gene polymorphisms are at higher risk of delayed memory impairment.

The COVID-19 virus can colonize the brain, leading to neuronal death and inflammation (7). This suggests that the virus can directly infect neurons, astrocytes, and vascular endothelial cells in the brain, damaging neural network connections and the integrity of the blood–brain barrier (40). Studies have found that the virus can aggregate around the hippocampus, brain stem, and cerebral blood vessels (41), the areas densely populated by neurons related to memory and cognition. Viral infection can damage synapses and the cytoskeleton, exacerbating neurodegenerative changes and loss of neural synapses (41). This may directly damage the neural circuits on which learning, memory, and executive control depend, leading to decreased cognitive function.

COVID-19 can induce cytokine storms and neuroinflammation, leading to neuronal damage and decreased cognitive function. Multiple inflammatory factors are significantly increased in COVID-19 patients, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) (42, 43). These factors can enhance microglial activity, promote neuroinflammation, and damage neurons and synaptic structures (44, 45). IL-6 can alter the balance of neurotransmitters, such as γ-aminobutyric acid in the brain, and damage neural connections and cognitive processes. TNF-α can damage the blood–brain barrier and enhance the entry of neurotoxic substances into the brain (46). This leads to loss of neural synapses, neuronal death, and reorganization of cognitive networks, resulting in decreased memory and executive function (47). Studies have found that neuroinflammatory markers significantly increase in brain regions closely related to cognitive function, such as the hippocampus, cerebellum, and anterior cingulate cortex (37). This indicates that neuroinflammation may have a greater impact on these brain regions and act with a viral infection to exacerbate neuronal damage and cognitive impairment. In addition, neuroinflammation is also associated with ventriculomegaly and decreased gray matter density, suggesting that it can lead to more extensive brain tissue damage and reorganization of cognitive networks. The cytokine storms and neuroinflammatory responses in COVID-19 patients can damage neurons, synapses, and cognitive network connections, which may be an important mechanism leading to their memory impairment and decreased executive function.

COVID-19 can lead to tissue hypoxia and microvascular lesions, affecting cerebral perfusion and the integrity of the blood–brain barrier, which may impair the function and cognition of brain areas such as the hippocampus. Ischemic lesions were detected in the brains of COVID-19 deceased patients. The S protein of the virus was detected in tissue sections, accompanied by tissue damage and cell death (39). COVID-19 patients often have hypoxemia and tissue hypoxia, and the oxygenated hemoglobin saturation of the brain tissue is also significantly reduced (48). This can lead to energy metabolism disorders and cell apoptosis in key brain areas such as the hippocampus, damaging neuronal structure and function (49). Studies have found that hippocampal volume and functional connectivity positively correlate with blood oxygen saturation (50). This suggests that hypoxia can directly damage the neural network

of the hippocampus and affect cognitive processes. In addition, COVID-19 is often accompanied by microscopic vascular lesions, leading to cerebral vasculitis, thrombosis, and microhemorrhage (51). COVID-19 patients risk multifocal microvascular bleeding and ischemic lesions in the subcortical and deep white matter (52). This reduces cerebral perfusion, damages the blood–brain barrier, and increases neurotoxic substances entering the brain, aggravating neuronal damage (53). Animal experiments have also confirmed that hypoxia and cerebral microvascular lesions can act together to aggravate vascular endothelial damage and damage-related brain regions (54).

COVID-19 can lead to sympathetic excitation and metabolic abnormalities, affecting the brain environment and cognitive function. COVID-19 patients are often accompanied by sympathetic excitation and metabolic disorders such as hyperglycemia, hyperhomocysteinemia, and insulin resistance (55, 56). This can damage the brain's structure and function, such as the hippocampus, by affecting the energy supply and neurotransmitter balance in the key brain areas (57). Hyperglycemia can produce excess free radicals and oxidative stress, damage hippocampal neurons, and is associated with cognitive impairment (58). Hyperhomocysteinemia can also damage the long-term potentiation of the hippocampus, leading to decreased cognitive function (59). Insulin resistance can reduce the transport of apolipoprotein E and cholesterol, affect neurotransmitter synthesis and release, and is associated with cognitive decline (60). The sympathetic excitation and metabolic abnormalities caused by COVID-19, especially hyperglycemia, hyperhomocysteinemia, and insulin resistance, can damage hippocampal neurons, energy supply, and neurotransmitter balance, thereby affecting cognitive processes and functions.

As shown in Figure 1, COVID-19 may impair cognitive function and memory through multiple mechanisms. These various mechanisms should be considered comprehensively when assessing patients' cognitive status and developing intervention plans. Antiviral and immunosuppressive therapies may reduce damage from viral infections and inflammation; improving cerebral perfusion and oxygen supply can correct the effects of hypoperfusion and hypoxia; drug or training methods to regulate the sympathetic nervous system and metabolism are also expected to play a role. In summary, a deeper understanding of the relevant mechanisms will help guide the overall management and cognitive protection of COVID-19 recoverers.

Further research on post-COVID cognitive impairment: key directions

Future research needs to explore the relationship between COVID-19 and cognitive impairment in more depth in the following aspects. First, COVID-19 patients still have some cognitive difficulties during recovery, including problems with memory, multitasking, processing speed, and attention. A large retrospective cohort study of over 2,30,000 patients found (61) that the risk of dementia within 6 months after COVID-19 infection was 2.33 times that of influenza patients during the same period. Studies using online cognitive tests and surveys to assess cognitive function found that 16% of patients developed new or worsening memory impairment, 18% had decreased attention, and 16% had decreased understanding, language expression, or other cognitive abilities. This suggests that COVID-19 may have long-term effects on the cognitive function of some patients, and we need to strengthen the monitoring and management of this population.

Second, studies have found that COVID-19 is associated with changes in the structure and function of the hippocampus and anterior cingulate cortex (62). The hippocampal volume of COVID-19 recoverers is smaller than that of the control group, suggesting neurodegenerative changes. In addition, COVID-19 is associated with weakened activation of the anterior cingulate cortex and ventricular enlargement, which can lead to decreased executive function. This suggests that COVID-19 may damage cognitive functions, such as learning, memory, and executive control, by affecting key brain regions such as the hippocampus and anterior cingulate cortex (63). COVID-19 can affect cognition through mechanisms (64–66) such as infecting neurons, activating microglia, and damaging vascular endothelial cells, while antiviral drugs may reduce neuronal damage caused by viral infection; immune regulation can alleviate viral-triggered neuroinflammation; and improving cerebral blood flow and oxygen supply can alleviate the effects of hypoxia and metabolic abnormalities on cognition. This provides important insights for clinical practice in cognitive rehabilitation and protection.

Studies have found a relationship between increased N-formylmethionine (fMet) levels and neutrophil activation in COVID-19 patients. Compared with healthy controls, COVID-19 patients, especially severe patients, have increased calprotectin, neutrophil extracellular traps (NETs), and fMet levels (67). Some studies show that inflammatory factors and cytokine levels are increased in the myelin and cerebrospinal fluid of Alzheimer's patients, suggesting that neutrophil activation may be involved in the pathogenesis of Alzheimer's disease (68). In addition, some studies have also found that inhibiting neutrophil function can alleviate cognitive impairment and pathological changes in Alzheimer's mice (69). This suggests that neuroinflammation and mitochondrial stress may play a role in COVID-19-induced neuronal damage. In addition, changes in the levels of proteins, such as Aβ42, tau, and neuron-specific enolase in the serum or cerebrospinal fluid, also provide clues to the mechanism of disease-induced neurodegeneration (70, 71). This may be related to the neurodegenerative diseases caused by the disease and provide a theoretical basis for biological markers and new drug development. Genomic studies can also help discover the molecular mechanisms by which the disease affects cognition. In addition, it has been suggested that certain natural compounds, including Ginkgo biloba extract, may hold promise in mitigating cognitive impairment resulting from long COVID-19 (72). However, these compounds' efficacy is yet to be firmly established, and further investigation is required to confirm their potential benefits.

Conclusion

Although current research is not yet systematic and in-depth, COVID-19 recoverers seem to be at higher risk of cognitive

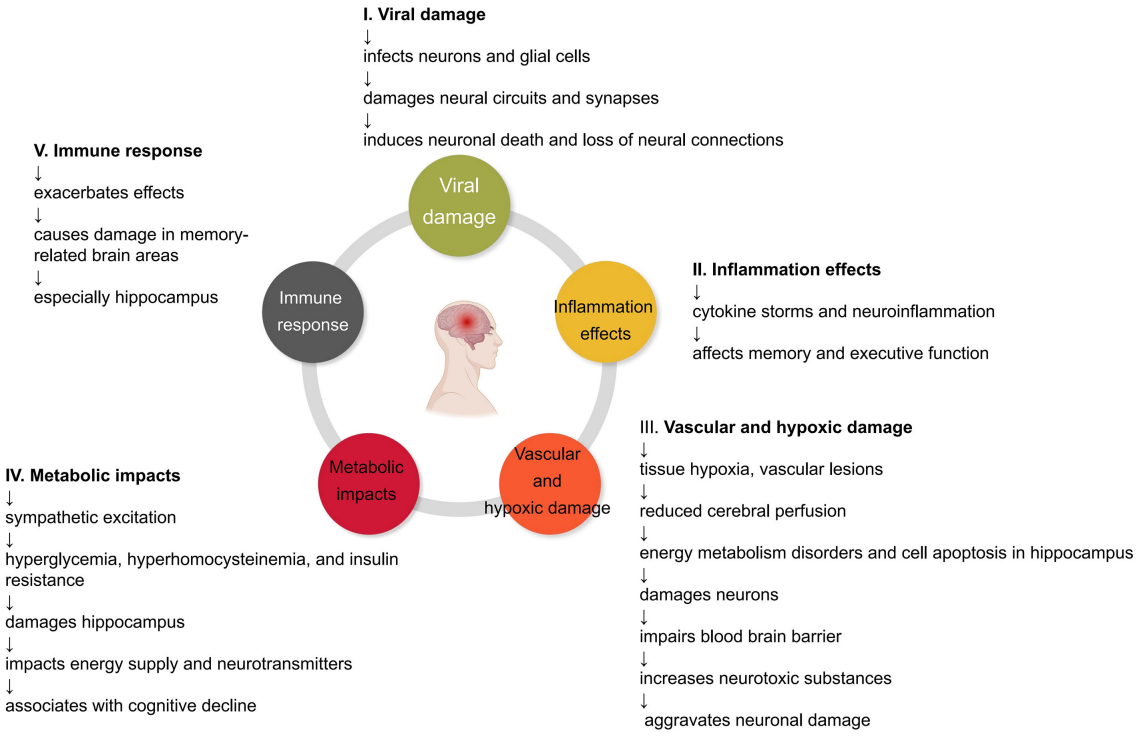


FIGURE 1
Impact of COVID-19 on the brain. Mechanisms by which COVID-19 may impair cognitive function and lead to memory loss. COVID-19 causes damage to the brain through direct viral infection, inflammation, vascular and hypoxic effects, metabolic impacts, and the body's immune response. These ultimately result in the loss of neural connections, reorganization of neural networks, and memory impairment.

impairment, which may be a key aspect of the potential long-term effects of the disease. Various mechanisms of COVID-19, such as viral infection, cytokine storm, microvascular lesions, hypoperfusion, hypoxia, and metabolic abnormalities, can act on the central nervous system together, causing neuronal dysfunction and damage, and then affecting learning, memory, and cognition (73). Recent studies have found that some COVID-19 recoverers have varying degrees of cognitive impairment, especially slower information processing speed, decreased working memory, and impaired executive function (36, 47). In addition, as a common symptom, post-COVID sleep disorder (PCSD) may negatively impact cognitive function. According to recent research (74), the incidence of PCSD may be over 70%, including various types of sleep disorders such as insomnia, hypersomnia, and daytime sleepiness (75, 76). Additionally, the severity of PCSD may be related to the severity of COVID-19 infection and treatment modalities. The COVID-19 virus may affect sleep through various mechanisms (74, 77, 78), including direct invasion of the central nervous system, induction of inflammatory response, and disruption of circadian rhythms. This suggests that we urgently need to conduct intensive monitoring and early identification for this population and develop targeted rehabilitation and intervention programs. Although the effects of COVID-19 on cognitive function are not fully understood, viral infection, neuroinflammation, and microvascular lesions may play an important role. This suggests that antiviral treatment, immune regulation, and improved microcirculation may benefit cognitive protection (79). Combined with multimodal neuroimaging, biomarker monitoring, and clinical assessment, this will help us stratify the risk of cognitive impairment and guide the individualized management of cognitive rehabilitation after COVID-19. In addition, as the scope of vaccination expands, we also need to pay attention to whether the vaccine can stimulate the immune response in the body and affect cognitive function to some extent. This will also be an important direction for future research (80). Combining basic and clinical research to comprehensively assess the impact of the COVID-19 epidemic on cognitive health will be critical.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

HL and ZW contributed to the initial concept and perspectives. ZL, ZheZ, and ZhuZ developed the initial version of the

manuscript. ZL, ZheZ, ZhuZ, and ZW reviewed and edited the manuscript along with HL. All authors read and approved the final manuscript.

Funding

The study was funded by the National Key R&D Program of the Ministry of Science and Technology 'Modernization of TCM' (No. 2022YFC3501400), Innovation Team and Talents Cultivation Program of National Administration of Traditional Chinese Medicine (No. ZYYCXTD-C-202007), the National Natural Science Foundation of China (No. 82004434), Special Training Program for Outstanding Young Scientific and Technological Talents (Innovation) of China Academy of Chinese Medical Sciences (No. ZZ-14-YQ-001), Special Training Program for the National Natural Science Foundation of Xiyuan Hospital, and China Academy of Chinese Medical Sciences (No. XY20-08).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Synowiec A, Szczepański A, Barreto-Duran E, Lie LK, Pyrc K. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): a systemic infection. *Clin Microbiol Rev.* (2021) 34:2. doi: 10.1128/CMR.00133-20

2. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Resp Med.* (2020) 8:475–81. doi: 10.1016/S2213-2600(20)30079-5

3. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis.* (2020) 20:669–77. doi: 10.1016/S1473-3099(20)30243-7

4. López J, Perez-Rojo G, Noriega C, Carretero I, Velasco C, Martinez-Huertas JA, et al. Psychological well-being among older adults during the COVID-19 outbreak: a comparative study of the young-old and the old-old adults. *Int Psychogeriatrics.* (2020) 32:1365–70. doi: 10.1017/S1041610220000964

5. Yu S, Yu M. Severe acute respiratory syndrome coronavirus 2-induced neurological complications. *Front Cell Develop Biol.* (2020) 8:605972. doi: 10.3389/fcell.2020.605972

6. Al-Tawfiq JA, Azhar EI, Memish ZA, Zumla A. Middle East respiratory syndrome coronavirus. *Semin Respir Crit Care Med.* (2021) 42:828–38. doi: 10.1055/s-0041-1733804

7. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol.* (2008) 82:7264–75. doi: 10.1128/JVI.00737-08

8. Miesbach W, Makris M. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. Clinical and applied thrombosis/hemostasis. *J Int Acad Clin Appl Thrombosis/Hemostasis.* (2020) 26:1076029620938149. doi: 10.1177/1076029620938149

9. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, Ueno M. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2 International journal of infectious diseases. *IJID.* (2020) 94:55–8. doi: 10.1016/j.ijid.2020.03.062

10. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol.* (2020) 19:383–4. doi: 10.1016/S1474-4422(20)30109-5

11. Méndez R, Balanzá-Martínez V, Luperdi SC, Estrada I, Latorre A, González-Jiménez P, et al. Short-term neuropsychiatric outcomes and quality of life in COVID-19 survivors. *J Intern Med.* (2021) 290:621–31. doi: 10.1111/joim.13262

12. Mazza MG, Palladini M, De Lorenzo R, Magnaghi C, Poletti S, Furlan R, et al. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: effect of inflammatory biomarkers at three-month follow-up. *Brain Behav Immun.* (2021) 94:138–47. doi: 10.1016/j.bbi.2021.02.021

13. Woo MS, Malsy J, Pöttgen J, Seddiq Zai S, Ufer F, Hadjilaou A, et al. Frequent neurocognitive deficits after recovery from mild COVID-19. *Brain Commun.* (2020) 2:fcaa205. doi: 10.1093/braincomms/fcaa205

14. Abdel-Mannan O, Eyre M, Löbel U, Bamford A, Eltze C, Hameed B, et al. Neurologic and radiographic findings associated with COVID-19 infection in children. *JAMA Neurol.* (2020) 77:1440–5. doi: 10.1001/jamaneurol.2020.2687

15. Song E, Zhang C, Israelow B, Lu-Culligan A, Prado AV, Skriabine S, et al. Neuroinvasion of SARS-CoV-2 in human and mouse brain. *J Exp Med.* (2021) 218:135. doi: 10.1084/jem.20202135

16. Yongzhi X. COVID-19-associated cytokine storm syndrome and diagnostic principles: an old and new Issue. *Emerg Microbes Infect.* (2021) 10:266–76. doi: 10.1080/22221751.2021.1884503

17. Francis AG, Elhadd K, Camera V, Ferreira Dos Santos M, Rocchi C, Adib-Samii P, et al. Acute inflammatory diseases of the central nervous system after SARS-CoV-2 vaccination. *Neurol Neuroimmunol Neuroinflamm.* (2023) 10:63. doi: 10.1212/NXI.0000000000200063

18. Porzionato A, Emmi A, Barbon S, Boscolo-Berto R, Stecco C, Stocco E, et al. Sympathetic activation: a potential link between comorbidities and COVID-19. *The FEBS J.* (2020) 287:3681–8. doi: 10.1111/febs.15481

19. Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of 'happy' hypoxemia in COVID-19. *Respir Res.* (2020) 21:198. doi: 10.1186/s12931-020-01462-5

20. Owens CD, Pinto CB, Detwiler S, Mukli P, Peterfi A, Szarvas Z, et al. Cerebral small vessel disease pathology in COVID-19 patients: a systematic review. *Ageing Res Rev.* (2023) 88:101962. doi: 10.1016/j.arr.2023.101962

21. Liu YH, Wang YR, Wang QH, Chen Y, Chen X, Li Y, et al. Post-infection cognitive impairments in a cohort of elderly patients with COVID-19. *Mol Neurodegener.* (2021) 16:48. doi: 10.1186/s13024-021-00469-w

22. Alonso-Lana S, Marquié M, Ruiz A, Boada M. Cognitive and neuropsychiatric manifestations of COVID-19 and effects on elderly individuals with dementia. *Front Aging Neurosci.* (2020) 12:588872. doi: 10.3389/fnagi.2020.588872

23. Hartung TJ, Neumann C, Bahmer T, Chaplinskaya-Sobol I, Endres M, Geritz J, et al. Fatigue and cognitive impairment after COVID-19: a prospective multicentre study. *EClinicalMedicine.* (2022) 53:101651. doi: 10.1016/j.eclinm.2022.101651

24. Crivelli L, Palmer K, Calandri I, Guekht A, Beghi E, Carroll W, et al. Changes in cognitive functioning after COVID-19: a systematic review and meta-analysis. *Alzheimer J Alzheimer's Assoc.* (2022) 18:1047–66. doi: 10.1002/alz.12644

25. Hugon J, Msika EF, Queneau M, Farid K, Paquet C. Long COVID: cognitive complaints (brain fog) and dysfunction of the cingulate cortex. *J Neurol.* (2022) 269:44–6. doi: 10.1007/s00415-021-10655-x

26. Hadad R, Khoury J, Stanger C, Fisher T, Schneer S, Ben-Hayun R, et al. Cognitive dysfunction following COVID-19 infection. *J Neurovirol.* (2022) 28:430–7. doi: 10.1007/s13365-022-01079-y

27. Baseler HA, Aksoy M, Salawu A, Green A, Asghar AUR. The negative impact of COVID-19 on working memory revealed using a rapid online quiz. *PLoS ONE.* (2022) 17:e0269353. doi: 10.1371/journal.pone.0269353

28. Daroische R, Hemminghyth MS, Eilertsen TH, Breitve MH, Chwiszczuk LJ. Cognitive impairment after COVID-19-a review on objective test data. *Front Neurol.* (2021) 12:699582. doi: 10.3389/fneur.2021.699582

29. Ariza M, Cano N, Segura B, Adan A, Bargalló N, Caldú X, et al. Neuropsychological impairment in post-COVID condition individuals with and without cognitive complaints. *Front Aging Neurosci.* (2022) 14:1029842. doi: 10.3389/fnagi.2022.1029842

30. Lu Y, Li X, Geng D, Mei N, Wu PY, Huang CC, et al. Cerebral micro-structural changes in COVID-19 patients - an MRI-based 3-month follow-up study. *EClinicalMedicine.* (2020) 25:100484. doi: 10.1016/j.eclinm.2020.100484

31. Rothstein TL. Cortical Grey matter volume depletion links to neurological sequelae in post COVID-19 "long haulers". *BMC Neurol.* (2023) 23:22. doi: 10.1186/s12883-023-03049-1

32. Miskowiak KW, Bech JL, Henriksen AC, Johnsen S, Podlekareva D, Marner L. Cerebral metabolic rate of glucose and cognitive tests in long COVID patients. *Brain Sci.* (2022) 13:23. doi: 10.3390/brainsci13010023

33. Muccioli L, Sighinolfi G, Mitolo M, Ferri L, Jane Rochat M, Pensato U, et al. Cognitive and functional connectivity impairment in post-COVID-19 olfactory dysfunction. *NeuroImage Clinical.* (2023) 38:103410. doi: 10.1016/j.nicl.2023.103410

34. Gunnarsson DV, Miskowiak KW, Pedersen JK, Hansen H, Podlekareva D, Johnsen S, Dall CH. Physical function and association with cognitive function in patients in a post-COVID-19 clinic-a cross-sectional study. *Int J Environ Res Public Health*. (2023) 20:5866. doi: 10.3390/ijerph20105866

35. Liu YH, Chen Y, Wang QH, Wang LR, Jiang L, Yang Y, et al. One-Year trajectory of cognitive changes in older survivors of COVID-19 in Wuhan, China: a longitudinal cohort study. *JAMA Neurol.* (2022) 79:509–17. doi: 10.1001/jamaneurol.2022.0461

36. Graham EL, Clark JR, Orban ZS, Lim PH, Szymanski AL, Taylor C, et al. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized COVID-19 "long haulers". *Annals Clin Translat Neurol.* (2021) 8:1073–85. doi: 10.1002/acn3.51350

37. Meinhardt J, Radke J, Dittmayer C, Franz J, Thomas C, Mothes R, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat Neurosci.* (2021) 24:168–75. doi: 10.1038/s41593-020-00758-5

38. Liu S, Hossinger A, Heumüller SE, Hornberger A, Buravlova O, Konstantoulea K, et al. Highly efficient intercellular spreading of protein misfolding mediated by viral ligand-receptor interactions. *Nat Commun.* (2021) 12:5739. doi: 10.1038/s41467-021-25855-2

39. Fontes-Dantas FL, Fernandes GG, Gutman EG, De Lima EV, Antonio LS, Hammerle MB, et al. SARS-CoV-2 Spike protein induces TLR4-mediated long-term cognitive dysfunction recapitulating post-COVID-19 syndrome in mice. *Cell Rep.* (2023) 42:112189. doi: 10.1016/j.celrep.2023.112189

40. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimer's Res Therapy.* (2020) 12:69. doi: 10.1186/s13195-020-00640-3

41. Stein SR, Ramelli SC, Grazioli A, Chung JY, Singh M, Yinda CK, et al. SARS-CoV-2 infection and persistence in the human body and brain at autopsy. *Nature.* (2022) 612:758–63. doi: 10.1038/s41586-022-05542-y

42. Jamilloux Y, Henry T, Belot A, Viel S, Fauter M, El Jammal T, et al. Should we stimulate or suppress immune responses in COVID-19? *Cytokine Anti-cytokine Intervent Autoimmun Rev.* (2020) 19:102567. doi: 10.1016/j.autrev.2020.102567

43. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol.* (2020) 92:814–8. doi: 10.1002/jmv.25801

44. Soung AL, Vanderheiden A, Nordvig AS, Sissoko CA, Canoll P, Mariani MB, et al. COVID-19 induces CNS cytokine expression and loss of hippocampal neurogenesis. *Brain J Neurol.* (2022) 145:4193–201. doi: 10.1093/brain/awac270

45. Blank T, Prinz M. Microglia as modulators of cognition and neuropsychiatric disorders. *Glia.* (2013) 61:62–70. doi: 10.1002/glia.22372

46. Banks WA, Ortiz L, Plotkin SR, Kastin AJ. Human interleukin (IL) 1 alpha, murine IL-1 alpha and murine IL-1 beta are transported from blood to brain in the mouse by a shared saturable mechanism. *J Pharmacol Exp Ther.* (1991) 259:988–96.

47. Hampshire A, Trender W, Chamberlain SR, Jolly AE, Grant JE, Patrick F, et al. Cognitive deficits in people who have recovered from COVID-19. *EClinicalMedicine.* (2021) 39:101044. doi: 10.1016/j.eclinm.2021.101044

48. Nóbrega F, Mauad VAQ, Borducchi DMM. Does COVID-19 really impact on the oxy-hemoglobin dissociation curve? *EJHaem.* (2020) 1:604–7. doi: 10.1002/jha2.126

49. Mussa BM, Srivastava A, Verberne AJM. COVID-19 and neurological impairment: hypothalamic circuits and beyond. *Viruses.* (2021) 13:498. doi: 10.3390/v13030498

50. Smith MA, Scholey AB. Nutritional influences on human neurocognitive functioning. *Front Hum Neurosci.* (2014) 8:358. doi: 10.3389/fnhum.2014.00358

51. Lee MH, Perl DP, Nair G, Li W, Maric D, Murray H, et al. Microvascular injury in the brains of patients with COVID-19. *N Engl J Med.* (2021) 384:481–3. doi: 10.1056/NEJMc2033369

52. Conklin J, Frosch MP, Mukerji SS, Rapalino O, Maher MD, Schaefer PW, et al. Susceptibility-weighted imaging reveals cerebral microvascular injury in severe COVID-19. *J Neurol Sci.* (2021) 421:117308. doi: 10.1016/j.jns.2021.117308

53. Theoharides TC, Kempuraj D. Role of SARS-CoV-2 spike-protein-induced activation of microglia and mast cells in the pathogenesis of neuro-COVID. *Cells.* (2023) 12:688. doi: 10.3390/cells12050688

54. Ball EE, Weiss CM, Liu H, Jackson K, Keel MK, Miller CJ, et al. Severe acute respiratory syndrome coronavirus 2 vasculopathy in a syrian golden hamster model. *Am J Pathol.* (2023) 193:690–701. doi: 10.1016/j.ajpath.2023.02.013

55. Nadwa EH, Al-Kuraishy HM, Al-Gareeb AI, Elekhnawy E, Albogami SM, Alorabi M, et al. Cholinergic dysfunction in COVID-19: frantic search and hoping for the best. *Naunyn-Schmiedeberg's Arch Pharmacol.* (2023) 396:453–68. doi: 10.1007/s00210-022-02346-9

56. Wong R, Lam E, Bramante CT, Johnson SG, Reusch J, Wilkins KJ, et al. Does COVID-19 infection increase the risk of diabetes? Current evidence. *Curr Diab Reports.* (2023) 3:1–10. doi: 10.1007/s11892-023-01515-1

57. Raza SM, Ebrahim F, Ekea H, Ali SK. COVID-19 Presenting as a Seizure: a Kenyan case report. *Cureus.* (2022) 14:e24431. doi: 10.7759/cureus.24431

58. McNeilly AD, Gallagher JR, Evans ML, de Galan BE, Pedersen-Bjergaard U, Thorens B, et al. Chronic hyperglycaemia increases the vulnerability of the hippocampus to oxidative damage induced during post-hypoglycaemic hyperglycaemia in a mouse model of chemically induced type 1 diabetes. *Diabetologia.* (2023) 66:1340–52. doi: 10.1007/s00125-023-05907-6

59. Zhou D, Sun Y, Qian Z, Wang Z, Zhang D, Li Z, et al. Long-term dietary folic acid supplementation attenuated aging-induced hippocampus atrophy and promoted glucose uptake in 25-month-old rats with cognitive decline. *J Nutr Biochem.* (2023) 117:109328. doi: 10.1016/j.jnutbio.2023.109328

60. Ertas B, Hazar-Yavuz AN, Topal F, Keles-Kaya R, Karakus Ö, Ozcan GS, et al. Rosa canina L. improves learning and memory-associated cognitive impairment by regulating glucose levels and reducing hippocampal insulin resistance in high-fat diet/streptozotocin-induced diabetic rats. *J Ethnopharmacol.* (2023) 313:116541. doi: 10.1016/j.jep.2023.116541

61. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236,379 survivors of COVID-19: a retrospective cohort study using electronic health records. *The Lancet Psychiatry.* (2021) 8:416–27. doi: 10.1016/S2215-0366(21)00084-5

62. Braga J, Lepra M, Kish SJ, Rusjan PM, Nasser Z, Verhoeff N, et al. Neuroinflammation after COVID-19 with persistent depressive and cognitive symptoms. *JAMA Psychiatry.* (2023). doi: 10.1001/jamapsychiatry.2023.1321

63. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature.* (2022) 604:697–707. doi: 10.1038/s41586-022-04569-5

64. Monje M, Iwasaki A. The neurobiology of long COVID. *Neuron.* (2022) 110:3484–96. doi: 10.1016/j.neuron.2022.10.006

65. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun.* (2020) 87:18–22. doi: 10.1016/j.bbi.2020.03.031

66. Leng A, Shah M, Ahmad SA, Premraj L, Wildi K, Li Bassi G, et al. Pathogenesis underlying neurological manifestations of long COVID syndrome and potential therapeutics. *Cells.* (2023) 12:5. doi: 10.3390/cells12050816

67. Kuley R, Duvvuri B, Wallin JJ, Bui N, Adona MV, O'Connor NG, et al. Mitochondrial N-formyl methionine peptides contribute to exaggerated neutrophil activation in patients with COVID-19. *Virulence.* (2023) 14:2218077. doi: 10.1080/21505594.2023.2218077

68. Giannelli R, Canale P, Del Carratore R, Falleni A, Bernardeschi M, Forini F, et al. Ultrastructural and molecular investigation on peripheral leukocytes in Alzheimer's disease patients. *Int J Mol Sci.* (2023) 24:909. doi: 10.3390/ijms24097909

69. Guillot-Sestier MV, Doty KR, Gate D, Rodriguez J. Jr., Leung BP, Rezai-Zadeh K, Town T. Il10 deficiency rebalances innate immunity to mitigate Alzheimer-like pathology. *Neuron.* (2015) 85:534–48. doi: 10.1016/j.neuron.2014.12.068

70. Reinhold D, Farztdinov V, Yan Y, Meisel C, Sadlowski H, Kühn J, et al. The brain reacting to COVID-19: analysis of the cerebrospinal fluid proteome, RNA and inflammation. *J Neuroinflammation.* (2023) 20:30. doi: 10.1186/s12974-023-02711-2

71. Toklu H, Ganti L, Crimi E, Cintron C, Hagan J, Serrano E. Cerebrospinal fluid findings and hypernatremia in COVID-19 patients with altered mental status. *Int J Emerg Med.* (2020) 13:63. doi: 10.1186/s12245-020-00327-4

72. Akanchise T, Angelova A. Ginkgo Biloba and long COVID: *in vivo* and *in vitro* models for the evaluation of nanotherapeutic efficacy. *Pharmaceutics.* (2023) 15:1562. doi: 10.3390/pharmaceutics15051562

73. He D, Yuan M, Dang W, Bai L, Yang R, Wang J, et al. Long term neuropsychiatric consequences in COVID-19 survivors: cognitive impairment and inflammatory underpinnings 15 months after discharge. *Asian J Psychiatr.* (2023) 80:103409. doi: 10.1016/j.ajp.2022.103409

74. Tedjasukmana R, Budikayanti A, Islamiyah WR, Witjaksono A, Hakim M. Sleep disturbance in post COVID-19 conditions: prevalence and quality of life. *Front Neurol.* (2022) 13:1095606. doi: 10.3389/fneur.2022.1095606

75. Premraj L, Kannapadi NV, Briggs J, Seal SM, Battaglini D, Fanning J, et al. Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: a meta-analysis. *J Neurol Sci.* (2022) 434:120162. doi: 10.1016/j.jns.2022.120162

76. Kalamara E, Pataka A, Boutou A, Panagiotidou E, Georgopoulou A, Ballas E, et al. Persistent sleep quality deterioration among post-COVID-19 patients: results from a 6-month follow-up study. *J Pers Med.* (2022) 12:11. doi: 10.3390/jpm12111909

77. Pellitteri G, Surcinelli A, De Martino M, Fabris M, Janes F, Bax F, et al. Sleep alterations following COVID-19 are associated with both neuroinflammation and psychological disorders, although at different times. *Front Neurol.* (2022) 13:929480. doi: 10.3389/fneur.2022.929480

78. Gupta R, Pandi-Perumal SR. SARS-CoV-2 infection: paving way for sleep disorders in long term! *Sleep Vigilance.* (2021) 5:1–2. doi: 10.1007/s41782-021-00145-5

79. Numbers K, Brodaty H. The effects of the COVID-19 pandemic on people with dementia. *Nat Rev Neurol.* (2021) 17:69–70. doi: 10.1038/s41582-020-00450-z

80. Kuehn M, LaMori J, DeMartino JK, Mesa-Frias M, Doran J, Korrapati L, et al. Assessing barriers to access and equity for COVID-19 vaccination in the US. *BMC Public Health.* (2022) 22:2263. doi: 10.1186/s12889-022-14636-1

frontiers | Frontiers in Pain Research

TYPE Mini Review
PUBLISHED 22 August 2023
DOI 10.3389/fpain.2023.1234099

OPEN ACCESS

EDITED BY
Thorsten Rudroff,
The University of Iowa, United States

REVIEWED BY
Pranav Prasoon,
University of Pittsburgh, United States

*CORRESPONDENCE
Antonios El Helou
dr.antonios.elhelou@horizonnb.ca

RECEIVED 15 June 2023
ACCEPTED 04 August 2023
PUBLISHED 22 August 2023

CITATION
Lavin A, LeBlanc F and El Helou A (2023) The impact of COVID-19 on chronic pain.
Front. Pain Res. 4:1234099.
doi: 10.3389/fpain.2023.1234099

The impact of COVID-19 on chronic pain

Abraham Lavin[1], Félix LeBlanc[1] and Antonios El Helou[1,2,3]*

[1]Faculty of Medicine, Université de Sherbrooke, Sherbrooke, QC, Canada, [2]Division of Neurosurgery, Horizon Health Network, Moncton, NB, Canada, [3]Faculty of Medicine, Memorial University of Newfoundland, St. John's, NL, Canada

A reduced quality of life is often a hefty burden that those with chronic pain are left to bear. This review of literature from PubMed, Google Scholar and other relevant studies focuses on the complex relationship between COVID-19 and chronic pain, which is challenging to study during the COVID-19 pandemic. In this review, we will briefly discuss the epidemiologic facts and risk factors, followed by the proposed pathophysiologic mechanisms. Furthermore, we will cover the therapeutic avenues regarding various molecules and their possible interactions, with the most promising being those whose mechanism of action can be directly linked to the pathophysiologic aspects of the condition. Finally, we will describe how to deal with a chronic pain patient who consults during the pandemic.

KEYWORDS

COVID-19, chronic pain, pathophysiology and mechanism, therapeutic options, pandemic

1. Introduction

The COVID-19 pandemic took the world by storm. This global crisis affected many dimensions of peoples' lives, such as mental health and wellbeing due to isolation and loneliness, job loss and financial instability, and illness and grief (1). Vulnerable populations, such as people living with chronic pain, were impacted significantly. COVID-19 had complex effects on both current and newly created pain, much like the illness itself (1). Notably, there was an increase in "pain"-related search phrases globally, indicating a greater public interest and concern during the pandemic (2). Employment insecurity, social isolation, and recommendations concerning physical distancing had burdened people in numerous nations, all of which possibly contributed to their psychological distress and physiological pain (3, 4).

Identifying the risk factors associated with any health condition is important to prevent its development (5). Some domains have been identified as contributors to the potential development of chronic pain among hospitalized COVID-19 patients (5). First, the risk of post-traumatic stress disorder, social isolation both during and after discharge, and psychological burdens particular to the pandemic are all related to mental health burdens, which can be potential risk factors for chronic pain development in COVID-19 patients (5). Subsequently, the neurological manifestations caused by COVID-19 infection have been also identified as possible risk factors (5). Moreover, intensive care unit–associated risks, such as prolonged ventilation and immobility, repeated prone position, neuromuscular block, and sepsis or procedural pain, are all considered chronic pain risk factors (5). There are also COVID-19 patient–related factors embodied by a high comorbidity prevalence and an elderly population (5). In addition, acute pain associated with COVID-19 infection is also a risk factor for chronic pain development (5, 6). Finally, the challenges linked to rehabilitation services have been reported to contribute to the risk of chronic pain development. These challenges include potentially overworked

rehabilitation services, poorly planned rehabilitation pathways, resource diversion from subsequent waves, insufficient concrete rehabilitative evidence related to COVID-19, fatigue, and multimorbidities (5).

In a controlled cross-sectional study, Soares et al. (7) compared 46 patients, who were discharged from the hospital following COVID-19, to a control group consisting of 73 patients, who were hospitalized during the same period but for reasons other than COVID-19. They demonstrated that *de novo* pain was significantly more prevalent in the COVID-19 group (65.2% vs. 11.0%, $p = 0.001$). In addition, 19.6% of the COVID-19 patients had new-onset chronic pain, compared to 1.4% ($p = 0.002$) of the control group. Thus, the study concluded that *de novo* chronic pain and new-onset pain were generally more prevalent in COVID-19 patients. Considering all of this, we realized the importance of studying chronic pain in patients with COVID-19, hence the relevance of this literature review.

2. Literature search

We searched for the keywords "COVID-19," "chronic pain," "pathophysiology and mechanism," "therapeutic options," and "pandemic" in PubMed and Google Scholar in May 2023 and then evaluated the present body of literature, considering all articles published before this date. The initial search yielded 1,131 articles, of which 56 were retained after the titles were analyzed,. We then analyzed these articles based on the abstract, type of study, and publication date to determine their relevance, of which 31 were retained. We included the English versions of articles including those written in foreign languages, mainly systematic reviews and some experimental studies that elucidated information pertinent to the keywords mentioned. In some instances, definitive websites and bibliographies of the selected articles were consulted for complementary information purposes.

3. Pain in COVID-19

Guerrero et al. (5) proposed a triage of patients into three diverse groups to demonstrate the disproportion in how COVID-19 affects different patients. The first group included those whose chronic pain first prevailed after COVID-19 infection, which may be categorized as a variety of post-viral chronic pain in which the pain is either directly related to organ damage caused by the acute infection or an entity referred to as long COVID-19 (8). Long COVID-19 is defined in the current literature as a post-viral syndrome, which comprises sleep disorders, chronic fatigue, and diffused myalgia (9, 10). This syndrome occurs in those who recover from acute COVID-19 infection with prolongation of the previously described symptoms for over 4 weeks (10). The pathology for this syndrome is not well defined and comprises primary symptoms related to the cardiovascular, neurological, psychological, and pulmonary systems such as, but not limited to, brain fog and other cognitive deficits, disordered sleep patterns, autonomic disturbances, dyspnea, anosmia, chest and joint pains, cardiac arrhythmias, and neuropathies (10). No diagnostic tools are currently available for this syndrome (10). The second group included those with exacerbating pre-existing chronic pain, most likely as a result of the pathophysiologic mechanisms described further (5). The third group included those who were feeling well before the pandemic but have since developed chronic pain. This group was mostly tied to the biopsychosocial model described below, as well as the various predisposing risk factors that were mentioned earlier (5).

4. Pathophysiology and mechanism

Shanthanna et al. (1) proposed a model that categorizes the reasoning into three main categories, i.e., systemic immune-inflammatory mechanisms, secondary mechanisms due to COVID-19 pathology or its associated treatments, and direct neuropathic mechanisms.

To begin, COVID-19 is thought to be neurotropic and capable of infiltrating host cells via the angiotensin-converting enzyme 2 (ACE2) receptors, which are present in the glial cells and neurons in the brain stem and regions, such as the paraventricular nucleus, rostral ventrolateral medulla, nucleus tractus solitarius, and subfornical organ (11, 12). Once it has infiltrated, there is a resulting microglial activation and astrogliosis which originate an extensive neuroinflammatory cascade, while the systemic inflammation associated with the infection disrupts the blood–brain barrier, causing subsequent extensive disruption of homeostasis within the brain and associated neuronal cell death (11). This systemic inflammation, which is characterized by a cytokine storm implicating interleukin-6, interleukin-10, and tumor necrosis factor-α, among others, results in the upsurge damage of various structures manifesting as joint pain and myalgia and other tissue pain observed in the new-onset chronic pain group (13, 14).

Studies have represented the implication of two pathways in pain, namely, the angiotensin-converting enzyme/angiotensin II/angiotensin II type 1 receptor (ACE/Ang II/AT1) as a pain transmission promoter in the dorsal horn and ACE2/angiotensin (I–VII)/Mas receptor as a pain moderator via the p38 mitogen-activated protein kinase phosphorylation inhibition (14–16). Studies have suggested that the ACE2 implication within the microglia and neurons of a mouse spinal dorsal horn led the group to hypothesize that the COVID-19 virus may infect ACE2-positive cells within the human spinal dorsal horn, culminating in a functional downturn of ACE2 that would then further cause an Ang II accumulation and a subsequent Ang (I–VII) depression and thereupon explain the possibility of SARS-CoV-2 spinal cord infection installation of pain (14, 16).

There are other proposed methods of entry, such as the one by Wu et al. (17) who described a blood circulatory pathway in which SARS-CoV-2 can directly infect the central nervous system, which

ultimately culminates in the same result as the previously described. The implication of the nervous system explains the manifestations of fatigue symptoms, which are similar to those seen in chronic fatigue syndrome or myalgic encephalitis (18, 19). Impacts on chronic pain may further be explained by pathologic immune mechanisms, such as resident astrocyte and microglial stimulation along with leukocyte activation (20, 21).

In their rat model study, Moutal et al. proposed that the neuropilin-1 receptor (NRP-1) is the key to the pathophysiologic mechanism as its activation results in neurotropism (13, 22). They described how the viral spike protein binds to the NRP-1 receptor, blocking the NRP-1 binding and vascular endothelial growth factor-A (23). This model also unveils anti-allogenic properties, which could advocate for the role of increased transmission as explained by diminished pain symptoms (23).

Hyperinflammation and dysautonomia may be seen predominantly in patients with comorbidities due to the involvement of the autonomic nervous system, particularly the sympathetic nervous system (22, 24–26).

Secondary mechanisms due to COVID-19 pathology or its associated treatments encompass many syndromes as a direct result of the virus' impact on chronic pain, such as that seen in intensive care unit admissions which may be analogous with post-intensive care-like syndrome and other secondary causes of pain (27). There is also evidence of an elevated stroke incidence among COVID-19 patients, as reported by Siepmann et al. (28) who conducted a meta-analysis of 165 patients, which may be a factor in the involvement of an increased post-stroke pain in those who survive. Finally, prolonged immobilization (>21 days) in prone ventilation positioning can result in other injuries such as peripheral nerve damage (29).

When it comes to analyzing the mechanism between COVID-19 and chronic pain, the current literature presents various options. A well-established model hypothesizes chronic pain as a biopsychosocial phenomenon that embodies a trident of biological, psychological, and social factors, all of which heavily influence and affect one another (30). With this model in mind, Guerrero et al. (5) proposed that given that the COVID-19 pandemic caused a prolonged state of not only financial but also social stress among many patients, this could not only cause a magnification in the prevalence of chronic pain but could also cause an aggravation of painful symptoms in those with pre-existing chronic pain. The group further goes on to establish that patients with known chronic pain were then placed in a difficult predicament, which consists of financial and personal loss, a new-found state of isolation, and new avenues needed to procure medical care which led to pain exacerbation (5).

5. Management and therapeutic options

Understanding the pathophysiology of acute post-COVID-19 pain has led to the proposal of various therapeutic options, such as the nervous system involvement and proinflammatory cytokine secretion, which point toward using low-dose naltrexone as a possible therapy for the perceived chronic pain as explained by its mechanism of influencing the release of the proinflammatory cytokines[1] (1, 31, 32). Opioids have been reported to have menacing side effects such as endocrine changes and immune system suppression (33). While the clinical implication of this remains uncertain, the idea that patients receiving opioids for chronic pain may be at a higher risk for COVID-19 and other infections is supported by the observational studies explaining the increased infection prevalence within this group (34, 35). Non-steroidal anti-inflammatory drugs (NSAIDs) have been used for chronic pain modulation (36). Based on the proposed mechanism that NSAIDs inhibit the cyclo-oxygenase enzymes (COX-1 and COX-2), there was an assumption that NSAIDs could lead to an increased ACE and, thus, the intensity of the SARS-CoV-2 infection, prompting the French health minister to urge against the use of NSAIDs (34, 37). Although NSAIDs can obscure early infection symptoms such as myalgias and fever, such recommendations have since been refuted by various regulatory bodies[2,3] (34, 38, 39). An expert panel has since recommended that all patients currently receiving NSAIDs continue their medication with prompt monitoring for side effects and report myalgias and mild fevers (34). Lower antibody levels were found in post-vaccination immunocompromised patients supporting the concern about the efficacy of patients receiving steroids and either the mRNA-based vaccine mRNA-1273 (Moderna) and BNT162b2 (Pfizer) or the viral vector AstraZeneca and Johnson & Johnson vaccine (40, 41). This concern is supported by the findings of Naranbhai et al. who discovered lower antibody levels in post-vaccination patients using steroids for cancer in a prospective cohort study that compared 1,001 infected patients to 1,638 control patients (42). These facts led The Faculty of Pain Medicine of the Royal College of Anaesthetists to advocate for caution regarding steroid injections throughout the COVID-19 pandemic[4] (43).

Treating those with chronic post-COVID-19 pain and the mechanism of sympathetic nervous system overactivity has led to the deliberation of using stellate ganglion blocks to effectively treat the presenting chronic pain (24, 25). The sympathetic stellate ganglion, which is located in the lamina prevertebral fasciae cervicalis at the height of the first rib head, affects the function of the areas that it supplies, such as the brain, lung, neck, upper extremity, heart, and vessels comprising endothelial function, interstitium, immune system, and microcirculation (24). The stellate ganglion modulates both brain areas involved in the governing processes of the immune system and the immune processing in the periphery, explaining its influence in areas

[1]https://clinicaltrials.gov/ct2/show/NCT04756128.

[2]https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19.

[3]https://www.ema.europa.eu/en/news/ema-gives-advice-use-non-steroidal-anti-inflammatories-covid-19.

[4]https://fpm.ac.uk/covid-19-fpm-response-concerns-over-safety-injected-steroids-pain-procedures.

beyond its immediate supply such as the intestine (24). During an immunological response, the immune system and the autonomic nervous system interact quickly, resulting in an inflammation caused by the onset of an immune system cytokine storm and associated tissue damage by sympathetic hyperactivity (24). With this mechanism in mind, the stellate ganglion block's modulation of the sympathetic immune system would reduce signals to the areas and functions that it supplies (mentioned above), thus modulating pain (24).

Finally, treating the group of patients who had chronic pain and developed one or several flare-ups in relation to the COVID-19 pandemic, either by direct post-viral infection or by the psychological burden of the general pandemic, led to greater utilization of the biopsychosocial model (34). This model includes the ability to obtain care from social workers, physical therapists, and psychologists to adequately manage pain (34). During the pandemic, many of these services were adapted to sanitary circumstances via telemedicine as demonstrated by the National Health Service in the United Kingdom, which adopted the use of Microsoft Teams to facilitate communication among professionals and patients, or by the provincial Ministries of Health in Canada[5], which loosened the regulations surrounding telemedicine (34, 44).

With regard to the impact of COVID-19 on chronic pain, it is not only important to have the therapeutic arsenal explained above at one's disposal but also, if not more important, to know when to use the proper treatment and have a solid plan when tackling this complex situation, and in this optic, a consensus within an international expert panel proposes a distinct model (34). In this suggested model, the first step to treat a patient with known chronic pain before the pandemic would be to arrange a phone call to establish the urgency of the consultation. If non-emergent, telemedicine visits should be scheduled when possible to avoid further aggravation, or virtual prescriptions should be issued if deemed necessary in the given context (34). If semi-emergent, case-by-case shared decision-making seems an acceptable approach (34). Finally, if urgent, an in-person consultation is justified, for example, in the case of an urgent procedure such as an intrathecal pump or neuromodulation malfunction or infection (34). Patients with pandemic-induced chronic pain could be treated by this model in the event of an acute exacerbation, but for long-term management, they should consult their regular healthcare provider and seek advice on which of the abovementioned therapies should be employed (34).

6. Discussion

The key to understanding the complex relationship between chronic pain and COVID-19 is the understanding of the underlying pathophysiologic mechanism, particularly the three main categories, i.e., systemic immune-inflammatory mechanisms, secondary mechanisms due to COVID-19 pathology or its associated treatments, and direct neuropathic mechanisms (1). The recent acknowledgments of the key receptors, such as NRP-1, the ACE/AngII/AT1, and ACE2/angiotensin (I–VII)/Mas receptor, along with the elucidation of the biopsychosocial model all facilitate the understanding of this phenomenon (14–16, 23, 30). Understanding these mechanisms allows elucidation of proper therapeutic options based on their mechanism of action to counter the pathophysiology, in particular, naloxone, NSAID, or the stellate ganglion block[6] (24, 25, 31, 36).

The definition of the targeted population is equally important and can be described by three groups. The first group consists of those whose chronic pain first prevailed after COVID-19 infection caused by direct organ damage sustained during acute infection manifested by post-viral chronic pain, which is referred to as long COVID-19 (8). The second and third groups consist of those who had pre-existing chronic pain and those who were well before the infection and have since developed chronic pain, respectively, with the last group being closely tied to the predisposing risk factors and the biopsychosocial model previously outlined (5).

In May 2023, the World Health Organization (WHO) issued a press release in which the Director-General announced that COVID-19 is an ongoing and established health issue and is no longer considered a public health emergency of worldwide concern[7] (45). Despite this announcement, there is yet to be a clear and precise strategy going forward on how to systematically approach the dilemma of the impact of COVID-19 on chronic pain.

7. Conclusion

In conclusion, COVID-19 has caused a profound impact by creating a new post-viral and persisting post-pandemic chronic pain syndrome and a large impact on those already living with chronic pain in many ways, often disproportionately. Some key characteristics are present within the patients that could predispose them to different outcomes when they are exposed to SARS-CoV-2. Understanding the implicated pathophysiologic mechanisms is key to not only understanding the clinical manifestation of the infection but also shedding light on some therapeutic options. Treatment will be often multidimensional to address all aspects of the condition and is essential to acknowledge the proper situation to use the appropriate therapy. Considering all the above, we recognize that conducting research

[5]https://www.healthcareitnews.com/news/emea/nhs-staff-receive-free-access-microsoft-teams-and-locum-s-nest.

[6]https://clinicaltrials.gov/ct2/show/NCT04756128.

[7]https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic.

with primary data such as an experimental study could be beneficial in providing further insights into this field. It is also noteworthy that findings cannot be generalized, but after the pandemic ended, it was declared that chronic pain will continue to be an issue; therefore, a multicenter prospective study is required to have accurate data and management plan.

Author contributions

AL wrote most of the literature review, while FL also contributed. FL, AL, and AEH contributed to the revision for submission. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Shanthanna H, Nelson AM, Kissoon N, Narouze S. The COVID-19 pandemic and its consequences for chronic pain: a narrative review. *Anaesthesia*. (2022) 77 (9):1039–50. doi: 10.1111/anae.15801

2. Szilagyi IS, Ullrich T, Lang-Illievich K, Klivinyi C, Schittek GA, Simonis H, et al. Google Trends for pain search terms in the world's most populated regions before and after the first recorded COVID-19 case: infodemiological study. *J Med Internet Res*. (2021) 23(4):e27214. doi: 10.2196/27214

3. Saladino V, Algeri D, Auriemma V. The psychological and social impact of COVID-19: new perspectives of well-being. *Front Psychol*. (2020) 11:577684. doi: 10.3389/fpsyg.2020.577684

4. COVID-19 Mental Disorders Collaborators. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet Lond Engl*. (2021) 398(10312):1700–12. doi: 10.1016/S0140-6736(21)02143-7

5. Guerrero M, Castroman P, Quiroga O, Berenguel Cook M, Narvaez Tamayo MA, Venturoni L, et al. Pain management and COVID-19: a Latin American perspective. *Cureus*. (2022) 14(3):e23100. doi: 10.7759/cureus.23100

6. van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology—where do lifestyle factors fit in? *Br J Pain*. (2013) 7(4):209–17. doi: 10.1177/2049463713493264

7. Soares FHC, Kubota GT, Fernandes AM, Hojo B, Couras C, Costa BV, et al. Prevalence and characteristics of new-onset pain in COVID-19 survivors, a controlled study. *Eur J Pain Lond Engl*. (2021) 25(6):1342–54. doi: 10.1002/ejp.1755

8. Pergolizzi JV, Raffa RB, Varrassi G, Magnusson P, LeQuang JA, Paladini A, et al. Potential neurological manifestations of COVID-19: a narrative review. *Postgrad Med*. (2022) 134(4):1–11. doi: 10.1080/00325481.2020.1837503

9. Halpin S, O'Connor R, Sivan M. Long COVID and chronic COVID syndromes. *J Med Virol*. (2021) 93(3):1242–3. doi: 10.1002/jmv.26587

10. Pergolizzi JV, LeQuang JA, Magnusson P, Myrcik D, Varrassi G. It's not over till it's over: a narrative review of long COVID. *Signa Vitae*. (2021) 17(3):21–30. doi: 10.22514/sv.2021.067

11. Steardo L, Steardo L, Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. *Acta Physiol Oxf Engl*. (2020) 229(3):e13473. doi: 10.1111/apha.13473

12. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci*. (2020) 11(7):995–8. doi: 10.1021/acschemneuro.0c00122

13. Manjavachi MN, Motta EM, Marotta DM, Leite DFP, Calixto JB. Mechanisms involved in IL-6-induced muscular mechanical hyperalgesia in mice. *Pain*. (2010) 151(2):345. doi: 10.1016/j.pain.2010.07.018

14. Su S, Cui H, Wang T, Shen X, Ma C. Pain: a potential new label of COVID-19. *Brain Behav Immun*. (2020) 87:159–60. doi: 10.1016/j.bbi.2020.05.025

15. Nemoto W, Nakagawasai O, Yaoita F, Kanno SI, Yomogida S, Ishikawa M, et al. Angiotensin II produces nociceptive behavior through spinal AT1 receptor-mediated p38 mitogen-activated protein kinase activation in mice. *Mol Pain*. (2013) 9:38. doi: 10.1186/1744-8069-9-38

16. Yamagata R, Nemoto W, Nakagawasai O, Takahashi K, Tan-No K. Downregulation of spinal angiotensin converting enzyme 2 is involved in neuropathic pain associated with type 2 diabetes mellitus in mice. *Biochem Pharmacol*. (2020) 174:113825. doi: 10.1016/j.bcp.2020.113825

17. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun*. (2020) 87:18–22. doi: 10.1016/j.bbi.2020.03.031

18. Mackay A. A paradigm for post-COVID-19 fatigue syndrome analogous to ME/CFS. *Front Neurol*. (2021) 12:701419. doi: 10.3389/fneur.2021.701419

19. Anand H, Ende V, Singh G, Qureshi I, Duong TQ, Mehler MF. Nervous system-systemic crosstalk in SARS-CoV-2/COVID-19: a unique dyshomeostasis syndrome. *Front Neurosci*. (2021) 15:727060. doi: 10.3389/fnins.2021.727060

20. Schurink B, Roos E, Radonic T, Barbe E, Bouman CSC, de Boer HH, et al. Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *Lancet Microbe*. (2020) 1(7):e290–9. doi: 10.1016/S2666-5247(20)30144-0

21. Yong SJ. Persistent brainstem dysfunction in long-COVID: a hypothesis. *ACS Chem Neurosci*. (2021) 12(4):573–80. doi: 10.1021/acschemneuro.0c00793

22. Al-kuraishy HM, Al-Gareeb AI, Qusti S, Alshammari EM, Gyebi GA, Batiha GES. COVID-19-induced dysautonomia: a menace of sympathetic storm. *ASN Neuro*. (2021) 13:17590914211057636. doi: 10.1177/17590914211057635

23. Moutal A, Martin LF, Boinon L, Gomez K, Ran D, Zhou Y, et al. SARS-CoV-2 spike protein co-opts VEGF-A/neuropilin-1 receptor signaling to induce analgesia. *Pain*. (2021) 162(1):243–52. doi: 10.1097/j.pain.0000000000002097

24. Fischer L, Barop H, Ludin SM, Schaible HG. Regulation of acute reflectory hyperinflammation in viral and other diseases by means of stellate ganglion block. A conceptual view with a focus on COVID-19. *Auton Neurosci*. (2022) 237:102903. doi: 10.1016/j.autneu.2021.102903

25. Porzionato A, Emmi A, Barbon S, Boscolo-Berto R, Stecco C, Stocco E, et al. Sympathetic activation: a potential link between comorbidities and COVID-19. *FEBS J*. (2020) 287(17):3681–8. doi: 10.1111/febs.15481

26. Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. *Clin Med*. (2021) 21(1):e63–7. doi: 10.7861/clinmed.2020-0896

27. Kemp HI, Corner E, Colvin LA. Chronic pain after COVID-19: implications for rehabilitation. *Br J Anaesth*. (2020) 125(4):436–40. doi: 10.1016/j.bja.2020.05.021

28. Siepmann T, Sedghi A, Simon E, Winzer S, Barlinn J, de With K, et al. Increased risk of acute stroke among patients with severe COVID-19: a multicenter study and meta-analysis. *Eur J Neurol*. (2021) 28(1):238–47. doi: 10.1111/ene.14535

29. Liu EA, Salazar T, Chiu E, Fleming TK, Bagay L, Brown DP, et al. Focal peripheral neuropathies observed in patients diagnosed with COVID-19: a case series. *Am J Phys Med Rehabil*. (2022) 101(2):164–9. doi: 10.1097/PHM.0000000000001924

30. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull*. (2007) 133(4):581–624. doi: 10.1037/0033-2909.133.4.581

31. HealthPartners Institute. Impact of colchicine and low-dose naltrexone on COVID-19 disease progression and clinical course in hospitalized patients.

clinicaltrials.gov (2023). Report No.: NCT04756128. Available at: https://clinicaltrials.gov/ct2/show/NCT04756128 (Accessed 16 May 2023).

32. Choubey A, Dehury B, Kumar S, Medhi B, Mondal P. Naltrexone a potential therapeutic candidate for COVID-19. *J Biomol Struct Dyn*. (2022) 40(3):1–8. doi: 10.1080/07391102.2020.1820379

33. Plein LM, Rittner HL. Opioids and the immune system—friend or foe. *Br J Pharmacol*. (2018) 175(14):2717–25. doi: 10.1111/bph.13750

34. Shanthanna H, Strand NH, Provenzano DA, Lobo CA, Eldabe S, Bhatia A, et al. Caring for patients with pain during the COVID-19 pandemic: consensus recommendations from an international expert panel. *Anaesthesia*. (2020) 75 (7):935–44. doi: 10.1111/anae.15076

35. Dublin S, Walker RL, Jackson ML, Nelson JC, Weiss NS, Von Korff M, et al. Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study. *J Am Geriatr Soc*. (2011) 59(10):1899–907. doi: 10.1111/j.1532-5415.2011.03586.x

36. Ho KY, Gwee KA, Cheng YK, Yoon KH, Hee HT, Omar AR. Nonsteroidal anti-inflammatory drugs in chronic pain: implications of new data for clinical practice. *J Pain Res*. (2018) 11:1937–48. doi: 10.2147/JPR.S168188

37. Day M. COVID-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. *Br Med J*. (2020) 368:m1086. doi: 10.1136/bmj.m1086

38. Center for Drug Evaluation and Research. FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. FDA (2020). Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19 (Accessed 17 May 2023).

39. EMA. EMA gives advice on the use of non-steroidal anti-inflammatories for COVID-19. European Medicines Agency (2020). Available at: https://www.ema.europa.eu/en/news/ema-gives-advice-use-non-steroidal-anti-inflammatories-covid-19 (Accessed 17 May 2023).

40. Deepak P, Kim W, Paley MA, Yang M, Carvidi AB, Demissie EG, et al. Effect of immunosuppression on the immunogenicity of mRNA vaccines to SARS-CoV-2. *Ann Intern Med*. (2021) 174(11):M21–1757. doi: 10.7326/M21-1757

41. Furer V, Eviatar T, Zisman D, Peleg H, Paran D, Levartovsky D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. *Ann Rheum Dis*. (2021) 80(10):1330–8. doi: 10.1136/annrheumdis-2021-220647

42. Naranbhai V, Pernat CA, Gavralidis A, St Denis KJ, Lam EC, Spring LM, et al. Immunogenicity and reactogenicity of SARS-CoV-2 vaccines in patients with cancer: the CANVAX Cohort Study. *J Clin Oncol*. (2022) 40(1):12–23. doi: 10.1200/JCO.21.01891

43. COVID-19: FPM response to concerns over safety of injected steroids for pain procedures. Faculty of Pain Medicine. Available at: https://fpm.ac.uk/covid-19-fpm-response-concerns-over-safety-injected-steroids-pain-procedures (Accessed 17 May 2023).

44. NHS staff to receive free access to Microsoft Teams and Locum's Nest. Healthcare IT News (2020). Available at: https://www.healthcareitnews.com/news/emea/nhs-staff-receive-free-access-microsoft-teams-and-locum-s-nest (Accessed 17 May 2023).

45. Statement on the fifteenth meeting of the IHR. (2005) Emergency Committee on the COVID-19 pandemic. Available at: https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic (Accessed 30 May 2023).

frontiers | Frontiers in Neurology

TYPE Mini Review
PUBLISHED 24 August 2023
DOI 10.3389/fneur.2023.1221266

OPEN ACCESS

EDITED BY
Christina M. Marra,
University of Washington, United States

REVIEWED BY
Christopher Ransom,
United States Department of Veterans Affairs, United States
Catherine DeMarino,
National Institutes of Health (NIH), United States

*CORRESPONDENCE
Ludivine Chamard-Witkowski
✉ ludivine.witkowski@vitalitenb.ca

RECEIVED 12 May 2023
ACCEPTED 27 July 2023
PUBLISHED 24 August 2023

CITATION
Saucier J, Comeau D, Robichaud GA and Chamard-Witkowski L (2023) Reactive gliosis and neuroinflammation: prime suspects in the pathophysiology of post-acute neuroCOVID-19 syndrome. *Front. Neurol.* 14:1221266. doi: 10.3389/fneur.2023.1221266

Reactive gliosis and neuroinflammation: prime suspects in the pathophysiology of post-acute neuroCOVID-19 syndrome

Jacob Saucier[1,2], Dominique Comeau[3], Gilles A. Robichaud[3,4,5] and Ludivine Chamard-Witkowski[1,2,3,6]*

[1]Centre de Formation Médicale du Nouveau-Brunswick, Moncton, NB, Canada, [2]Faculté de Médecine et des Sciences de la Santé, Université de Sherbrooke, Sherbrooke, QC, Canada, [3]Centre de médecine de précision du Nouveau-Brunswick, Vitality Health Network, Moncton, NB, Canada, [4]Department of Chemistry and Biochemistry, Université de Moncton, Moncton, NB, Canada, [5]Atlantic Cancer Research Institute, Moncton, NB, Canada, [6]Department of Neurology, Dr. Georges-L.-Dumont University Hospital Centre, Vitality Health Network, Moncton, NB, Canada

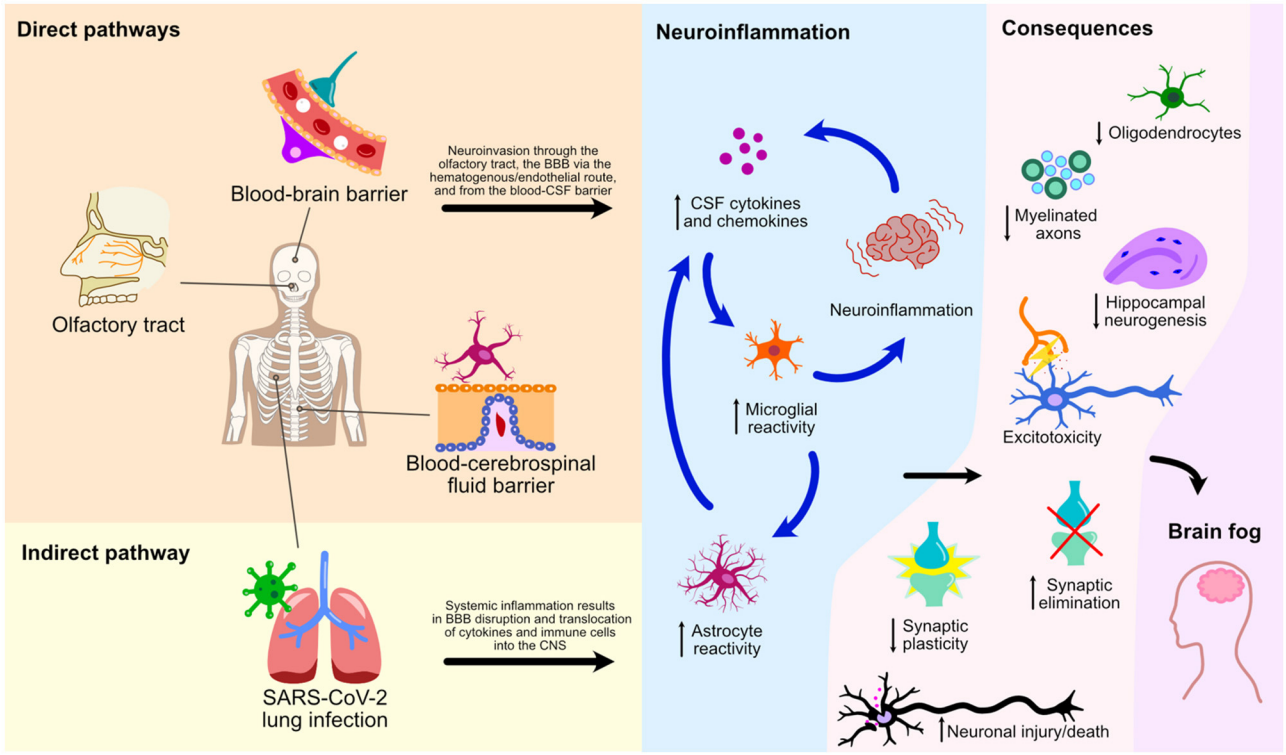
Introduction: As the repercussions from the COVID-19 pandemic continue to unfold, an ever-expanding body of evidence suggests that infection also elicits pathophysiological manifestations within the central nervous system (CNS), known as neurological symptoms of post-acute sequelae of COVID infection (NeuroPASC). Although the neurological impairments and repercussions associated with NeuroPASC have been well described in the literature, its etiology remains to be fully characterized.

Objectives: This mini-review explores the current literature that elucidates various mechanisms underlining NeuroPASC, its players, and regulators, leading to persistent neuroinflammation of affected individuals. Specifically, we provide some insights into the various roles played by microglial and astroglial cell reactivity in NeuroPASC and how these cell subsets potentially contribute to neurological impairment in response to the direct or indirect mechanisms of CNS injury.

Discussion: A better understanding of the mechanisms and biomarkers associated with this maladaptive neuroimmune response will thus provide better diagnostic strategies for NeuroPASC and reveal new potential mechanisms for therapeutic intervention. Altogether, the elucidation of NeuroPASC pathogenesis will improve patient outcomes and mitigate the socioeconomic burden of this syndrome.

KEYWORDS

post-COVID syndrome, NeuroPASC, reactive gliosis, neuroinflammation, microglial reactivity, reactive astrocytes



GRAPHICAL ABSTRACT

1. Introduction

It has been established that the pathophysiology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entails long-term symptomatic repercussions in infected patients. The Center for Disease Control and Prevention (CDC) defines post-acute sequelae of COVID-19 (PASC) as the persistence of COVID-19 symptoms beyond 4 weeks of the initial infection (1). PASC is a multi-organ disease with a plethora of clinical manifestations including dyspnea, cough, fibrotic changes on pulmonary imaging, palpitations, chest pain, thromboembolic events, chronic kidney injury, fatigue, endocrine disruption, hair loss, and multiple neuropsychiatric manifestations (2).

The long-term impact of COVID-19 on the central nervous system (CNS) has been a growing area of concern, with its consequences referred to as post-acute neurological symptoms of COVID-19 (NeuroPASC). NeuroPASC's most prevalent symptom, cognitive impairment, has been reported in 28.85% of patients following COVID-19 infection according to a recent systematic review and meta-analysis (3). However, upon neuropsychological evaluation, cognitive deficits have been objectified in over 50% of COVID-19 patients (4–8). The term "*brain fog*" has been extensively used in the literature and mainstream media to illustrate the cognitive state of NeuroPASC. It refers to a non-specific constellation of symptoms, including the subjective complaints of poor attention, executive function, and problem solving (9), that may impede daily activities and interpersonal relationships (10). Various conditions may mimic COVID-19's brain fog, including anxiety and mood disorders, traumatic brain injury, chronic fatigue syndrome, and cancer-related cognitive impaired, coined "chemo-fog" (10). Nonetheless, other longstanding neurological symptoms such as fatigue, headache, myalgia, dysautonomia, deficits in verbal fluency, attention loss, executive functions, and memory impairments have been objectified following SARS-CoV-2 infection (6, 9, 11). Recently, cognitive inhibition deficits were reported to be highly prevalent among COVID-19 cases as 38.8% of patients expressed sustained deficits in cognitive inhibition for up to 16 months following COVID-19 infection (8). While other cognitive domains such as cognitive efficiency and executive functions longitudinally improved, cognitive inhibition remained persistently poor over time. An extensive literature has described the psychiatric manifestations of NeuroPASC. Accordingly, a recent meta-analysis has documented the prevalence of long-term neuropsychiatric manifestations following SARS-CoV-2 infection, including sleep disturbances (27.4%), fatigue (24.4%), anxiety (19.1%), and post-traumatic stress disorder (PTSD) (15.7%) (12). Similarly, clinically relevant depressive symptoms in convalescent individuals were estimated between 21 and 45% in COVID-19 patients (13). Efforts to identify risk factors of NeuroPASC development following SARS-CoV-2 infection have produced heterogeneous results across different cohorts (14). While cognitive impairment was greater in ICU compared to non-ICU patients in some studies (8, 15, 16), other reports did not observe any differences in cognitive impairment in the function of infection severity (7, 17). Nonetheless, consistent findings across studies identified female sex (18, 19), older age (19, 20), and previous dementia or cognitive complaints (19, 21) as risk factors for NeuroPASC development.

Several theories have been proposed to explain these neurocognitive symptoms, including inflammatory changes, hypoxia, coagulopathy, vascular endothelial, dysfunction and direct viral invasion of the neurological tissue (22). Although the precise mechanisms remain elusive, six mechanisms have been proposed: i) systemic immune response-mediated neural dysregulation; ii) direct CNS invasion; iii) auto-immune responses; iv) latent pathogen reactivation; v) cerebrovascular thrombosis; and vi) multi-organ dysfunction (23). In this mini-review, we have highlighted the leading hypotheses and pathological mechanisms supporting NeuroPASC, through the consequential disturbance of reactive microglia and astroglia, which lead to persistent neurocognitive symptoms of PASC.

1.1. Glial cell reactivity

Maintenance of optimal cognitive function is a complex process that requires coordination between neuron function and glial cells (24). In recent years, significant interest has been allocated to glial cell (i.e., microglia, astrocytes, and oligodendrocytes) dysfunction during cognitive impairment. In fact, the dysregulation of glial cell function leads to cognitive impairment associated with numerous neuropathologies, including metabolic syndromes (24) and neurodegenerative diseases such as Parkinson's (25) and Alzheimer's (26) diseases. Microglia, the resident immune phagocytes of the CNS, are essential for learning, memory, and behavior regulation in the adult brain (27). In addition to immune surveillance and phagocytosis, microglia are also responsible for other crucial functions in the CNS, including synaptic pruning and synaptogenesis, axon fasciculation and neurite formation, programmed cell death, astrocyte activation and proliferation, and oligodendrocyte differentiation and myelogenesis (27) (Figure 1). Based on the concept of cellular polarization, cells were separated into two phenotypically distinct sub-populations characterized by opposing effects on the CNS. Specifically, the classical (M1) microglial subset was believed to be responsible to produce pro-inflammatory mediators, which induced inflammation and neurotoxicity. Conversely, M2 was assumed to release anti-inflammatory factors, which confer neuroprotectivity. With the advent of technology, M1 and M2 microglia are portrayed as brute oversimplifications to illustrate antagonistic states in both healthy and diseased brains (28). Microglia are likely to be significantly more complex as microglial subset identity and function are intricately regulated by microglial metabolic states and the environmental profiles of signaling mediators (e.g., cytokines and neurotransmitters) (24).

Complex microglial–astrocyte interactions also form a delicate equilibrium in CNS health. Indeed, cellular dysfunction from either cell population or the maladaptive synergistic interactions between microglia and astrocytes can result in neurotoxicity and alter synaptic plasticity through numerous mechanisms (29, 30). With a crucial role in brain homeostasis, astrocytes regulate CNS blood flow, glucose metabolism, and the recycling of neurotransmitters (24). Astrocytes are also depicted as master regulators of synaptic activity by controlling synaptic junction plasticity and mediating

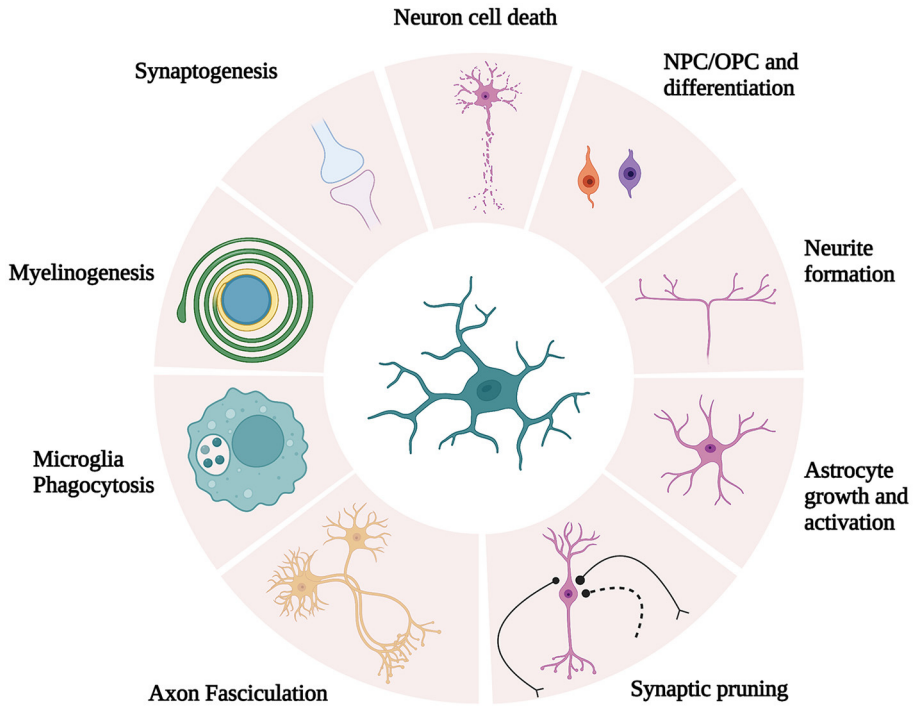


FIGURE 1
Schematic illustration of microglia function. Microglia are responsible for crucial functions in the CNS, including synaptic pruning and synaptogenesis, axon fasciculation and neurite formation, programmed cell death, astrocyte activation and proliferation, and oligodendrocyte differentiation and myelogenesis. [Modified and reproduced from Wright-Jin and Gutmann (27), Microglia as Dynamic Cellular Mediators of Brain Function, with the permission of Cell Press.].

synapse elimination to avoid excitotoxicity (31, 32). Reminiscent of microglia's obsolete nomenclature, astrocytes are classified into two distinct sub-populations (A1 and A2) based on their reactivity and function (30). On the one hand, A1 reactive astrocytes produce pro-inflammatory soluble mediators, which are mainly induced by the NF-κB signaling cascade (33). On the other hand, A2 reactive astrocytes generate anti-inflammatory mediators and many neurotrophic factors induced by STAT3 activation. As a result, reactive A1 astrocytes provoke neurotoxicity and neuronal death, whereas A2 astrocytes promote survival and neuron growth (33).

Upon cerebral insult, astrocytes undergo drastic phenotype change referred to as reactive astrocytosis, induced due to an upregulation of pro-inflammatory cytokines by neuroinflammatory microglia such as (interleukin) IL-1α, IL-1β, tumor necrosis factor-alpha (TNF-α), and the complement component 1q (C1q) (29, 30, 33). As a result, neurotoxic A1 reactive astrocytes display decreased function in synaptic formation and phagocytic capability. Furthermore, A1 reactive astrocytes promote significant neurotoxicity, which leads to cell death of cortical neurons and mature differentiated oligodendrocytes (30, 34). Moreover, inflammatory microglia further accentuate NF-κB signaling, leading to A1 astrocyte population remodeling and neurodegeneration (35). A study by Saggu et al. (36) has shown that astroglial-mediated NF-κB activation is associated with white matter damage and cognitive impairments in vascular dementia models (36). While microglial activation alone is insufficient to initiate cell death in the CNS, microglial activation potentially enhances neurological damage by inducing reactive astrocytosis, resulting in neurodegeneration (30).

As for oligodendrocytes, they are responsible for axonal myelination, which regulates action potential conduction velocity, essential for neural circuit dynamics (37). Oligodendrocytes are also important contributors to neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, and multiple system atrophy. More recently, studies have shown that, in addition to myelination, oligodendrocytes are required for the integrity and survival of axons independent of myelin itself (38). Mechanistically, oligodendrocytes foster glycolytic metabolism, which provides axons with energy-rich metabolites.

Altogether, the coordinated signaling between microglia, astrocytes, and oligodendrocytes is essential for homeostasis and CNS health.

2. SARS-CoV-2-mediated activation of glial cells

2.1. Indirect pathway: peripheral immune cell activation and CNS infiltration

Acute and chronic CNS inflammation alike have drastic repercussions on glial circuitry and cytokine expression profiles, which result in dysfunctional immune signaling and synaptic plasticity (39). As a result of the intricate equilibrium that composes glial cell homeostasis, various neuroinflammatory states including chemotherapy (40) and notably COVID-19 infection (41), disrupts glial lineage, pertaining to glial population proliferation, differentiation, and maturation. Following COVID-19 infection, an upregulation of pro-inflammatory chemokine-enhanced microglial populations and an impairment of oligodendrogenesis in mice models led to neurological disturbance in the absence of direct viral invasion (41).

Neuroinflammation underlies one of the leading theories to explain CNS injury during SARS-CoV-2 infection and is a consequence of the well-documented systemic cytokine storm and subsequent increase in blood–brain barrier (BBB) permeability (14, 42). Through its spike surface glycoprotein, SARS-CoV-2 enters the host cells by binding to its angiotensin-2 converting enzyme (ACE-2) receptors, which consequently initiates an important inflammatory response (13, 43). Brain–blood barrier disruption from systemic inflammation facilitates neuroinflammation through neural invasion of inflammatory cytokines, which further stimulates cytokine secretion from the microglia (42). Accordingly, a study in rats has shown that exposure to a partial subunit of the SARS-CoV-2 spike protein (i.e., S1 protein subunit) elicits innate immune response through a pathogen-associated molecular pattern (PAMP), which triggers microglial activation and neuroinflammation in the absence of active virions (44). The S1 spike protein also activates the NRLP3 inflammasome that plays a pivotal role in innate immunity and inflammatory signaling triggered by PAMPs (45). This pathway leads to NF-κB activation, pro-inflammatory cytokine production (i.e., IL-1β and IL-18), and subsequent glial reactivity, all of which are associated with neurodegenerative diseases (46). Meanwhile, microglial activation *via* NF-κB signaling induces reactive astrocytosis, which in turn leads to excitotoxicity, white matter damage, and loss of myelin plasticity, in addition to oligodendrocyte and neuronal cell death (14, 35, 44).

Neuroinflammatory pathways that alter CNS homeostasis are linked to cognitive and neuropsychiatric complications (43). The systemic immune-inflammation index, which reflects the immune response and systemic inflammation based on a ratio of peripheral lymphocyte, neutrophil, and platelet counts (SII = platelets × neutrophils/lymphocytes), has been found to predict depressive symptomatology and cognitive dysfunction 3 months following initial infection (47). Even in the absence of direct CNS viral infiltration, consequential production of peripheral cytokine profiles associated with the host's antiviral response may be sufficient to induce neuroinflammatory reactions and/or compromise the integrity of the blood–brain interface. As a result, peripheral immune cells migrate through the BBB into the CNS and induce microglia-derived cytokines, which interfere with neurotransmission (14, 42). These mechanisms have mostly been established using experimental models. For example, mild respiratory illness in AAV-hACE2 mice (48) following intranasal delivery of SARS-CoV-2 was sufficient to induce potent microglial reactivity in the sub-cortical white matter upon pathological examination of the mice brain tissue (41). Moreover, Klein et al. (49) compared the hamster models of SARS-CoV-2 to pathological specimens of human patients deceased from COVID-19, demonstrating similar pathological changes in the absence of viral neuroinvasion. These changes included abnormal BBB permeability, microglial activation, loss of hippocampal neurogenesis, and expression of IL-1β and IL-6 within sub-cortical structures (49).

Neuroinflammation during acute SARS-CoV-2 infection may consequently induce brain parenchyma and vessel alterations that further foster the inflammation of neurons and supportive cells (14). Additionally, such neuroinflammation could be a catalyst for microvascular thrombosis and ischemic brain injury during the COVID-19 infection (50). Magnetic resonance imaging (MRI) from a deceased COVID-19 patient revealed volumetric and micro-structural brain abnormalities, which were accompanied by several neuropathological lesions reminiscent of vascular and demyelinating etiology (51). Any combination of these events could lead to BBB disruption and subsequent immune cell infiltration of the CNS causing microglial activation and neuroinflammation in the absence of direct viral invasion of the CNS.

2.2. Direct pathways

Glial activation and neurotoxicity may result from the direct routes of SARS-CoV-2 infection. In a study where transgenic mice models expressing recombinant human ACE-2 were infected with SARS-CoV-2, investigators found viral particle (spike protein) infiltration within the CNS and an abundance of activated microglia in the proximity of the infected tissue (46). The utilization of human monocyte-derived microglia infected with SARS-CoV-2 revealed that viruses enter these cells through ACE-2 receptor binding in the absence of viral replication. More interestingly, they observed that the infected cells induced NLRP3 inflammasome activation and a potent pro-inflammatory response accompanied by IL-1β overexpression (46). Mechanistically, these neuroinflammatory events were shown to be NF-κB dependent as the utilization of NF-κB inhibitors led to complete inhibition of Il-1β release. Another study conducted by Samudyata et al. (52) established a brain organoid model with innately developing microglia (52). Such *in vitro* invasion assays on microglial cells co-cultured with SARS-CoV-2 demonstrate the loss of post-synaptic termini and neuronal cell death. Transcriptomic profiling of microglia exposed to SARS-CoV-2 revealed gene expression signatures that closely resembled neurodegenerative disorders (52). Nevertheless, it is worth noting that SARS-CoV-2 antigens and RNA have rarely been detected in the CSF of COVID-19 patients (53, 54) while only detected in a minority of human brain autopsies (55). Heterogenous study results have resulted in controversy surrounding the neuroinvasive properties of SARS-CoV-2. This section will explore pathways by which CNS infiltration of SARS-CoV-2 of viral proteins may result in microglial activation and neuroinflammation during COVID-19 infection.

2.2.1. Olfactory route

The presence of ACE-2 receptors along the olfactory tract suggests that the neurological manifestations of COVID-19 could be caused by direct neurological infiltration *via* the olfactory route (56, 57), a common entry site to several other respiratory viruses (58). CNS viral dissemination to the amygdala, hippocampus, and entorhinal cortex could then be possible through the connecting olfactory bulb, where SARS-COV-2 RNA has been found in approximately 20% of post-mortem brains from deceased COVID-19 patients (59). Numerous imaging studies also support this hypothesis (59–61). For example, neuroimaging from a cohort of 785 participants (including 401 participants scanned before and after COVID-19 infection) discovered significant longitudinal effects in SARS-CoV-2 cases including a decrease of thickness and tissue contrast from the orbitofrontal cortex and the parahippocampal gyrus gray matter, changes in tissue damage markers in olfactory cortex-related regions, and a global reduction in brain volume (61). Previously infected individuals from the latter cohort also demonstrated cognitive decline post-infection. Together, imaging data originating mainly from the limbic system could highlight COVID-19-mediated neurodegeneration through the olfactory pathways, neuroinflammatory events, and loss of sensory input caused by anosmia (61). Other imaging studies in COVID-19 patients using MRI cerebral imaging have enabled researchers to observe an increase in olfactory bulb signal intensity and volume size (60). Positron emission tomography (PET) has also shown reduced 18-fludeoxyglucose of orbitofrontal hypometabolism in patients with anosmia (62). Altogether, these findings suggest a role for imaging technologies in the detection and progression of direct neurological infiltration and pathogenesis of COVID-19 infection through the olfactory tract.

2.2.2. Hematogenous spread and endothelial pathology

Perturbation of BBB permeability has been well documented during the infection of various respiratory viruses (63). Of note, cerebral endothelial cells, which comprise the BBB, are prone to SARS-CoV-2 infection through cell surface expression of receptors NRP1, BSG, and low levels of ACE-2 (64). Furthermore, SARS-CoV-2 has been shown to cross the BBB by transcellular pathways, accompanied by basement membrane disruption in mice models (65). As a result, vascular permeability increases and leads to perivascular cell infiltration and neuronal cell death. Wenzel et al. (64) have demonstrated brain endothelial cells infection; the expression of SARS-CoV-2 main protease (Mpro) cleaves the host protein NF-κB essential modulator (NEMO), which is an essential modulator of NF-κB-mediated survival (64). By ablating NEMO, M^{pro} induces microvascular pathology, BBB disruption, endothelial cell death, and neuroinflammation. Similarly, ACE-2 (66) and NRP1 (67) receptors can be found in astrocytes, which are in direct contiguity with the BBB. Astrocyte infection by SARS-CoV-2 is further supported by the detection of the S1 spike gene transcripts and protein in the cerebral vasculature of COVID-19 patients (64) and the description of S1 spike-positive astrocyte in post-mortem human samples (67). Subsequently, *in vitro* neural stem cell-derived human astrocytes were exposed to SARS-CoV-2, resulting in astrocyte infection through spike-NRP1 interactions (67). The resulting astrocyte phenotype decreased neuronal viability while promoting neuronal apoptosis (67).

Previous studies have also demonstrated the occurrence of neuropathological events mediated by the S1 protein of SARS-CoV-2. Accordingly, SARS-CoV-2 virions are known to spontaneously shed S1 protein subunits, which can be found in the plasma of COVID-19 patients (44, 68). This pro-inflammatory protein

has also been found in human cerebral endothelial cells upon autopsy in the absence of viral RNA and is strongly co-localized with inflammatory mediators including caspase-3, TNF-α and IL-6 (69). In mouse models, S1 spike protein injection leads to endothelial cell damage with increased expression of TNF-α and IL-6, which co-localized with the S1 spike subunit (69). Similarly, non-primate models have demonstrated the presence of SARS-CoV-2 nucleocapsid protein in endothelial cells of the cerebral vasculature (70). Altogether, the expression of SARS-CoV-2 compatible receptors in cerebral structures, in addition to the discovery of SARS-CoV-2 genetic material and viral proteins in the endothelial tissue and astrocytes, suggests that viral invasion or viral protein infiltration of cerebral vasculature could be a mechanism that leads to microglial activation and neuroinflammation.

2.2.3. Cerebrospinal fluid

Another proposed route for SARS-CoV-2 infection is through the cerebrospinal fluid (CSF). In a study utilizing human-pluripotent-stem-cell-derived brain organoids to examine SARS-CoV-2 neurotropism, ACE-2 positive choroid plexus epithelial cells were amenable to infection, which leads to an initial disruption of the blood–CSF barrier followed by a subsequent complete breakdown of barrier integrity (71). Infection of these organoids has been associated with transcriptional dysregulation and cell death, suggestive of a neuroinflammatory response and deficits in cellular functions (72). Although some studies have shown SARS-CoV-2 PCR positivity in patient's CSF samples, other studies have contradicted this notion (73). While the neuroinvasive properties of SARS-CoV-2 through the blood–CSF barrier have not been confirmed, a more likely mechanism involves barrier leakage, leading to the translocation of immune cells and cytokines that sustain neuroinflammation (71).

3. Reactive gliosis as a culprit of NeuroPASC

3.1. Current evidence of microglial reactivity in NeuroPASC

A recent study on AAV-hACE2 mice models with mild SARS-CoV-2 respiratory infection has demonstrated a prominent increase in pro-inflammatory cytokine and chemokine profiles (e.g., IFN-γ, IL-6, TNF-α, CXCL10, CCL7, CCL2, and CCL11) in the CSF and serum samples as rapid as 7 days post-infection (41). Longitudinal evaluation of pro-inflammatory mediators revealed that while serum levels of these mediators normalized after 7 weeks, there was a progressive increase of CSF cytokines/chemokines levels over time. Notably, CCL11, a cytokine associated with cognitive impairment (74), remained persistently elevated in the CSF over time, suggesting that isolated respiratory infection with SARS-CoV-2 can result in prolonged changes in CSF cytokine profiles, leading to persistent neuroinflammation (41). The latter study has also demonstrated that mice infected with SARS-CoV-2 displayed white matter microglial reactivity for at least 7 weeks, which culminated in oligodendrocyte death, axonal demyelination, and impaired mechanisms of cellular homeostasis and neuron generation in the hippocampus. These findings align with recent studies highlighting BBB disruption, microglial activation, aberrant cytokine expression, and suppression of hippocampal neurogenesis in brain samples from post-mortem COVID-19 patients (49). Moreover, Schultheiß et al. (75) demonstrated elevated serum cytokine profiles up to 8 months post-infection in a cohort of COVID-19 patients manifesting mostly mild-to-moderate infection severity (75). Interestingly, persistently elevated levels of serum IL-1β, IL-6, and TNF-α correlated with PASC symptoms of dyspnea, fatigue, and cognitive impairment. Further examination also suggested that these cytokines were constitutively secreted by resident monocytes/macrophages in the lungs (75). In parallel, a study by Peluso et al. (76) revealed that an increase in plasma IL-6, TNF-α and glial fibrillary acidic protein (GFAP), an axonal structural protein and biomarker of glial cell activation, predicts NeuroPASC symptoms in SARS-CoV-2 infected patients (76).

Cognitive dysfunction is also correlated with increased immunoregulatory pathway protein expression and a downregulation of inflammatory and antiviral response proteins (77). Moreover, individuals with NeuroPASC exhibit deficient systemic humoral immunity response to various SARS-CoV-2 antigens (Spike, S1, S2, RBC, and Nc) when compared to non-PASC COVID-19 control patients. Elevated levels of serum IgG specific to SARS-CoV-2 are associated with improved NeuroPASC clinical outcomes possibly due to enhanced viral clearance (78), while individuals who experience severe neurological injury following acute COVID-19 infection tend to elicit elevated levels of CSF SARS-CoV-2 specific antibodies (79). Distinct T-cell response and effector signatures in addition to unique CSF humoral responses highlight the significance of humoral immunity alterations and pathogenic outcomes of NeuroPASC (77, 78). Taking into consideration that mild respiratory infection and systemic inflammation can lead to BBB permeability disturbances combined with microglial reactivity (41), one could suggest that immunologic alterations (77, 78) and persistent systemic inflammation following COVID-19 (75) may be a catalyst for chronic neuroinflammation and glial reactivity in previously primed microglia.

3.2. Microglial priming and persistent neuroinflammation in NeuroPASC

Considering the detrimental role of persistent microglial reactivity in neurodegenerative diseases, such reactive states could also be key to NeuroPASC pathogenesis. Accordingly, a key concept in AD trajectory known as microglial priming is associated with aging and systemic inflammation (80). Fundamentally, microglia priming renders them more susceptible to secondary inflammatory events, which in turn promotes microglial differentiation to pro-inflammatory subtypes and triggers an exaggerated inflammatory response in response to subsequent stimuli (80). This phenomenon may explain why the prevalence of NeuroPASC is higher in older adults (20). Although the specific mechanisms initiating microglial priming remain to be elucidated, it is generally accepted that chronic inflammation and/or repetitive inflammatory stimuli are a governing factor. Recently, Albornoz et al. (46) have demonstrated that the SARS-CoV-2 S1 spike protein acts as an

NLRP3 inflammasome and microglial primer, setting the stage for increased reactivity to inflammatory stimuli (46). Persistent glial reactivity and chronic neuroinflammation in neurodegenerative diseases can be attributed to an exaggerated inflammatory response upon repeated exposition to pathological stimuli (80), such as β-amyloid plaques and alpha-synuclein in AD (80) and Parkinson's disease (PD) (81), respectively. Similarly, the persistent systemic inflammation in PASC (75) could represent a stimulus with the capacity to longitudinally promote microglial reactivity, leading to maladaptive neuroinflammation in microglia previously primed during the wake of SARS-CoV-2 infection. Keeping these mechanisms in mind, SARS-CoV-2 infection and pathogenesis could potentially trigger neurodegenerative events reminiscent of AD and PD (82). As such, there exists a positive correlation between COVID-19 infection and its severity with the risk of AD development (83). Moreover, COVID-19 may exacerbate motor and non-motor symptoms in PD patients (84).

There are considerable parallels between SARS-CoV-2 and influenza sequelae. Iosifescu et al. (20) and Taquet et al. (85) compared neurological and psychiatric sequelae following these viral infections. The incidence of long-term COVID-19 and influenza-related neuro-sequelae was 2.58 and 2.06% (20) and 3.01 and 1.83% (85), respectively. The average onset of NeuroPASC symptoms was 138 days following the initial infection vs. 238 days for influenza sequelae (20). The occurrence of altered mental status was significantly greater in NeuroPASC patients (17%), but there were no statistically significant differences in other clinical signs and symptoms when compared to influenza. These symptoms include anxiety, depression, dizziness, fatigue, headaches, nausea, seizures, and strokes (20). From a pathophysiological perspective, respiratory influenza infection elicits neuroinflammation through pro-inflammatory cytokines secretion and microglial reactivity (86, 87). These processes alter BBB permeability, structural hippocampal plasticity, and may underlie cognitive dysfunction (86, 87). Fernández-Castañeda et al. (41) compared CSF pro-inflammatory cytokine profiles at 7 days and 7 weeks post-infection between mice models of SARS-CoV-2 and H1N1 influenza, revealing distinct profiles, with some overlap. Of note, CCL11, a cytokine associated with cognitive impairment (74) remained persistently elevated in both SARS-COV-2 and H1N1 models. A comparison of microglial reactivity revealed similar hippocampal pathology at 7 days and 7 weeks post-infection. However, unlike respiratory COVID, sub-cortical white matter integrity in H1N1 mice was preserved at 7 weeks, with a resolution of acute microglial reactivity and oligodendrocyte loss (41).

Alternatively, microglial activation during acute SARS-CoV-2 infection could be sufficient to induce maladaptive inflammatory pathways, leading to chronic neuroinflammation and NeuroPASC in the absence of longitudinal peripheral stimuli. This phenomenon has been described following traumatic brain injury (TBI) in human brain samples, where densely packed reactive microglia are responsible for chronic neuroinflammation and white matter degradation (88). In fact, persistent inflammatory pathology was observed in over a quarter of TBI cases and for up to 18 years following the initial brain injury (88). Studies also showed that the ensuing microglial activation and neuroinflammation from TBI results in cognitive impairment and predispose to AD (89).

A comparable syndrome is cancer-therapy-related cognitive impairment, commonly referred to as "chemo-fog," which is characterized by mild-to-moderate impairments in memory, attention, executive functioning, and processing speed (90). The term itself and the affected neuropsychological domains resemble the "brain fog" currently used to describe NeuroPASC cognitive impairment. Furthermore, accumulating evidence suggests that chemotherapies and cranial radio-irradiation elicit a persistent microglial activation beyond the duration of treatment, leading to neuroinflammation, loss of hippocampal neurogenesis, and neuronal plasticity in addition to white matter pathology, all of which represent the core features of NeuroPASC pathology (91). Hence, it is plausible that microglial activation persists beyond the initial inflammatory stimuli in NeuroPASC, aligning with the findings observed in traumatic brain injury (TBI) and cancer-related cognitive impairment.

Globally, the resolution of neuroinflammation is essential to mitigate neurological damage. Accordingly, this is the precise role of microglia and astrocytes subsets with tissue repair and anti-inflammatory functions (33, 92). However, in neurodegenerative conditions, neuroinflammation is a crucial pathological driver as it tends to be chronically active and fails to resolve (92). Moreover, the anti-inflammatory phenotypes of microglia, which promote the clearance of inflammation in a healthy setting, are altered in neurodegenerative diseases (92). Comprehension of the delicate balance in glial cell networks and function is therefore essential to understand the complex processes governing neurodegeneration. For example, while M1 and M2 microglia are portrayed as oversimplifications to illustrate antagonistic states in both healthy and diseased brains, studies have reported distinct microglial sub-populations known as disease-associated microglia (DAM) in Alzheimer's disease (AD) (93). This unique subset of microglial cells has been specifically associated with neurodegenerative disorders and remains undetectable in healthy human brain samples. Similarly, distinct microglia populations with unique signatures have been identified in mice models, characterized by altered homeostatic gene expression and chemokine profiles that show significant overlap with DAM (41). Although the complete elucidation of DAM cells and their role in neurological disorders remains under investigation, further studies are required to map the intricate networks and function of glial cells in NeuroPASC.

4. Discussion

This mini-review has explored numerous cellular processes and pathways by which SARS-CoV-2 affects the CNS leading to glial reactivity and NeuroPASC (Figure 2). We illustrate an indirect pathway, characterized by the absence of direct viral invasion of the CNS, where microglial activation and neuroinflammation are consequential repercussions of systemic inflammation and BBB breakdown. These events, therefore, result in the translocation of peripheral cytokines and immune cells to the CNS, culminating in microglial activation and neurological damage. Of note, the S1 spike protein subunit of the SARS-CoV-2 could also lead to microglial priming, setting the tone for microglial reactivity

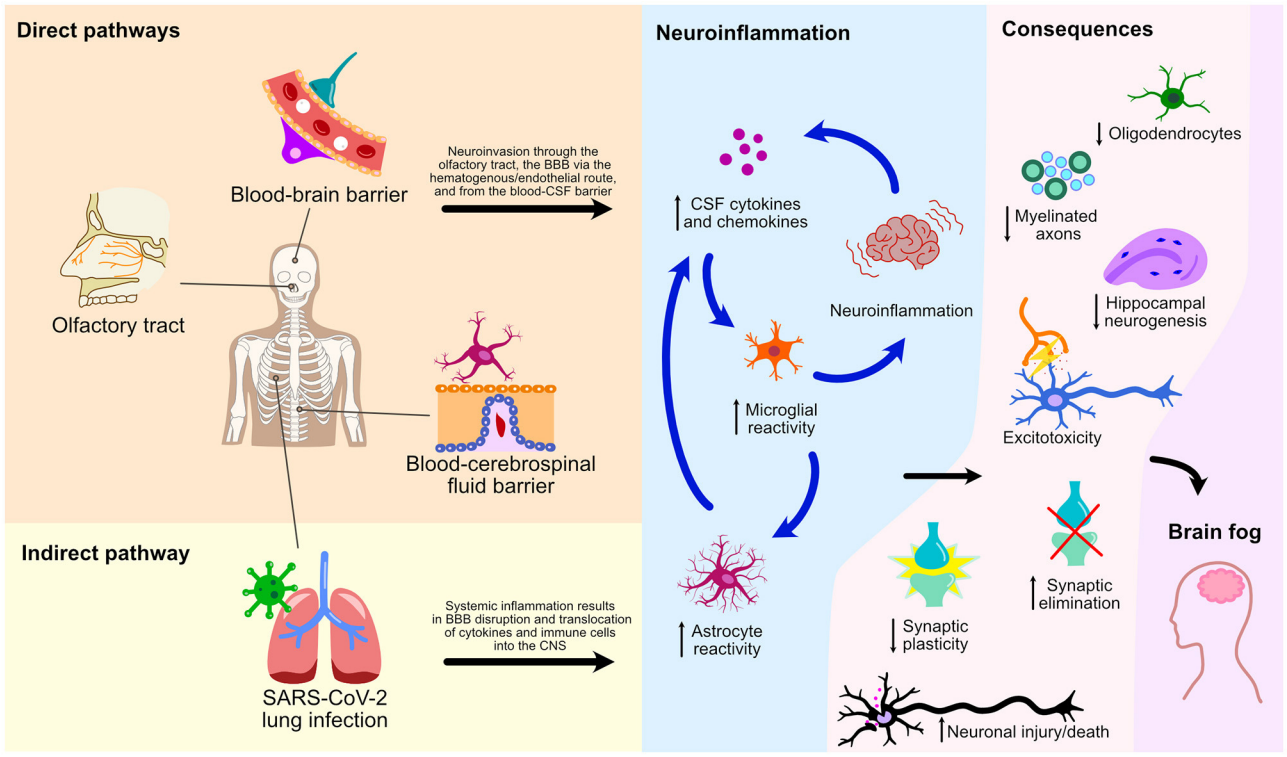


FIGURE 2
Direct and indirect pathways of NeuroPASC. Schematic representation of various pathways and their consequences on microglial reactivity and neuroinflammation of the CNS following the SARS-CoV-2 infection are depicted.

and neuroinflammatory response in a viral neuroinvasion-independent manner. We herein discussed three pathways of direct neuroinvasion that could potentially lead to microglial reactivity: i) through the olfactory bulb; ii) via a hematogenous/endothelial path; and iii) through the CSF. It is likely that microglial reactivity results from a combination of these mechanisms as they are not mutually exclusive (Figure 2).

Reactive microglia are responsible for a plethora of CNS repercussions, including synaptic plasticity impairment (94, 95), inappropriate synaptic elimination, dysfunction of hippocampal neurogenesis, and memory loss (96). Secretion of the microglial pro-inflammatory cytokines also leads to numerous neuropsychiatric manifestations, including apathy, cognitive impairment, anxiety, depression, and learning disability (97). The impact of reactive gliosis has also been well documented using SARS-CoV-2 experimental models (41, 49, 52). In sum, recent data suggest that persistent neuroinflammation could explain the significant prevalence of neuropsychiatric symptoms observed in COVID-19 patients.

While controversy surrounds the legitimacy of NeuroPASC as a distinct neuroinflammatory syndrome, evidence suggests that it possesses distinct microglial subtypes (41), humoral immunity signatures (78), and T-cell activation and effector signatures (77). Despite arising from different CNS insults, the consequences of microglial reactivity, such as white matter injury, impaired hippocampal neurogenesis, and loss of myelin plasticity are similar across various syndromes. These include NeuroPASC, cancer-related cognitive impairment, cognitive dysfunction following traumatic brain injury, and influenza infection. Consequently, it should come as no surprise that the clinical translation of these shared pathological lesions takes nearly identical forms. Pharmacologically targeting these reactive pathways may hold the key to treating numerous neurodegenerative and chronic neuroinflammatory diseases.

A thorough understanding of NeuroPASC pathophysiology and microglial reactivity is primordial to the development of disease-altering therapy. It is the first step toward alleviating the important socioeconomic burden of post-acute COVID-19 syndrome and its neurocognitive sequelae, a global health problem (98).

Author contributions

JS: literature review, original and final manuscript redaction, and review. DC: original manuscript review. GR: final manuscript review and redaction. LC-W: original and final manuscript review. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. CDC (2020). Healthcare Workers [WWW Document]. Cent. Dis. Control Prev. URL Available online at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html (accessed April 2, 2023).

2. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nat Med.* (2021) 27:601–15. doi: 10.1038/s41591-021-01283-z

3. Natarajan A, Shetty A, Delanerolle G, Zeng Y, Zhang Y, Raymont V, et al. A systematic review and meta-analysis of long COVID symptoms. *Syst Rev.* (2023) 12:88. doi: 10.1186/s13643-023-02250-0

4. García-Sánchez C, Calabria M, Grunden N, Pons C, Arroyo JA, Gómez-Anson B, et al. Neuropsychological deficits in patients with cognitive complaints after COVID-19. *Brain Behav.* (2022) 12:e2508. doi: 10.1002/brb3.2508

5. Hosp JA, Dressing A, Blazhenets G, Bormann T, Rau A, Schwabenland M, et al. Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. *Brain J Neurol.* (2021) 144:1263–76. doi: 10.1093/brain/awab009

6. Mattioli F, Stampatori C, Righetti F, Sala E, Tomasi C, De Palma G. Neurological and cognitive sequelae of Covid-19: a four month follow-up. *J Neurol.* (2021) 268:4422–8. doi: 10.1007/s00415-021-10579-6

7. Miskowiak KW, Johnsen S, Sattler SM, Nielsen S, Kunalan K, Rungby J, et al. Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity and association with illness variables. *Eur Neuropsychopharmacol.* (2021) 46:39–48. doi: 10.1016/j.euroneuro.2021.03.019

8. Saucier J, Jose C, Beroual Z, Al-Qadi M, Chartrand S, Libert E, et al. Cognitive inhibition deficit in long COVID-19: An exploratory study. *Front Neurol.* (2023) 14. doi: 10.3389/fneur.2023.1125574

9. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine.* (2021) 38:101019. doi: 10.1016/j.eclinm.2021.101019

10. Chasco EE, Dukes K, Jones D, Comellas AP, Hoffman RM, Garg A. Brain fog and fatigue following COVID-19 infection: an exploratory study of patient experiences of long COVID. *Int J Environ Res Public Health.* (2022) 19:15499. doi: 10.3390/ijerph192315499

11. Moghimi N, Di Napoli M, Biller J, Siegler JE, Shekhar R, McCullough LD, et al. The Neurological Manifestations of Post-Acute Sequelae of SARS-CoV-2 infection. *Curr Neurol Neurosci Rep.* (2021) 21:44. doi: 10.1007/s11910-021-01130-1

12. Badenoch JB, Rengasamy ER, Watson C, Jansen K, Chakraborty S, Sundaram RD, et al. Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. *Brain Commun.* (2022) 4:fcab297. doi: 10.1093/braincomms/fcab297

13. Mazza MG, Palladini M, Poletti S, Benedetti F. Post-COVID-19 depressive symptoms: epidemiology, pathophysiology, and pharmacological treatment. *CNS Drugs.* (2022) 36:681–702. doi: 10.1007/s40263-022-00931-3

14. Thye AY-K, Law JW-F, Tan LT-H, Pusparajah P, Ser H-L, Thurairajasingam S, et al. Psychological Symptoms in COVID-19 Patients: Insights into Pathophysiology and Risk Factors of Long COVID-19. *Biology.* (2022) 11:61. doi: 10.3390/biology11010061

15. Mattioli F, Piva S, Stampatori C, Righetti F, Mega I, Peli E, et al. Neurologic and cognitive sequelae after SARS-CoV2 infection: Different impairment for ICU patients. *J Neurol Sci.* (2022) 432:120061. doi: 10.1016/j.jns.2021.120061

16. Vannorsdall TD, Brigham E, Fawzy A, Raju S, Gorgone A, Pletnikova A, et al. Cognitive dysfunction, psychiatric distress, and functional decline after COVID-19. *J Acad Consult-Liaison Psychiatry.* (2022) 63:133–43. doi: 10.1016/j.jaclp.2021.10.006

17. Woo MS, Malsy J, Pöttgen J, Seddiq Zai S, Ufer F, Hadjilaou A, et al. Frequent neurocognitive deficits after recovery from mild COVID-19. *Brain Commun.* (2020) 2:fcaa205. doi: 10.1093/braincomms/fcaa205

18. Ch'en PY, Gold LS, Lu Q, Ye T, Andrews JS, Patel P. Exploring risk factors for persistent neurocognitive sequelae after hospitalization for COVID-19. *Ann Clin Transl Neurol.* (2023) 51:801. doi: 10.1002/acn3.51801

19. Gonçalves NG, Aliberti MJ, Bertola L, Avelino-Silva T, Dias MB, Apolinario D, et al. Dissipating the fog: Cognitive trajectories and risk factors 1 year after COVID-19 hospitalization. *Alzheimers Dement J Alzheimers Assoc.* (2023) 12:993. doi: 10.1002/alz.12993

20. Iosifescu AL, Hoogenboom WS, Buczek AJ, Fleysher R, Duong TQ. New-onset and persistent neurological and psychiatric sequelae of COVID-19 compared to influenza: A retrospective cohort study in a large New York City healthcare network. *Int J Methods Psychiatr Res.* (2022) 31:e1914. doi: 10.1002/mpr.1914

21. Apple AC, Oddi A, Peluso MJ, Asken BM, Henrich TJ, Kelly JD, et al. Risk factors and abnormal cerebrospinal fluid associate with cognitive symptoms after mild COVID-19. *Ann Clin Transl Neurol.* (2022) 9:221–6. doi: 10.1002/acn3.51498

22. Solomon T. Neurological infection with SARS-CoV-2 - the story so far. *Nat Rev Neurol.* (2021) 17:65–6. doi: 10.1038/s41582-020-00453-w

23. Monje M, Iwasaki A. The neurobiology of long COVID. *Neuron.* (2022) 110:3484–96. doi: 10.1016/j.neuron.2022.10.006

24. Henn RE, Noureldein MH, Elzinga SE, Kim B, Savelieff MG, Feldman EL. Glial-neuron crosstalk in health and disease: A focus on metabolism, obesity, and cognitive impairment. *Neurobiol Dis.* (2022) 170:105766. doi: 10.1016/j.nbd.2022.105766

25. Lecours C, Bordeleau M, Cantin L, Parent M, Paolo TD, Tremblay M-È. Microglial Implication in Parkinson's Disease: Loss of Beneficial Physiological Roles or Gain of Inflammatory Functions? Front. *Cell Neurosci.* (2018) 12:282. doi: 10.3389/fncel.2018.00282

26. Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, Ramakrishnan S, et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science.* (2016) 352:712–6. doi: 10.1126/science.aad8373

27. Wright-Jin EC, Gutmann DH. Microglia as dynamic cellular mediators of brain function. *Trends Mol Med.* (2019) 25:967–79. doi: 10.1016/j.molmed.2019.08.013

28. Ransohoff RM. A polarizing question: do M1 and M2 microglia exist? *Nat Neurosci.* (2016) 19:987–91. doi: 10.1038/nn.4338

29. Liddelow SA, Marsh SE, Stevens B. Microglia and astrocytes in disease: dynamic duo or partners in crime? *Trends Immunol.* (2020) 41:820–35. doi: 10.1016/j.it.2020.07.006

30. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature.* (2017) 541:481–7. doi: 10.1038/nature21029

31. Chung W-S, Allen NJ, Eroglu C. Astrocytes control synapse formation, function, and elimination. *Cold Spring Harb Perspect Biol.* (2015) 7:a020370. doi: 10.1101/cshperspect.a020370

32. Mederos S, González-Arias C, Perea G. Astrocyte–Neuron Networks: A Multilane Highway of Signaling for Homeostatic Brain Function. *Front Synaptic Neurosci.* (2018) 10. doi: 10.3389/fnsyn.2018.00045

33. Zamanian JL, Xu L, Foo LC, Nouri N, Zhou L, Giffard RG, et al. Genomic analysis of reactive astrogliosis. *J Neurosci Off J Soc Neurosci.* (2012) 32:6391–410. doi: 10.1523/JNEUROSCI.6221-11.2012

34. Guttenplan KA, Weigel MK, Prakash P, Wijewardhane PR, Hasel P, Rufen-Blanchette U, et al. Neurotoxic reactive astrocytes induce cell death via saturated lipids. *Nature.* (2021) 599:102–7. doi: 10.1038/s41586-021-03960-y

35. Villarreal A, Vidos C, Monteverde Busso M, Cieri MB, Ramos AJ. Pathological Neuroinflammatory Conversion of Reactive Astrocytes Is Induced by Microglia and Involves Chromatin Remodeling. *Front Pharmacol.* (2021) 12:689346. doi: 10.3389/fphar.2021.689346

36. Saggu R, Schumacher T, Gerich F, Rakers C, Tai K, Delekate A, et al. Astroglial NF-kB contributes to white matter damage and cognitive impairment in a mouse model of vascular dementia. *Acta Neuropathol Commun.* (2016) 4:76. doi: 10.1186/s40478-016-0350-3

37. Smith RS, Koles ZJ. Myelinated nerve fibers: computed effect of myelin thickness on conduction velocity. *Am J Physiol.* (1970) 219:1256–8. doi: 10.1152/ajplegacy.1970.219.5.1256

38. Mot AI, Depp C, Nave K-A. An emerging role of dysfunctional axon-oligodendrocyte coupling in neurodegenerative diseases. *Dialogues Clin Neurosci.* (2018) 20:283–92. doi: 10.31887/dcns.2018.20.4/amot

39. Wu Y, Dissing-Olesen L, MacVicar BA, Stevens B. Microglia: dynamic mediators of synapse development and plasticity. *Trends Immunol.* (2015) 36:605–13. doi: 10.1016/j.it.2015.08.008

40. Dietrich J, Han R, Yang Y, Mayer-Pröschel M, Noble M. CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo. *J Biol.* (2006) 5:22. doi: 10.1186/jbiol50

41. Fernández-Castañeda A, Lu P, Geraghty AC, Song E, Lee MH, Wood J, et al. Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. *Cell.* (2022) 185:2452–2468.e16. doi: 10.1016/j.cell.2022.06.008

42. Balcioglu YH, Yesilkaya UH, Gokcay H, Kirlioglu SS. May the central nervous system be fogged by the cytokine storm in COVID-19? An Appraisal. *J Neuroimmune Pharmacol.* (2020) 15, 343–344. doi: 10.1007/s11481-020-09932-9

43. da Silva Lopes L, Silva RO, de Sousa Lima G, de Araújo Costa AC, Barros DF, Silva-Néto RP. Is there a common pathophysiological mechanism between COVID-19 and depression? *Acta Neurol Belg.* (2021) 121:1117–22. doi: 10.1007/s13760-021-01748-5

44. Frank MG, Nguyen KH, Ball JB, Hopkins S, Kelley T, Baratta MV, et al. SARS-CoV-2 spike S1 subunit induces neuroinflammatory, microglial and behavioral sickness responses: Evidence of PAMP-like properties. *Brain Behav Immun.* (2022) 100:267–77. doi: 10.1016/j.bbi.2021.12.007

45. Blevins HM, Xu Y, Biby S, Zhang S. The NLRP3 inflammasome pathway: a review of mechanisms and inhibitors for the treatment of inflammatory diseases. *Front Aging Neurosci.* (2022) 14:879021. doi: 10.3389/fnagi.2022.879021

46. Albornoz EA, Amarilla AA, Modhiran N, Parker S, Li XX, Wijesundara DK, et al. SARS-CoV-2 drives NLRP3 inflammasome activation in human microglia through spike protein. *Mol Psychiatry.* (2022) 10:1–16. doi: 10.1101/2022.01.11.475947

47. Mazza MG, Palladini M, De Lorenzo R, Magnaghi C, Poletti S, Furlan R, et al. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: Effect of inflammatory biomarkers at three-month follow-up. *Brain Behav Immun.* (2021) 94:138–47. doi: 10.1016/j.bbi.2021.02.021

48. Israelow B, Song E, Mao T, Lu P, Meir A, Liu F, et al. Mouse model of SARS-CoV-2 reveals inflammatory role of type I interferon signaling. *J Exp Med.* (2020) 217:e20201241. doi: 10.1084/jem.20201241

49. Klein R, Soung A, Sissoko C, Nordvig A, Canoll P, Mariani M, et al. COVID-19 induces neuroinflammation and loss of hippocampal neurogenesis. *Res Sq.* (2021) 3:1031824. doi: 10.21203/rs.3.rs-1031824/v1

50. South K, McCulloch L, McColl BW, Elkind MS, Allan SM, Smith CJ. Preceding infection and risk of stroke: An old concept revived by the COVID-19 pandemic. *Int J Stroke.* (2020) 15:722–32. doi: 10.1177/1747493020943815

51. Reichard RR, Kashani KB, Boire NA, Constantopoulos E, Guo Y, Lucchinetti CF. Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. *Acta Neuropathol (Berl).* (2020) 140:1–6. doi: 10.1007/s00401-020-02166-2

52. Samudyata, Oliveira AO, Malwade S, Rufino de Sousa N, Goparaju SK, Gracias J, et al. SARS-CoV-2 promotes microglial synapse elimination in human brain organoids. *Mol Psychiat.* (2022) 27:3939–3950. doi: 10.1038/s41380-022-01786-2

53. Destras G, Bal A, Escuret V, Morfin F, Lina B, Josset L. Systematic SARS-CoV-2 screening in cerebrospinal fluid during the COVID-19 pandemic. *Lancet Microbe.* (2020) 1:e149. doi: 10.1016/S2666-5247(20)30066-5

54. Hanson BA, Visvabharathy L, Ali ST, Kang AK, Patel TR, Clark JR, et al. Plasma biomarkers of neuropathogenesis in hospitalized patients with COVID-19 and those with postacute sequelae of SARS-CoV-2 infection. *Neurol Neuroimmunol Neuroinflam.* (2022) 9:e1151. doi: 10.1212/NXI.0000000000001151

55. Mukerji SS, Solomon IH. What can we learn from brain autopsies in COVID-19? *Neurosci Lett.* (2021) 742:135528. doi: 10.1016/j.neulet.2020.135528

56. Anwar MM, Badawi AM, Eltablawy NA. Can the coronavirus infection penetrates the brain resulting in sudden anosmia followed by severe neurological disorders? *eNeurologicalSci.* (2020) 21:100290. doi: 10.1016/j.ensci.2020.100290

57. Ziuzia-Januszewska L, Januszewski M. Pathogenesis of Olfactory Disorders in COVID-19. *Brain Sci.* (2022) 12:449. doi: 10.3390/brainsci12040449

58. van Riel D, Verdijk R, Kuiken T. The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. *J Pathol.* (2015) 235:277–87. doi: 10.1002/path.4461

59. Serrano GE, Walker JE, Arce R, Glass MJ, Vargas D, Sue LI, et al. Mapping of SARS-CoV-2 Brain Invasion and Histopathology in COVID-19 Disease. *medRxiv 2021.02.15.21251511.* (2021). doi: 10.1101/2021.02.15.21251511

60. Ammar A, Distinguin L, Chetrit A, Safa D, Hans S, Carlier R, et al. Transient modifications of the olfactory bulb on MR follow-up of COVID-19 patients with related olfactory dysfunction. *J Neuroradiol.* (2022) 49:329–32. doi: 10.1016/j.neurad.2022.03.003

61. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature.* (2022). doi: 10.1101/2021.06.11.21258690

62. Karimi-Galougahi M, Yousefi-Koma A, Bakhshayeshkaram M, Raad N, Haseli S. 18FDG PET/CT Scan Reveals Hypoactive Orbitofrontal Cortex in Anosmia of COVID-19. *Acad Radiol.* (2020) 27:1042–3. doi: 10.1016/j.acra.2020.04.030

63. Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM. Neurologic Alterations Due to Respiratory Virus Infections. *Front Cell Neurosci.* (2018) 12:386. doi: 10.3389/fncel.2018.00386

64. Wenzel J, Lampe J, Müller-Fielitz H, Schuster R, Zille M, Müller K, et al. The SARS-CoV-2 main protease Mpro causes microvascular brain pathology by cleaving NEMO in brain endothelial cells. *Nat Neurosci.* (2021) 24:1522–33. doi: 10.1038/s41593-021-00926-1

65. Zhang L, Zhou L, Bao L, Liu J, Zhu H, Lv Q, et al. SARS-CoV-2 crosses the blood-brain barrier accompanied with basement membrane disruption without tight junctions alteration. *Signal Transduct Target Ther.* (2021) 6:337. doi: 10.1038/s41392-021-00719-9

66. Chen R, Wang K, Yu J, Howard D, French L, Chen Z, et al. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in the human and mouse brains. *Front Neurol.* (2020) 11:573095. doi: 10.3389/fneur.2020.573095

67. Crunfli F, Carregari VC, Veras FP, Silva LS, Nogueira MH, Antunes ASLM, et al. Morphological, cellular, and molecular basis of brain infection in COVID-19 patients. *Proc Natl Acad Sci U S A.* (2022) 119:e2200960119. doi: 10.1073/pnas.2200960119

68. Zhang L, Jackson CB, Mou H, Ojha A, Peng H, Quinlan BD, et al. SARS-CoV-2 spike-protein D614G mutation increases virion spike density and infectivity. *Nat Commun.* (2020) 11:6013. doi: 10.1038/s41467-020-19808-4

69. Nuovo GJ, Magro C, Shaffer T, Awad H, Suster D, Mikhail S, et al. Endothelial cell damage is the central part of COVID-19 and a mouse model induced by injection of the S1 subunit of the spike protein. *Ann Diagn Pathol.* (2021) 51:151682. doi: 10.1016/j.anndiagpath.2020.151682

70. Rutkai I, Mayer MG, Hellmers LM, Ning B, Huang Z, Monjure CJ, et al. Neuropathology and virus in brain of SARS-CoV-2 infected non-human primates. *Nat Commun.* (2022) 13:1745. doi: 10.1038/s41467-022-29440-z

71. Pellegrini L, Albecka A, Mallery DL, Kellner MJ, Paul D, Carter AP, et al. SARS-CoV-2 infects the brain choroid plexus and disrupts the blood-CSF barrier in human brain organoids. *Cell Stem Cell.* (2020) 27:951–961.e5. doi: 10.1016/j.stem.2020.10.001

72. Jacob F, Pather SR, Huang WK, Zhang F, Wong SZ, Zhou H, et al. Human pluripotent stem cell-derived neural cells and brain organoids reveal SARS-CoV-2 neurotropism predominates in choroid plexus epithelium. *Cell Stem Cell.* (2020) 27:937–950.e9. doi: 10.1016/j.stem.2020.09.016

73. Johansson A, Mohamed MS, Moulin TC, Schiöth HB. Neurological manifestations of COVID-19: A comprehensive literature review and discussion of mechanisms. *J Neuroimmunol.* (2021) 358:577658. doi: 10.1016/j.jneuroim.2021.577658

74. Villeda SA, Luo J, Mosher KI, Zou B, Britschgi M, Bieri G, et al. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature.* (2011) 477:90–4. doi: 10.1038/nature10357

75. Schultheiß C, Willscher E, Paschold L, Gottschick C, Klee B, Henkes S-S, et al. The IL-1β, IL-6, and TNF cytokine triad is associated with post-acute sequelae of COVID-19. *Cell Rep Med.* (2022) 3:100663. doi: 10.1016/j.xcrm.2022.100663

76. Peluso MJ, Sans HM, Forman CA, Nylander AN, Ho H-E, Lu S, et al. Plasma markers of neurologic injury and inflammation in people with self-reported neurologic postacute sequelae of SARS-CoV-2 infection. *Neurol Neuroimmunol Neuroinflam.* (2022) 9:e200003. doi: 10.1212/NXI.0000000000200003

77. Visvabharathy L, Hanson BA, Orban ZS, Lim PH, Palacio NM, Jimenez M, et al. T cell responses to SARS-CoV-2 in people with and without neurologic symptoms of long COVID. *medRxiv 2021.08.08.21261763.* (2022). doi: 10.1101/2021.08.08.21261763

78. Spatola M, Nziza N, Deng Y, Jung W, Yuan D, Dinoto A, et al. Neurologic sequelae of COVID-19 are determined by immunologic imprinting from previous coronaviruses. *Brain J Neurol.* (2023) 21:awad155. doi: 10.1093/brain/awad155

79. Cunningham JL, Virhammar J, Rönnberg B, Dopico XC, Kolstad L, Albinsson B, et al. Antibody responses to severe acute respiratory syndrome coronavirus 2 in the serum and cerebrospinal fluid of patients with coronavirus disease 2019 and neurological symptoms. *J Infect Dis.* (2022) 225:965–70. doi: 10.1093/infdis/jiab153

80. Li J-W, Zong Y, Cao X-P, Tan L, Tan L. Microglial priming in Alzheimer's disease. *Ann Transl Med.* (2018) 6:176. doi: 10.21037/atm.2018.04.22

81. Ouchi Y, Yagi S, Yokokura M, Sakamoto M. Neuroinflammation in the living brain of Parkinson's disease. *Parkinsonism Relat Disord.* (2009) 15:S200–204. doi: 10.1016/S1353-8020(09)70814-4

82. Rai SN, Tiwari N, Singh P, Singh AK, Mishra D, Imran M, et al. Exploring the paradox of COVID-19 in neurological complications with emphasis on Parkinson's and Alzheimer's disease. *Oxid Med Cell Longev.* (2022) 2022:3012778. doi: 10.1155/2022/3012778

83. Li C, Liu J, Lin J, Shang H. COVID-19 and risk of neurodegenerative disorders: A Mendelian randomization study. *Transl Psychiatry.* (2022) 12:283. doi: 10.1038/s41398-022-02052-3

84. Cilia R, Bonvegna S, Straccia G, Andreasi NG, Elia AE, Romito LM, et al. Effects of COVID-19 on Parkinson's disease clinical features: a community-based case-control study. *Mov Disord.* (2020) 35:1287–92. doi: 10.1002/mds.28170

85. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med.* (2021) 18:e1003773. doi: 10.1371/journal.pmed.1003773

86. Hosseini S, Wilk E, Michaelsen-Preusse K, Gerhauser I, Baumgärtner W, Geffers R, et al. Long-term neuroinflammation induced by influenza a virus infection and the impact on hippocampal neuron morphology and function. *J Neurosci.* (2018) 38:3060–80. doi: 10.1523/JNEUROSCI.1740-17.2018

87. Jurgens HA, Amancherla K, Johnson RW. Influenza infection induces neuroinflammation, alters hippocampal neuron morphology, and impairs cognition in adult mice. *J Neurosci.* (2012) 32:3958–68. doi: 10.1523/JNEUROSCI.6389-11.2012

88. Johnson VE, Stewart JE, Begbie FD, Trojanowski JQ, Smith DH, Stewart W. Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain J Neurol.* (2013) 136:28–42. doi: 10.1093/brain/aws322

89. Dinet V, Petry KG, Badaut J. Brain-immune interactions and neuroinflammation after traumatic brain injury. *Front Neurosci.* (2019) 13:1178. doi: 10.3389/fnins.2019.01178

90. Wefel JS, Kesler SR, Noll KR, Schagen SB. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. *CA Cancer J Clin.* (2015) 65:123–38. doi: 10.3322/caac.21258

91. Gibson EM, Monje M. Microglia in cancer therapy-related cognitive impairment. *Trends Neurosci.* (2021) 44:441–51. doi: 10.1016/j.tins.2021.02.003

92. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol.* (2015) 14:388–405. doi: 10.1016/S1474-4422(15)70016-5

93. Keren-Shaul H, Spinrad A, Weiner A, Matcovitch-Natan O, Dvir-Szternfeld R, Ulland TK, et al. A unique microglia type associated with restricting development of Alzheimer's disease. *Cell.* (2017) 169:1276–1290.e17. doi: 10.1016/j.cell.2017.05.018

94. Avital A, Goshen I, Kamsler A, Segal M, Iverfeldt K, Richter-Levin G, et al. Impaired interleukin-1 signaling is associated with deficits in hippocampal memory processes and neural plasticity. *Hippocampus.* (2003) 13:826–34. doi: 10.1002/hipo.10135

95. Ragozzino D, Di Angelantonio S, Trettel F, Bertollini C, Maggi L, Gross C, et al. Chemokine fractalkine/CX3CL1 negatively modulates active glutamatergic synapses in rat hippocampal neurons. *J Neurosci.* (2006) 26:10488–98. doi: 10.1523/JNEUROSCI.3192-06.2006

96. Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. *Science.* (2003) 302:1760–5. doi: 10.1126/science.1088417

97. Salvador AF, de Lima KA, Kipnis J. Neuromodulation by the immune system: a focus on cytokines. *Nat Rev Immunol.* (2021) 21:526–41. doi: 10.1038/s41577-021-00508-z

98. Nicola M, Alsafi Z, Sohrabi C, Kerwan A, Al-Jabir A, Iosifidis C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): A review. *Int J Surg Lond Engl.* (2020) 78:185–93. doi: 10.1016/j.ijsu.2020.04.018

frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 12 October 2023
DOI 10.3389/fneur.2023.1258352

OPEN ACCESS

EDITED BY
Thorsten Rudroff,
The University of Iowa, United States

REVIEWED BY
Lorenzo Muccioli,
University of Bologna, Italy
Jaime Daniel Mondragón,
University Medical Center Groningen,
Netherlands

*CORRESPONDENCE
Tim Q. Duong
✉ tim.duong@einsteinmed.edu
Montek S. Boparai
✉ Montek.Boparai@stonybrookmedicine.edu

RECEIVED 13 July 2023
ACCEPTED 27 September 2023
PUBLISHED 12 October 2023

CITATION
Boparai MS, Musheyev B, Hou W, Mehler MF and Duong TQ (2023) Brain MRI findings in severe COVID-19 patients: a meta-analysis.
Front. Neurol. 14:1258352.
doi: 10.3389/fneur.2023.1258352

Brain MRI findings in severe COVID-19 patients: a meta-analysis

Montek S. Boparai[1,2]*, Benjamin Musheyev[1], Wei Hou[2], Mark F. Mehler[3] and Tim Q. Duong[2]*

[1]Renaissance School of Medicine at Stony Brook University, Stony Brook, NY, United States, [2]Department of Radiology, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, NY, United States, [3]Department of Neurology, Montefiore Health System and Albert Einstein College of Medicine, Bronx, NY, United States

Introduction: Neurocognitive symptoms and dysfunction of various severities have become increasingly recognized as potential consequences of SARS-CoV-2 infection. Although there are numerous observational and subjective survey-reporting studies of neurological symptoms, by contrast, those studies describing imaging abnormalities are fewer in number.

Methods: This study conducted a metanalysis of 32 studies to determine the incidence of the common neurological abnormalities using magnetic resonance imaging (MRI) in patients with COVID-19.

Results: We also present the common clinical findings associated with MRI abnormalities. We report the incidence of any MRI abnormality to be 55% in COVID-19 patients with perfusion abnormalities (53%) and SWI abnormalities (44%) being the most commonly reported injuries. Cognitive impairment, ICU admission and/or mechanical ventilation status, older age, and hospitalization or longer length of hospital stay were the most common clinical findings associated with brain injury in COVID-19 patients.

Discussion: Overall, the presentation of brain injury in this study was diverse with no substantial pattern of injury emerging, yet most injuries appear to be of vascular origin. Moreover, analysis of the association between MRI abnormalities and clinical findings suggests that there are likely many mechanisms, both direct and indirect, by which brain injury occurs in COVID-19 patients.

KEYWORDS

COVID-19, magnetic resonance imaging, brain, neurocognitive, cerebral microbleeds (CMB), infarct

Introduction

Coronavirus Disease 2019 (COVID-19) (1, 2) characteristically involves multiple organ systems, including the central and peripheral nervous system. SARS-CoV-2 infection has been associated with a range of neurological phenomena, which are still incompletely understood. Severe acute neurological events include ischemic stroke, intracranial hemorrhage, encephalopathy, seizure disorders, extrapyramidal syndromes, neuromuscular pathologies, various immune-mediated neuroinflammatory disorders, and dysautonomias (3). In this context, neurocognitive symptoms and dysfunction of various severities have become increasingly recognized as potential consequences of SARS-CoV-2 infection. While brain dysfunction might be attributed to the effects of critical care illness among hospitalized patients, emerging data indicate that brain effects are also prevalent among less severely ill,

non-hospitalized and even mildly symptomatic patients (4). Although there are numerous observational and subjective survey-reporting studies of neurological symptoms, by contrast, those studies describing imaging abnormalities are fewer in number.

This study conducted a metanalysis to determine the incidence of the common neurological abnormalities using magnetic resonance imaging (MRI) in patients with COVID-19. This study expands on a previous metanalysis of COVID-19 neuroimaging performed early in the pandemic (5) providing a more contemporary and elaborate analysis. We also present the common clinical findings associated with MRI abnormalities.

Methods

Eligibility criteria and evidence search

Using Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), we conducted a systematic review of studies which reported neurological MRI findings in COVID-19 patients (Figure 1). A PubMed, Embase and Google Scholar database search from January 1, 2020, to June 17, 2022, was performed. Additional papers found outside of these searches were added at the authors' discretion. The search parameters can be found in the Supplementary Information. Cross-sectional, case–control, and cohort studies were included in the analyses. Studies that were excluded included: (1) case reports, case series, review papers, and conference abstracts; (2) papers not written in English; (3) protocol papers, letters to the editor, preprint papers, and healthcare provider surveys without data; and (4) papers that did not use MRI as a data metric.

The title and abstract of papers after the initial search were assessed by two independent reviewers, MB and BM, and only studies approved by both reviewers were included. Disputes regarding the inclusion of a paper were decided by a third reviewer, TD.

Data collection and analysis

Study characteristics, including author, study type, origin, sample size and other qualitative findings were manually collected. The incidence of any brain MRI abnormality as well as the incidence of common specific and subspecific brain MRI abnormalities after SARS-CoV-2 infection were collected manually.

Results

The initial search resulted in 491 articles with no duplicates. After assessing the title and abstract, 452 papers were removed. An

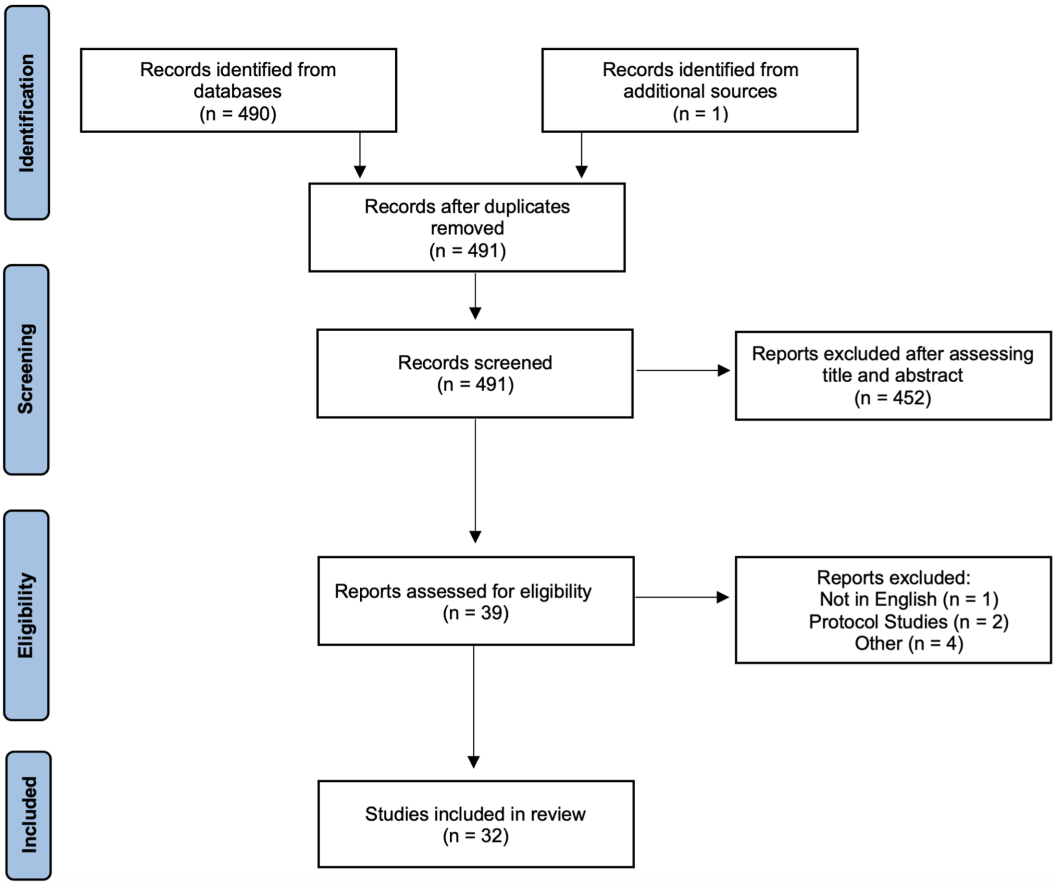


FIGURE 1
PRISMA diagram illustrating the study eligibility criteria.

additional seven papers which did not meet the inclusion criteria were removed after assessing the entire paper. Thirty-two papers were included in the final study. Table 1 summarizes the study characteristics and main findings.

Incidence of brain MRI abnormalities

Figure 2 illustrates the incidence of brain MRI abnormalities after SARS-CoV-2 infection. The incidence of any brain MRI abnormality after SARS-CoV-2 infection was 55% (461/837 patients). The most common brain abnormalities in order of incidence were perfusion abnormalities (53%), susceptibility weighted imaging (SWI) abnormality (44%), white matter lesions (32%), gray matter lesions (23%), infarct/ischemia (22%), cerebral microbleeds (CMB; 21%), leptomeningeal enhancement (LME; 21%), fluid attenuated inversion recovery (FLAIR) abnormality (19%), olfactory bulb abnormalities (15%), hemorrhage (15%), encephalopathy (14%), posterior reversible encephalopathy syndrome (PRES; 4%), cytotoxic lesions of the corpus callosum (CLOCC; 3%) and thrombosis (2%). Subspecific information regarding brain MRI abnormalities are presented in Table 2.

The incidence of acute infarcts (17%) was more common than chronic (11%) and subacute infarcts (6%). Lacunar infarcts were the most common (26%) followed by territorial arterial infarcts (14%) and watershed infarcts (12%). Cortical stroke was not reported in any studies whereas the incidence of subcortical stroke was found to be 11% in one study.

The incidence of lobar CMBs (21%) was slightly higher than diffuse CMBs (18%). The incidence of CMBs in the subcortical and deep WM was 19 and 11%, respectively. The most commonly affected subcortical structures were the corpus callosum (16%), pons/cerebellum (7%), and basal ganglia (5%).

Hypoperfusion abnormalities (48%) were more common than hyperperfusion abnormalities (10%). The incidence of seizure-related perfusion abnormalities was 12%. Perfusion abnormalities secondary to ischemic lesions was 5%.

The incidence of subcortical WM changes was 81%. The incidence of periventricular and juxtacortical WM changes was 44% each. The most common sites for WM changes were the brainstem (29%), precentral gyrus (29%), corpus callosum (27%), cerebellum (19%), middle cerebellar peduncles (17%), and basal ganglia (2%).

Non-confluent FLAIR abnormalities (9%) were more common than confluent ones (5%). The most common locations were the frontal lobe (15%), parietal lobe (11%), occipital lobe (10%), medial temporal lobe (8%), brainstem (7%), temporal lobe (4%), corpus callosum (3%), and middle cerebellar peduncles (2%).

The incidence of cortical, juxtacortical, and subcortical on DWI was 56, 30, and 25%, respectively. A combined incidence of deep and periventricular WM SWI abnormality (30%) was reported in one study. The most common sites for SWI abnormalities were cerebellum (38%), thalami (31%), corpus callosum (28%), brainstem (19%), basal ganglia (2%), and pons (2%).

The incidence of venous thrombosis (4%) was marginally higher than arterial thrombosis (2%).

Figure 3 shows the inter-study heterogeneity for the commonly reported brain MRI abnormalities.

Clinical measures associated with MRI abnormalities

Twelve studies in this review reported a statistical ($p < 0.05$) association between at least one clinical datapoint and an MRI abnormality. The most commonly reported associations were cognitive impairment (6), followed by ICU and/or mechanical ventilation status (5), older age (4 studies), hospitalization or longer length of hospital stay (4), and ARDS (2). The most commonly reported laboratory marker was elevated WBC count (3), higher D-Dimer (2), higher creatinine (2) and decreased hemoglobin (2). Table 3 qualitatively outlines the MRI abnormality and the associated clinical parameter for each of the 12 studies.

Discussion

In this metanalysis, we report the pooled incidence of the commonly reported brain MRI abnormalities in patients with COVID-19. The pooled incidence of any brain MRI abnormality was found to be 55% [Proportion = 0.65; 95% CI = 54–76%; I^2 = 94%]. The five most commonly studied abnormalities were WM lesions [Proportion = 0.39; 95% CI = 11–66%; I^2 = 99%], cerebral microbleeds [Proportion = 0.29; 95% CI = 16–38%; I^2 = 95%], hemorrhage [Proportion = 0.16; 95% CI = 9–22%; I^2 = 74%], infarct [Proportion = 0.18; 95% CI = 11–21%; I^2 = 65%], and encephalopathy [Proportion = 0.12; 95% CI = 3–18%; I^2 = 94%]. Perfusion abnormalities (53%) and SWI abnormalities (47%) were the two brain abnormalities with the highest incidence. The most reported clinical characteristic and laboratory value with a statistically significant association with at least one brain MRI abnormality was cognitive impairment and elevated WBC count, respectively. Together, these results show that brain MRI abnormalities after SARS-CoV-2 infection are common and that clinical associations may provide insight into identifying at-risk patients as well as possible combinatorial and intersectional mechanisms of brain injury in COVID-19.

There is considerable heterogeneity in the results reported in this meta-analysis, a finding which is similar to a smaller meta-analysis performed earlier in the pandemic (5). There are a few reasons for the observed heterogeneity. First, there is substantial interstudy variation in patient populations, study designs, and end-outcomes. Second, the neurological presentation of COVID-19 is itself very heterogenous. Unlike other pathogens, such as Lyme Disease and Herpes Simplex Virus (38), which may reveal distinct patterns of injury on brain MRI, there is no unanimous pattern of brain injury with SARS-CoV-2, likely due to multifactorial and synergistic mechanisms of direct and indirect injury responses. Indirect effects include respiratory distress, sepsis, hypoxia, cardiovascular distress, host-mediated proinflammatory responses, hypercoagulation, amongst many others. Whether the heterogeneity seen in our study is the result of interstudy variation or the result of the inherent diversity of SARS-CoV-2-mediated brain injury remains to be seen.

The incidence of any brain MRI abnormality was found to be 55%. This number is likely greatly inflated given that the majority of studies included in this meta-analysis looked at patients that had severe COVID-19. Indeed, a previous study found the rate of brain MRI abnormalities to be less than 1% (51/5430) when looking at all COVID-19 patients regardless of severity (39), although this is likely

TABLE 1 Study characteristics.

Paper	Author	Study design	Country	Date	Pts (N)	M:F	Follow-up time	Main findings
Neurological complications in critical patients with COVID-19	Abenza-Abildúa (6)	Retrospective	Spain	July 29 2020	30	72:28	Acute (time not given)	COVID-19 was definite cause neurological symptoms in 20% of patients. Symptoms were not associated with imaging findings.
Cerebral Microbleeds and Leukoencephalopathy in Critically Ill Patients With COVID-19	Shashank Agarwal (7)	Retrospective	USA	July 8 2020	115	N/A	LE or CMB = 27 (10.3) days No LE or CMB = 10.6 (12.9) days	30.4% of patients had CMB and LE on neuroimaging. These findings were associated with lower neurological status (GCS).
Retrospective Observational Study of Brain MRI Findings in Patients with Acute SARS-CoV-2 Infection and Neurologic Manifestations	Lydia Chougar (8)	Cross-Sectional	France	July 7 2020	73	66:34	22.3 ± 15.7 days	59% of patients had an abnormal MRI finding. The pattern of WM enhancement and basal ganglia involvement seen in COVID-19 is unlike any other previously characterized condition/pathology.
Unusual Microbleeds in Brain MRI of Covid-19 Patients	Aikaterini Fitsiori (9)	Retrospective*	Switzerland	June 24 2020	9	78:22	Acute (time not given)	MRI revealed an atypical predilection for the corpus callosum. Severe hypoxemia and ventilation status was common among all patients with MRI abnormalities.
Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients	Julie Helms (10)	Prospective	France	July 26 2020	28	N/A	Acute (time not given)	Brain lesions and perfusions abnormalities seen on MRI strengthen the case for a COVID-19 associated encephalopathy and/or encephalitis.
Brain MRI Findings in Patients in the Intensive Care Unit with COVID-19 Infection	Sedat G. Kandemirli (11)	Retrospective	Turkey	May 5 2020	27	78:22	Acute (time not given)	44% of patients who underwent brain MRI had acute findings. The main differential diagnoses for the pattern of injury seen are encephalitis and hypoxia.
Nervous System Involvement in Coronavirus Disease 2019:	Stefanos Klironomos (12)	Retrospective	Sweden	July 30 2020	43	N/A	Median 34 days	Intra axial abnormalities, leukoencephalopathy were common. Pattern of imaging is similar to endotheliopathy and microthrombosis.
Neurologic and neuroimaging findings in patients with COVID-19	Stephane Kremer (13)	Retrospective	France	June 9 2020	64	67:33	Acute (can calculate if needed)	Imaging abnormalities were heterogenous in nature, and associated clinical symptoms were also heterogenous. Three clinic radiological profiles were identified: ischemic stroke, LME, and encephalitis.
Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study	Stephane Kremer (14)	Retrospective	France	June 16 2020	190	81:19	Acute (time not given)	54% of patients experienced COVID-19 related hemorrhagic lesions (macro and micro). These were associated with worse neurological status. 43% showed signal abnormalities in the medical temporal lobe.

(Continued)

TABLE 1 (Continued)

Paper	Author	Study design	Country	Date	Pts (N)	M:F	Follow-up time	Main findings
Increase in Ventricle Size and the Evolution	Shashank Agarwal (15)	Retrospective	USA	February 6 2021	21	86:14	First MRI = 22 [14–30] Second MRI = 49 [39–60]	Increased ventricle size between the two MRIs. Some patients showed worsening of WM changes on second MRI, some showed improved, but the majority remained stable.
Brain MRI in SARS-CoV-2 pneumonia patients with newly developed neurological manifestations suggestive of brain involvement	Batil Alonazi (16)	Retrospective	Saudi Arabia	October 5 2021	46	28:72	5 days	MRI abnormalities were more common in patients who presented with non-focal neurological manifestation or had a lower GCS.
Clinical and Radiological Profiles of COVID-19 Patients with Neurological Symptomatology: A Comparative Study	Maria de Fatima Viana Vasco Aragao (17)	Retrospective	Brazil	April 27 2021	35	57:43	Acute (time not given)	Neuroimaging evaluation of olfactory bulbs showed lesions in 12/12 patients. Given this, anosmia may be considered a central neurological symptom rather than a flu-like symptom.
Collicular Hyperactivation in Patients with COVID-19: A New Finding on Brain MRI and PET/CT	Chammas (18)	Retrospective	France	March 11 2021	72	N/A	Acute (30 days) Follow-up at 3-month	17% of patient had hyperperfusion of the lower colliculi on acute imaging which was less pronounced at follow-up.
Susceptibility-weighted imaging reveals cerebral microvascular injury in severe COVID-19	John Conklin (19)	Retrospective	USA	January 4 2021	16	N/A	Acute (time not given)	Hemorrhagic and ischemic microvascular lesions are common in COVID-19 patients with neurological deficits. These imaging findings were confirmed in one patient at autopsy.
Coronavirus Disease (COVID-19)-Related Disseminated Leukoencephalopathy: A Retrospective Study of Findings on Brain MRI	Colbey W. Freeman (20)	Retrospective	USA	August 31 2020	59	N/A	Acute (time not given)	10.2% of patients had findings consistent with the authors definition of COVID-19-related disseminated leukoencephalopathy.
Yield of Head Imaging in Ambulatory and Hospitalized Patients With SARS-CoV-2: A Multi-Center Study of 8,675 Patients	Melanie R. F. Greenway (21)	Retrospective	USA	December 16 2020	23	58:42	Acute (0–30 days)	Rate of brain imaging and cerebrovascular events was low. No association between rate of cerebrovascular events and disease severity was found.
Brain MRI and neuropsychological findings at long-term follow-up after COVID-19 hospitalization: an observational cohort study	Lovisa Hellgren (22)	Ambidirectional	Sweden	October 12 2021	35	80:20	7 months post-admission	25/35 patients had an abnormal MRI at the 7-month follow up. Increased age and a higher premorbid function category were associated with an abnormal brain MRI at follow up.

(Continued)

TABLE 1 (Continued)

Paper	Author	Study design	Country	Date	Pts (N)	M:F	Follow-up time	Main findings
Association of Clinical, Biological, and Brain Magnetic Resonance Imaging Findings With Electroencephalographic Findings for Patients With COVID-19	Virginie Lambrecq (23)	Retrospective	France	March 15 2021	57	N/A	Acute (time not given)	72% of patient presented with an abnormal brain MRI. Patient with COVID-19 encephalopathy were more likely to present with WM-enhancing lesions on MRI.
Abnormal MRI findings of the orbital or visual pathways in patients with severe COVID-19: Observations from the French multicenter COVID-19 cohort	Augustin Lecler (24)	Retrospective	France	October 18 2021	129	67:33	Acute (time not given)	13% of patients with severe COVID-19 had abnormal findings of the orbit or visual pathway on brain MRI. Visual impairments may go unnoticed in patients under sedation due to COVID-19.
Cerebral vasculitis of medium-sized vessels as a possible mechanism of brain damage in COVID-19 patients	Francois Lersy (25)	Retrospective	France	May 3 2021	69	67:33	Acute (can calculate time)	16% of COVID-19 patients had a brain MRI consistent with cerebral vasculitis. Cerebral vasculitis was significantly less common in patients without SARS-CoV-2 infection.
Critical illness-associated cerebral microbleeds for patients with severe COVID-19: etiologic hypotheses	Francois Lersy (26)	Retrospective	France	November 8 2020	80	84:16	26 (20–31) days with WM microhemorrhages. 12 (6–18) days without WM microhemorrhages	24% of patients presented with COVID-19 associated cerebral microbleeds (CIAM). Patients with CIAM presented with worse neurological status than those without CIAM.
Central Nervous System Injury in Patients With	Edith Fabiola Mendez Elizondo (27)	Retrospective	Mexico	September 17 2021	47	N/A	Acute (time not given)	13% of patients with COVID-19 were found to have microbleeds. Presentation of patients was heterogenous with various brain pathologies seen on MRI.
Distinct pattern of microsusceptibility changes on brain magnetic resonance imaging (MRI) in critically ill patients	Majda M. Thurnher (28)	Retrospective	Austria	March 2 2021	48	50:50	Acute (time not given)	A distinct SWI susceptibility (microbleed) pattern is seen in patients who undergo ECMO. Pattern on injury was diffuse without relation to any specific vascular territory.
Long COVID-19: Objectifying most self-reported neurological symptoms	Julia Bungenberg (29)	Cross-sectional	Germany	December 15 2021	42	N/A	29.3 weeks (3.3–57.9)	MRI findings were within normal clinical references despite deficiencies in cognitive performance. This may indicate that even MRI is not sensitive enough to detect subtle brain changes in COVID-19.
Cognitive, EEG, and MRI features of COVID-19 survivors: a 10-month study	Giordano Cecchetti (30)	Retrospective	Italy	February 22 2022	36	69:31	2 months	Patients with COVID-19 had greater WM hyperintensities in the right frontal and eight parietooccipital lobe compared to healthy controls. This finding corelated with worse memory function.

(Continued)

TABLE 1 (Continued)

Paper	Author	Study design	Country	Date	Pts (N)	M:F	Follow-up time	Main findings
Evolution of Neuroimaging Findings in Severe COVID-19 Patients with Initial Neurological Impairment: An Observational Study	François Lersy (31)	Retrospective	France	April 26 2022	31	74:26	Acute 3 months 6 months	Brain MRI abnormalities typically regress (normalize) or remain stable over time. New complications months after COVID-19 are rare and their relation to COVID-19 is difficult to discern.
Cerebral Microbleeds Assessment and Quantification in COVID-19 Patients With Neurological Manifestations	Angela Napolitano (32)	Retrospective	Italy	April 7 2022	63	62:38	61 days	22% of patients had evidence on CMBs on MRI. The pattern of CMB was callosal and juxtacortical which has been previously seen in patients requiring mechanical ventilation;
Early postmortem brain MRI findings in COVID-19 non-survivors	Tim Coolen (33)	Prospective	Belgium	October 6 2020	19	74:26	13.67 (2.07–23.75) hours postmortem	Hemorrhagic, olfactory, and PRES-related brain lesion were common findings in deceased COVID-19 patients. No brainstem abnormalities were observed, arguing against brainstem contribution to respiratory distress.
Disorders of Consciousness Associated With COVID-19	David Fischer (34)	Prospective	USA	January 18 2022	12	42:58	Acute (exact time not given)	Microhemorrhages and leukoencephalopathy 55 and 45% of patients, respectively. Patients with severe COVID-19 are likely to have less brain interconnectivity than healthy controls.
Neurologic manifestations associated with COVID-19: a multicentre registry	Elodie Meppiel (35)	Retrospective	France	Nov 13 2020	222	61:39	24 days	Infarcts, encephalitis, and encephalopathy were the most common imaging abnormalities reported. Overall, neurological manifestations of COVID-19 are vast and heterogenous.
Neuroimaging Findings of Hospitalized Covid-19 Patients: A Canadian Retrospective Observational Study	Vibeeshan Jegatheeswaran (36)	Retrospective	Canada	April 21 2021	422	54:46	94 days	The main MRI findings were macrohemorrhages, SWI abnormalities, and acute ischemia. ICU patients were more likely to have positive imaging findings.
Brain Imaging of Patients with COVID-19: Findings at an Academic Institution during the Height of the Outbreak in New York City	Lin (37)	Retrospective	USA	July 17 2020	278	59:41	Acute (time not given)	Infarcts (acute and subacute) were the most common findings on brain MRI. 12% of patients had cranial nerve abnormalities and 6% had critical illness-associated microbleeds.

(Continued)

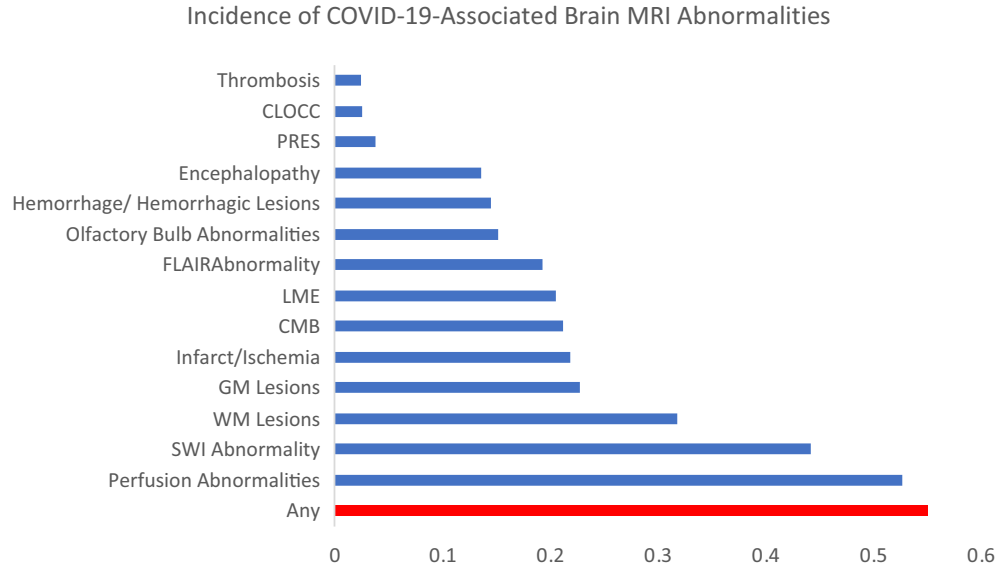


FIGURE 2
Incidence of the most common COVID-19-associated brain MRI abnormalities. CLOCC, cytotoxic lesions of the corpus callosum; PRES, posterior reversible encephalopathy syndrome; FLAIR, fluid-attenuated inversion recovery; LME, leptomeningeal enhancement; CMB, cerebral microbleeds; GM, gray matter; WM, white matter; SWI, susceptibility weighted imaging.

an underestimation given that not all patients in the aforementioned study were referred for MRI analysis. Regardless, the findings of our meta-analysis are likely more useful to the clinician managing a critically ill COVID-19 patient in the ICU than the clinician managing a milder form of the disease.

Clinicians should be aware that the presentation of brain injury in COVID-19 can be diverse, although the majority of brain abnormalities in COVID-19 appear to be cerebrovascular events. The two injuries with the highest prevalence are perfusion abnormalities and SWI abnormalities, the latter of which usually indicates a cerebral microbleed and/or calcification (40). Infarcts, hemorrhages, cerebral microbleeds, and thrombosis are also of cerebrovascular origin. On the other hand, olfactory bulb lesions are likely exclusively associated with nerve damage (17). The source of the rest of the abnormalities can vary.

The question of how much COVID-19 contributes to abnormal brain MRI findings is unclear, especially since the patients indicated for brain MRI are often the sickest patients with several comorbidities that may present as confounders. However, longitudinal studies with multiple time points can provide some insight into this question. Lersy et al. show that 79% of patients had partial or complete regression of abnormal brain MRI findings at 189 days follow-up (31). Furthermore, Chammas et al. showed a marked decreased in collicular hyperintensity at 3-month follow-up (18). It is more likely that this type of dynamic neuro-evolution would be due an acute insult rather than pre-existing chronic conditions. Likewise, Agarwal et al. demonstrated an increase in ventricle size at a 22-day follow-up MRI that is likely due to an acute infectious process rather than chronic processes like alcoholism or neurodegenerative diseases which progress over a longer period of time (15). COVID-19 does contribute to acute brain injury, however, the extent to which the findings reported in brain MRI papers is due to COVID-19 vs. comorbidities is difficult to assess. Future studies should utilize pre- and post-COVID MRI scans as well as matched controls to better determine the extent to which COVID-19 causes brain injury. The UK Biobank study of 785 participants is a good example of such a study (41).

Analysis of the association between MRI abnormalities and clinical findings provides an insight into the mechanism of brain injury in COVID-19. Given that ACE2 receptors and associated SARS-CoV-2 virions are expressed on brain endothelial cells, direct injury mediated by SARS-CoV-2 is theoretically possible (42). However, a direct mechanism of injury is highly unlikely given that only 1.6% (3/184) of patients across 9 studies in our meta-analysis were found to have to have SARS-CoV-2 RNA in their CSF via RT-PCR. Indeed, indirect mechanisms of brain injury seem more plausible, one of which is mechanical ventilation – a known contributor to various neurological injuries including intracranial hemorrhages, ischemic stroke, and hypoxic ischemic encephalopathy (43). This mechanism is supported by multiple papers in our analysis which show an association between mechanical ventilation and the presence of CMBs, WM microhemorrhages, and encephalopathy on MRI (7, 26, 32). It should be noted, however, that patients who do not undergo mechanical ventilation can still present with acute MRI abnormalities suggesting that while mechanical ventilation may contribute to the development neurological abnormalities, it is not the only mechanism at play. The cytokine storm hypothesis is another hypothesis supported by multiple papers which show an association between abnormal MRI findings and elevated inflammatory markers (14, 18, 32). Moreover, a non-specific inflammatory response is more consistent with the heterogenous presentation that is seen on brain MRI. Thrombosis is another potential mechanism for brain injury supported by the association of abnormal MRI findings with elevated D-Dimer, though this association is relatively non-specific (7, 26). Lastly, cerebral

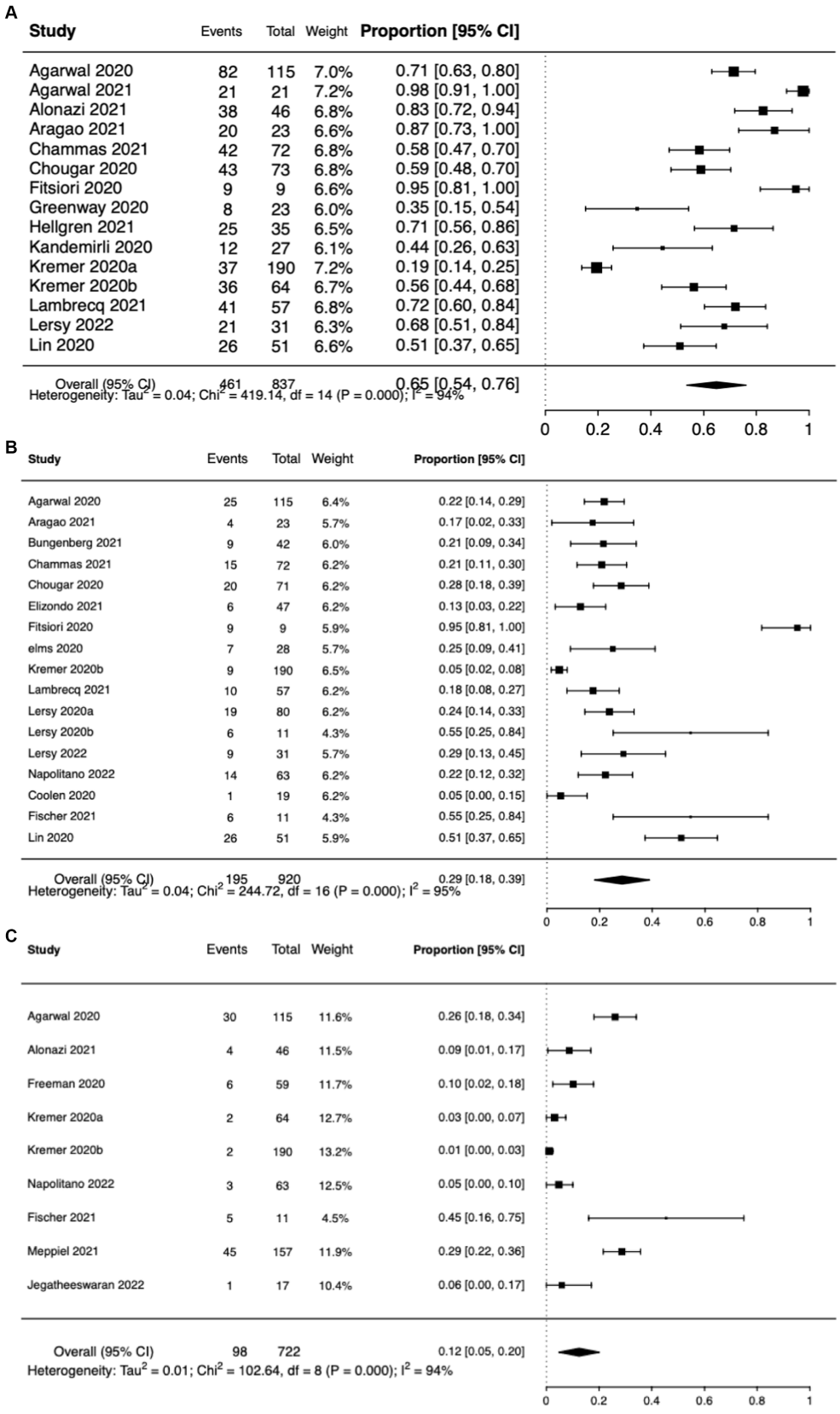


FIGURE 3 (Continued)

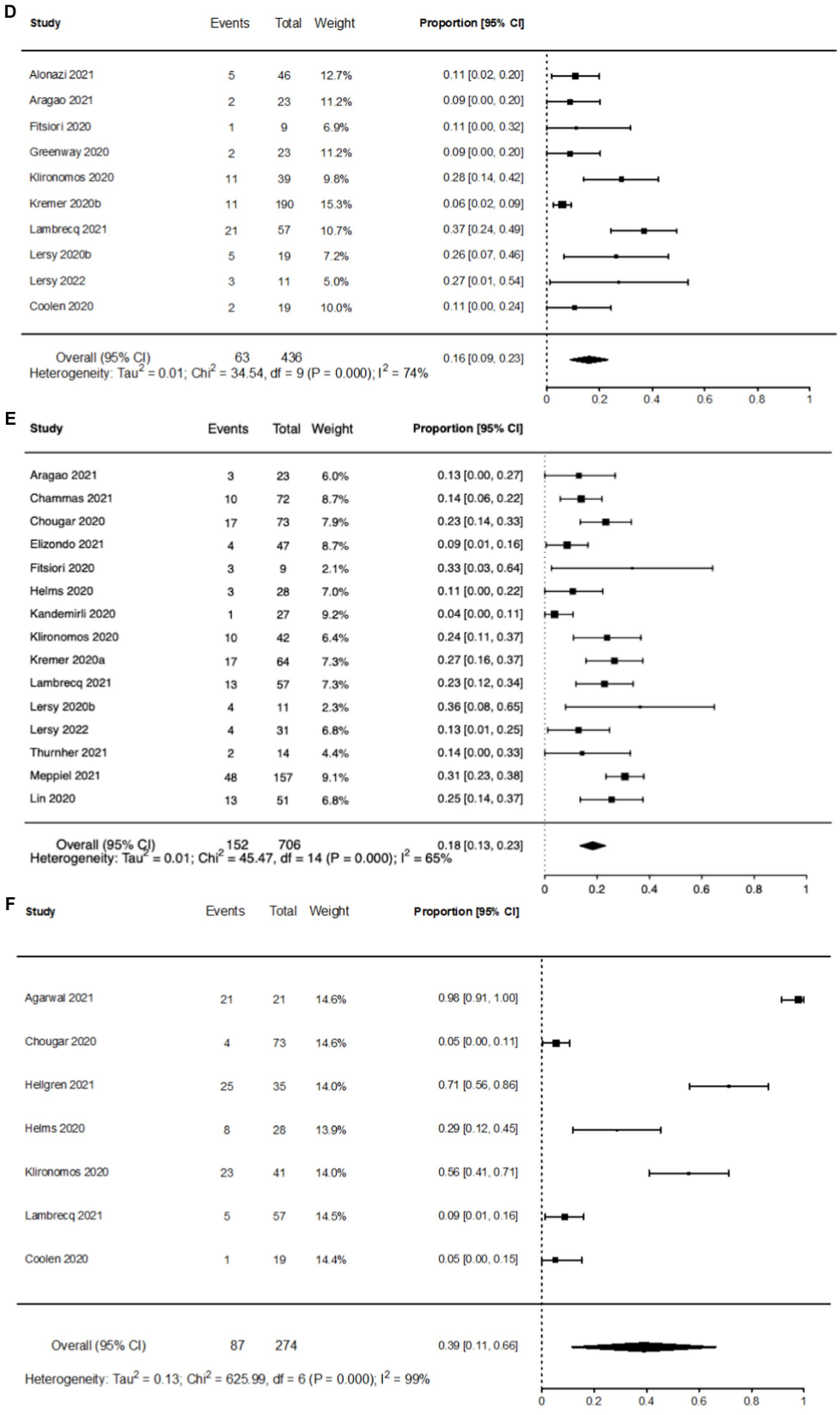


FIGURE 3 (Continued)

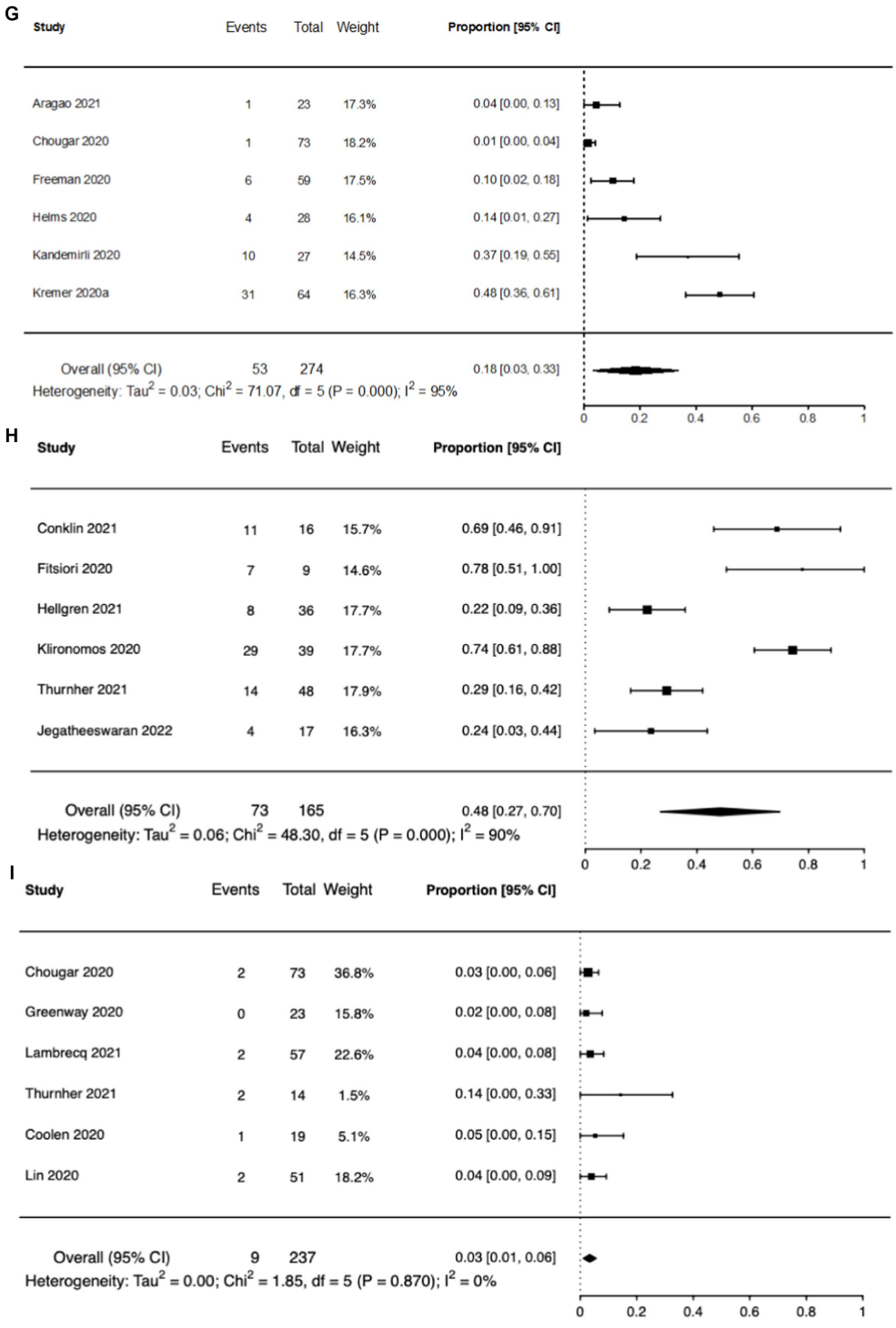


FIGURE 3 (Continued)

vasculitis is another possible mechanism (25). Overall, the mechanism of brain injury in COVID-19 is likely due to multiple, indirect mechanisms, including microvascular infarction and post-infarction hemorrhage.

In addition to possible mechanism of injury, associations between clinical findings and abnormal MRI may provide a predictive model for identifying patients who are likely to present with abnormal MRI findings. Napolitano et al. for example, have determined a CSF inflammatory profile in patients with cerebral microbleeds, though the invasiveness of a lumbar puncture is a large drawback to CSF profiling (32). Future studies should evaluate the possibility of creating such predictive models but using easier to obtain data points.

It is unlikely that specific brain injuries in COVID-19 contribute to acute neurocognitive dysfunction. Many papers in our analysis

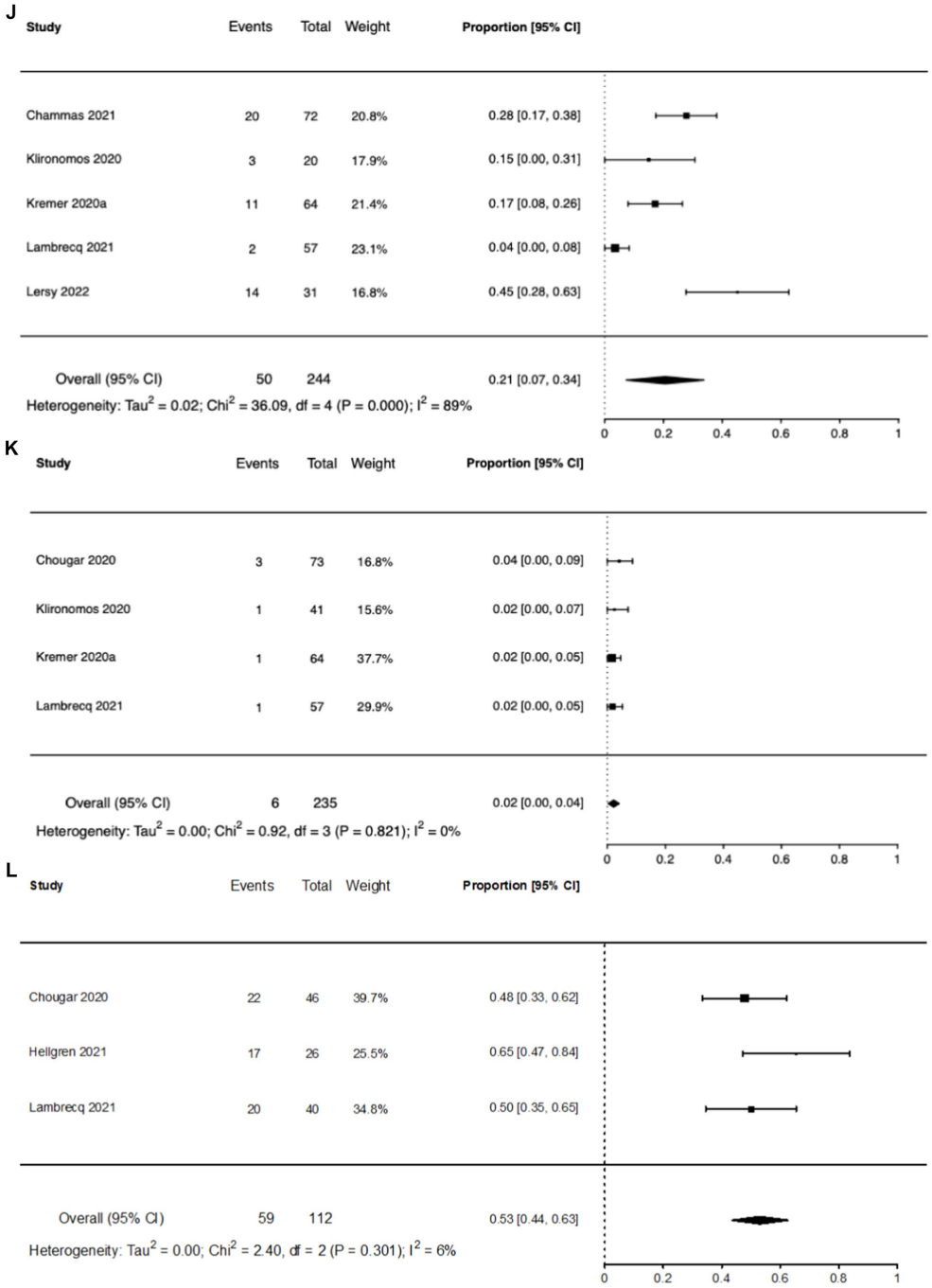


FIGURE 3 (Continued)

show an association between lower cognitive functioning and various acute brain MRI abnormalities but no specific imaging pattern has yet emerged. Indeed, these associations are likely the result of confounding bias due to critical care illness. Other modalities, such as EEG and neurocognitive testing, can be used to corroborate MRI findings. A similar conclusion is drawn in terms of long-term cognitive dysfunction, AKA 'brain fog' in COVID-19 patients (44, 45). A 7-month follow up study showed no difference in cognitive functioning between patients with and without MRI abnormalities suggesting that 'brain fog' cannot routinely be determine by MRI (22). Additional long-term MRI studies are needed to determine (1) whether 'brain fog' is due to neurological injury and (2) whether that injury can be identified on MRI analysis.

There are several limitations with this meta-analysis study. First, we chose to analyze only MRI imaging findings to assess the neurological complications of COVID-19 because MRI can detect a broad range of anatomical abnormalities with high sensitivity. CT and other brain imaging modalities should also be explored. Most of the studies included in this analysis did not have propensity-matched control groups and/or pre-COVID-19 brain MRI scans for

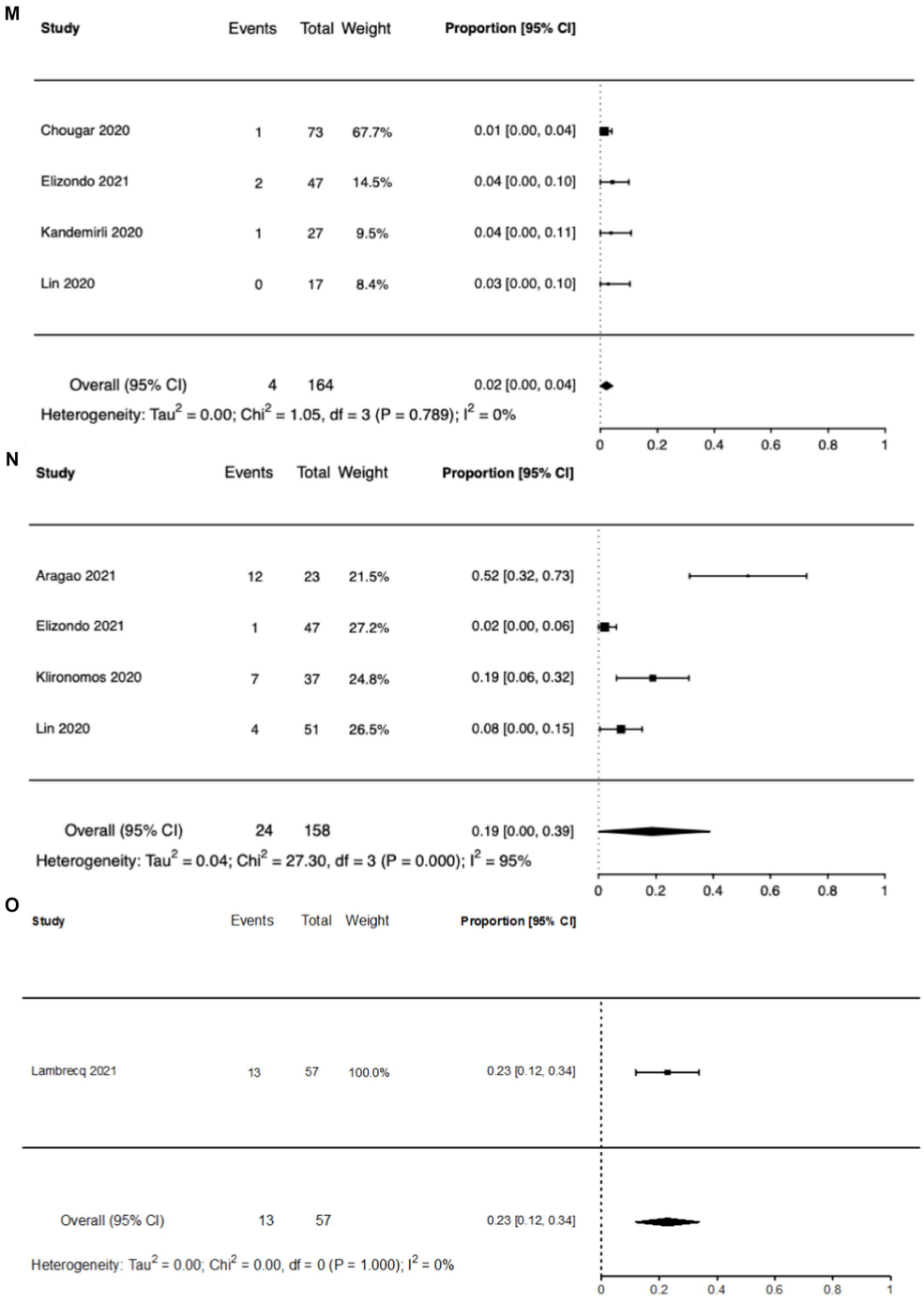


FIGURE 3
Forest plots of reported brain MRI abnormalities. **(A)** Any brain MRI abnormality. **(B)** Cerebral microbleeds. **(C)** Encephalopathy. **(D)** Hemorrhage. **(E)** Infarct. **(F)** White matter lesions. **(G)** FLAIR abnormality. **(H)** SWI Abnormality. **(I)** Posterior reversible encephalopathy syndrome. **(J)** Leptomeningeal enhancement. **(K)** Cytotoxic lesion of the corpus callosum. **(L)** Perfusion abnormalities. **(M)** Thrombosis. **(N)** Olfactory bulb abnormalities. **(O)** Gray matter lesions.

comparison. Therefore, some findings may be attributable to pre-existing conditions rather than caused or exacerbated by COVID-19. There is publication bias as the patients with more severe COVID-19 disease are more likely to be reported in the literature. Finally, unintentional reporting bias could be present given that virtually all papers in this meta-analysis were retrospective studies.

Conclusion

Improved understanding of the imaging findings associated with neurological signs and symptoms amongst COVID-19 patients and survivors will help to identify common neurological injuries, inform the care of at-risk patients, and understand the mechanism of neurological injury and the progression of brain effects of COVID-19.

TABLE 2 Common neurological MRI abnormalities in COVID-19 patients.

MRI abnormality		No. of Pts (%)
Infarct		152/706 (22)
	Acute	65/378 (17)
	Subacute	5/82 (6)
	Chronic	21/188 (11)
	Lacunar	14/55 (26)
	Territorial	20/146 (14)
	Watershed	9/75 (12)
	Subcortical	1/9 (11)
CMB		195/920 (21)
	Diffuse	37/209 (18)
	Lobar	35/171 (21)
	Deep WM	25/222 (11)
	Subcortical WM	33/171 (19)
	Corpus callosum	48/302 (16)
	Pons/cerebellum	15/212 (7)
	Basal ganglia	4/83 (5)
Perfusion abnormalities		59/112 (53)
	Seizure Related	9/46 (12)
	2° to Ischemic Lesions	4/46 (5)
	Hypoperfusion	19/40 (48)
	Hyperperfusion	4/40 (10)
WM Lesions		87/274 (32)
	Periventricular	46/104 (44)
	Juxtacortical	27/62 (44)
	Subcortical	17/21 (81)
	Corpus callosum	11/41 (27)
	Middle cerebellar peduncles	7/41 (17)
	Cerebellum	4/21 (19)
	Brainstem	6/21 (29)
	Basal ganglia	1/42 (2)
	Precentral gyrus	6/21 (29)
FLAIR abnormality		53/274 (19)
	Confluent	12/262 (5)
	Non-confluent	23/262 (9)
	Frontal lobe	4/27 (15)
	Parietal lobe	3/27 (11)
	Occipital lobe	5/50 (10)
	Temporal lobe	2/50 (4)
	Medial temporal lobe	20/262 (8)
	Corpus callosum	7/249 (3)
	Middle cerebellar peduncle	4/268 (2)
	Brainstem	4/59 (7)
SWI abnormality		73/165 (44)
	Cortical	9/16 (56)
	Subcortical	18/73 (25)
	Juxtacortical	17/56 (30)
	Deep and Periventricular WM	10/33 (30)
	Cerebellum	6/16 (38)
	Thalami	5/16 (31)
	Basal ganglia	1/64 (2)
	Brainstem	3/16 (19)
	Corpus callosum	34/120 (28)
	Pons	1/48 (2)
Thrombosis		4/164 (2)
	Venous	3/77 (4)
	Arterial	1/47 (2)
Hemorrhage		63/436 (15)
GM Lesions		13/57 (23)
Leptomeningeal enhancement		50/244 (21)
Encephalopathy		98/722 (14)
CLOCC		6/235 (3)
PRES		9/237 (4)
Olfactory bulb abnormalities		24/158 (15)

(Continued)

CMB, cerebral microbleeds; WM, white matter; FLAIR, fluid-attenuated inversion recovery; SWI, susceptibility weighted imaging; GM, gray matter; CLOCC, cytotoxic lesions of the corpus callosum.

In this meta-analysis of the neurological MRI findings in COVID-19 patients, we report the incidence of any MRI abnormality to be 55%. The dynamic nature of these abnormalities suggests that the observed brain injury is, at least in part, the result of a SARS-CoV-2 related (para)infectious process rather than chronic comorbidities. Although the presentation of COVID-19 brain injury on MRI is diverse, most injuries appear to be of vascular origin. Moreover, analysis of the association between MRI abnormalities and clinical findings suggests that there are likely many mechanisms by which brain injury occurs in COVID-19. The use of these clinical associations to form predictive models for identifying patients likely to present with MRI abnormalities should be explored by future studies. These studies should also investigate the neurological and neurocognitive manifestations associated with brain MRI abnormalities. Brain MRI studies with longer follow-up intervals are needed to provide detailed assessment of the neurological sequelae of COVID-19. Brain MRI studies analyzing patients with mild COVID-19 are also necessary.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

TABLE 3 Clinical findings associated with MRI abnormalities.

Author	MRI abnormality	Association(s)	Non-association(s)
Agarwal (2020) (7)	CMB and/or encephalopathy	Age (higher), GCS at time of MRI (lower), Ventilation duration (higher), Moderate, severe hypoxemia, Length of hospital stay (higher), Time from admission to MRI (higher), mRS at discharge (higher), Peak INR (higher), Peak D-dimer (higher), Platelet count nadir (lower)	Sex, BMI, Hyperlipidemia, Diabetes Mellitus, Hypertension, Admission platelets Admission D-dimer, Admission Fibrinogen Admission INR
Chougar (2020) (8)	≥5 microhemorrhages, Microhemorrhage with corpus callosum involvement, Perfusion abnormalities, Multifocal WM lesions, Basal ganglia lesion	ICU admission	–
Kremer (2020) (14)	Hemorrhagic lesions	ARDS, ICU admission, Time from symptom onset to brain MRI (higher), Abnormal wakefulness in ICU, WBC count (higher), Hemoglobin (lower), Blood urea (higher)	Sex, Age, Oxygen therapy, Death, Neurological manifestations except abnormal wakefulness, Lymphocyte count, Platelet count, CRP, Ferritin, ALT, AST, Creatinine, PTT, Fibrinogen, D-dimer, CSF analysis
Kremer (2020) (13)	Ischemic stroke	Age (older), Corticospinal tract involvement	Sex, Headache, Seizure, Anosmia, Ageusia, Disorder of consciousness, Confusion, Oxygen therapy, Death
	Encephalitis	Age (younger), ARDS	
	LME	Agitation	
Chammas (2021) (18)	Hyperperfusion of the colliculi	Admission WBC count (higher), Seizures, LME	Severity of disease
Hellgren (2021) (22)	Any abnormal brain MRI	Age (higher), Premorbid function category (higher), Visuospatial Index (lower)	Sex, Days in hospital, ICU care, Mechanical ventilation, CRP, D-dimer, Neurocognition, Fatigue, Depression, Anxiety
Lersy (2020) (26)	WM microhemorrhages	ICU duration (higher), Hospital duration (higher), Time between intubation and MRI (higher), Disturbance of consciousness, Confusion, Agitation, Urea (higher), D-Dimer (higher), Creatinine (higher), Dialysis	Sex, Age, Cardiovascular Risk Factors, Seizures, Corticospinal tract involvement, Pathological wakefulness when sedatives were stopped
Lersy (2020) (25)	Imaging consistent with cerebral vasculitis	Age (higher)	Sex, Diabetes, Hypertension, Hyperlipidemia, Smoking, Obesity
Bungenberg (2021) (29)	CMB	Hospitalization, Worse visuospatial processing	Age
Cecchetti (2022) (30)	Higher WM volume in left frontal region	Cardiovascular risk factors	–
	Higher WM volume in left parieto-occipital region	Poor memory and recall performance	–
Napolitano (2022) (32)	CMB	Hospitalization, Time to MRI (higher), Invasive mechanical ventilation, Leukoencephalopathy, Inflammatory CSF, WBC (higher), Lymphocytes (higher), Hemoglobin (lower), CRP (lower), Procalcitonin (lower), PT (lower), Fibrinogen (lower)	Sex, Age, Dyslipidemia, Heart disease, Diabetes, Hypertension, COPD, Confusion, Visual Impairment, Stroke, Seizure, Anosmia, Neuropathy, Platelet count, LDH, aPTT, D-dimer

*MRI and/or CT.

Author contributions

MB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. BM: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. WH: Data curation, Visualization, Writing – original draft. MM: Writing – review & editing. TD: Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1258352/full#supplementary-material

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. (2020) 382:727–33. doi: 10.1056/NEJMoa2001017

2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5

3. Anand H, Ende V, Singh G, Qureshi I, Duong TQ, Mehler MF. Nervous system-systemic crosstalk in SARS-CoV-2/COVID-19: a unique Dyshomeostasis syndrome. *Front Neurosci*. (2021) 15:727060. doi: 10.3389/fnins.2021.727060

4. Liguori C, Pierantozzi M, Spanetta M, Sarmati L, Cesta N, Iannetta M, et al. Subjective neurological symptoms frequently occur in patients with SARS-CoV2 infection. *Brain Behav Immun*. (2020) 88:11–6. doi: 10.1016/j.bbi.2020.05.037

5. Choi Y, Lee MK. Neuroimaging findings of brain MRI and CT in patients with COVID-19: a systematic review and meta-analysis. *Eur J Radiol*. (2020) 133:109393. doi: 10.1016/j.ejrad.2020.109393

6. Abenza-Abildúaa MJ, Ramírez-Prietob MT, Moreno-Zabaletab R, Arenas-Vallsb N, Salvador-Mayab MA, Algarra-Lucasa C, et al. Neurological complications in critical patients with COVID-19. *Neurologia*. (2020) 35:621–7. doi: 10.1016/j.nrl.2020.07.014

7. Agarwal S, Jain R, Dogra S, Krieger P, Lewis A, Nguyen V, et al. Cerebral microbleeds and leukoencephalopathy in critically ill patients with COVID-19. *Stroke*. (2020) 51:2649–55. doi: 10.1161/STROKEAHA.120.030940

8. Chougar L, Shor N, Weiss N, Galanaud D, Leclercq D, Mathon B, et al. Retrospective observational study of brain MRI findings in patients with acute SARS-CoV-2 infection and neurologic manifestations. *Radiology*. (2020) 297:E313–23. doi: 10.1148/radiol.2020202422

9. Fitsiori A, Pugin D, Thieffry C, Lalive P, Vargas MI. COVID-19 is associated with an unusual pattern of brain microbleeds in critically ill patients. *J Neuroimaging*. (2020) 30:593–7. doi: 10.1111/jon.12755

10. Helms J, Kremer S, Merdji H, Schenck M, Severac F, Clere-Jehl R, et al. Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients. *Crit Care*. (2020) 24:491. doi: 10.1186/s13054-020-03200-1

11. Kandemirli SG, Dogan L, Sarikaya ZT, Kara S, Akinci C, Kaya D, et al. Brain MRI findings in patients in the intensive care unit with COVID-19 infection. *Radiology*. (2020) 297:E232–5. doi: 10.1148/radiol.2020201697

12. Klironomos S, Tzortzakakis A, Kits A, Ohberg C, Kollia E, Ahoromazdae A, et al. Nervous system involvement in coronavirus disease 2019: results from a retrospective consecutive neuroimaging cohort. *Radiology*. (2020) 297:E324–34. doi: 10.1148/radiol.2020202791

13. Kremer S, Lersy F, Anheim M, Merdji H, Schenck M, Oesterle H, et al. Neurologic and neuroimaging findings in patients with COVID-19: a retrospective multicenter study. *Neurology*. (2020) 95:e1868–82. doi: 10.1212/WNL.0000000000010112

14. Kremer S, Lersy F, Sèze J, Ferré J-C, Maamar A, Carsin-Nicol B, et al. Brain MRI findings in severe COVID-19: a retrospective observational study. *Radiology*. (2020) 297:E242–51. doi: 10.1148/radiol.2020202222

15. Agarwal S, Melmed K, Dogra S, Jain R, Conway J, Galetta S, et al. Increase in ventricle size and the evolution of white matter changes on serial imaging in critically ill patients with COVID-19. *Neurocrit Care*. (2021) 35:491–500. doi: 10.1007/s12028-021-01207-2

16. Alonazi B, Farghaly AM, Mostafa MA, Al-Watban JA, Zindani SA, Altaimi F, et al. Brain MRI in SARS-CoV-2 pneumonia patients with newly developed neurological manifestations suggestive of brain involvement. *Sci Rep*. (2021) 11:20476. doi: 10.1038/s41598-021-00064-5

17. Aragao M, Leal MC, Andrade PHP, Cartaxo Filho OQ, Aragao LV, Fonseca TM, et al. Clinical and radiological profiles of COVID-19 patients with neurological symptomatology: a comparative study. *Viruses*. (2021) 13. doi: 10.3390/v13050845

18. Chammas A, Bund C, Lersy F, Brisset JC, Ardellier FD, Kremer S, et al. Collicular Hyperactivation in patients with COVID-19: a new finding on brain MRI and PET/CT. *AJNR Am J Neuroradiol*. (2021) 42:1410–4. doi: 10.3174/ajnr.A7158

19. Conklin J, Frosch MP, Mukerji SS, Rapalino O, Maher MD, Schaefer PW, et al. Susceptibility-weighted imaging reveals cerebral microvascular injury in severe COVID-19. *J Neurol Sci*. (2021) 421:117308. doi: 10.1016/j.jns.2021.117308

20. Freeman CW, Masur J, Hassankhani A, Wolf RL, Levine JM, Mohan S. Coronavirus disease (COVID-19)-related disseminated leukoencephalopathy: a retrospective study of findings on brain MRI. *AJR Am J Roentgenol*. (2021) 216:1046–7. doi: 10.2214/AJR.20.24364

21. Greenway MRF, Erben Y, Huang JF, Siegel JL, Lamb CJ, Badi MK, et al. Yield of head imaging in ambulatory and hospitalized patients with SARS-CoV-2: a multi-center study of 8675 patients. *Neurohospitalist*. (2021) 11:221–8. doi: 10.1177/1941874420980622

22. Hellgren L, Birberg Thornberg U, Samuelsson K, Levi R, Divanoglou A, Blystad I. Brain MRI and neuropsychological findings at long-term follow-up after COVID-19 hospitalisation: an observational cohort study. *BMJ Open*. (2021) 11:e055164. doi: 10.1136/bmjopen-2021-055164

23. Lambrecq V, Hanin A, Munoz-Musat E, Chougar L, Gassama S, Delorme C, et al. Association of Clinical, biological, and brain magnetic resonance imaging findings with electroencephalographic findings for patients with COVID-19. *JAMA Netw Open*. (2021) 4:e211489. doi: 10.1001/jamanetworkopen.2021.1489

24. Lecler A, Cotton F, Lersy F, Kremer S, Heran F. Group SFsCs. Abnormal MRI findings of the orbital or visual pathways in patients with severe COVID-19: observations from the French multicenter COVID-19 cohort. *J Neuroradiol*. (2021) 48:331–6. doi: 10.1016/j.neurad.2021.07.004

25. Lersy F, Anheim M, Willaume T, Chammas A, Brisset JC, Cotton F, et al. Cerebral vasculitis of medium-sized vessels as a possible mechanism of brain damage in COVID-19 patients. *J Neuroradiol*. (2021) 48:141–6. doi: 10.1016/j.neurad.2020.11.004

26. Lersy F, Willaume T, Brisset JC, Collange O, Helms J, Schneider F, et al. Critical illness-associated cerebral microbleeds for patients with severe COVID-19: etiologic hypotheses. *J Neurol*. (2021) 268:2676–84. doi: 10.1007/s00415-020-10313-8

27. Mendez Elizondo EF, Valdez Ramirez JA, Barraza Aguirre G, Dautt Medina PM, Berlanga EJ. Central nervous system injury in patients with severe acute respiratory syndrome coronavirus 2: MRI findings. *Cureus*. (2021) 13:e18052. doi: 10.7759/cureus.18052

28. Thurnher MM, Boban J, Roggla M, Staudinger T. Distinct pattern of microsusceptibility changes on brain magnetic resonance imaging (MRI) in critically ill patients on mechanical ventilation/oxygenation. *Neuroradiology*. (2021) 63:1651–8. doi: 10.1007/s00234-021-02663-5

29. Bungenberg J, Humkamp K, Hohenfeld C, Rust MI, Ermis U, Dreher M, et al. Long COVID-19: objectifying most self-reported neurological symptoms. *Ann Clin Transl Neurol*. (2022) 9:141–54. doi: 10.1002/acn3.51496

30. Cecchetti G, Agosta F, Canu E, Basaia S, Barbieri A, Cardamone R, et al. Cognitive, EEG, and MRI features of COVID-19 survivors: a 10-month study. *J Neurol*. (2022) 269:3400–12. doi: 10.1007/s00415-022-11047-5

31. Lersy F, Bund C, Anheim M, Mondino M, Noblet V, Lazzara S, et al. Evolution of neuroimaging findings in severe COVID-19 patients with initial neurological impairment: An observational study. *Viruses*. (2022) 14. doi: 10.3390/v14050949

32. Napolitano A, Arrigoni A, Caroli A, Cava M, Remuzzi A, Longhi LG, et al. Cerebral microbleeds assessment and quantification in COVID-19 patients with neurological manifestations. *Front Neurol*. (2022) 13:884449. doi: 10.3389/fneur.2022.884449

33. Coolen T, Lolli V, Sadeghi N, Rovai A, Trotta N, Taccone FS, et al. Early postmortem brain MRI findings in COVID-19 non-survivors. *Neurology*. (2020) 95:e2016–27. doi: 10.1212/WNL.0000000000010116

34. Fischer D, Snider SB, Barra ME, Sanders WR, Rapalino O, Schaefer P, et al. Disorders of consciousness associated with COVID-19: a prospective multimodal study of recovery and brain connectivity. *Neurology*. (2022) 98:e315–25. doi: 10.1212/WNL.0000000000013067

35. Meppiel E, Peiffer-Smadja N, Maury A, Bekri I, Delorme C, Desestret V, et al. Neurologic manifestations associated with COVID-19: a multicentre registry. *Clin Microbiol Infect*. (2021) 27:458–66. doi: 10.1016/j.cmi.2020.11.005

36. Jegatheeswaran V, Chan MWK, Chakrabarti S, Fawcett A, Chen YA. Neuroimaging findings of hospitalized Covid-19 patients: a Canadian retrospective observational study. *Can Assoc Radiol J*. (2022) 73:179–86. doi: 10.1177/08465371211002815

37. Lin E, Lantos JE, Strauss SB, Phillips CD, Campion TR Jr, Navi BB, et al. Brain imaging of patients with COVID-19: findings at an academic institution during the height of the outbreak in new York City. *AJNR Am J Neuroradiol*. (2020) 41:2001–8. doi: 10.3174/ajnr.A6793

38. Kastrup OWI, Maschke M. Neuroimaging of infections. *NeuroRx*. (2005) 2:324–32. doi: 10.1602/neurorx.2.2.324

39. Usta NC, Bulut E. Evaluation of intracranial vascular and non-vascular pathologies in patients hospitalized due to COVID-19 infection. *Acta Neurol Taiwanica*. (2022) 31:91–100.

40. Halefoglu AM, Yousem DM. Susceptibility weighted imaging: clinical applications and future directions. *World J Radiol*. (2018) 10:30–45. doi: 10.4329/wjr.v10.i4.30

41. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, et al. SARS-CoV-2 is associated with changes in brain structure in UK biobank. *Nature*. (2022) 604:697–707. doi: 10.1038/s41586-022-04569-5

42. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. (2004) 203:631–7. doi: 10.1002/path.1570

43. Illum B, Odish M, Minokadeh A, Yi C, Owens RL, Pollema T, et al. Evaluation, treatment, and impact of neurologic injury in adult patients on extracorporeal membrane oxygenation: a review. *Curr Treat Options Neurol*. (2021) 23:15. doi: 10.1007/s11940-021-00671-7

44. Iosifescu AL, Hoogenboom WS, Buczek AJ, Fleysher R, Duong TQ. New-onset and persistent neurological and psychiatric sequelae of COVID-19 compared to influenza: a retrospective cohort study in a large new York City healthcare network. *Int J Methods Psychiatr Res*. (2022) 31:e1914. doi: 10.1002/mpr.1914

45. Eligulashvili A, Darrell M, Miller C, Lee J, Congdon S, Lee JS, et al. COVID-19 patients in the COVID-19 recovery and engagement (CORE) clinics in the Bronx. *Diagnostics (Basel)*. (2023) 13. doi: 10.3390/diagnostics13010119

frontiers | Frontiers in Neurology

TYPE Mini Review
PUBLISHED 24 November 2023
DOI 10.3389/fneur.2023.1233079

OPEN ACCESS

EDITED BY
Govind Nair,
National Institutes of Health (NIH), United States

REVIEWED BY
Akram A. Hosseini,
Nottingham University Hospitals NHS Trust, United Kingdom
Hernan Chaves,
Fundación Para la Lucha Contra las Enfermedades Neurológicas de la Infancia (FLENI), Argentina
Liane S. Canas,
King's College London, United Kingdom

*CORRESPONDENCE
Ludivine Chamard-Witkowski
✉ ludivine.witkowski@vitalitenb.ca

†These authors have contributed equally to this work and share first authorship

RECEIVED 25 July 2023
ACCEPTED 08 November 2023
PUBLISHED 24 November 2023

CITATION
Cull O, Al Qadi L, Stadler J, Martin M, El Helou A, Wagner J, Maillet D and Chamard-Witkowski L (2023) Radiological markers of neurological manifestations of post-acute sequelae of SARS-CoV-2 infection: a mini-review. *Front. Neurol.* 14:1233079. doi: 10.3389/fneur.2023.1233079

Radiological markers of neurological manifestations of post-acute sequelae of SARS-CoV-2 infection: a mini-review

Olivia Cull[1,2†], Lina Al Qadi[1,2†], Josiane Stadler[1,2], Mykella Martin[1,2], Antonios El Helou[2,3,4,5], Jeffrey Wagner[3,6], Danica Maillet[7] and Ludivine Chamard-Witkowski[2,7,8*]

[1]Centre de formation médicale du Nouveau Brunswick, University of Sherbrooke, Moncton, NB, Canada, [2]New Brunswick Center for Precision Medicine, Moncton, NB, Canada, [3]Faculty of Medicine, Dalhousie University, Halifax Regional Municipality, Halifax, NS, Canada, [4]Faculty of Medicine, Memorial University, St John's, NL, Canada, [5]Department of Neurosurgery, The Moncton Hospital, Moncton, NB, Canada, [6]Department of Diagnostic Imaging, The Moncton Hospital, Moncton, NB, Canada, [7]Vitalité Health Network, Dr. Georges-L.-Dumont University Hospital Centre, Moncton, NB, Canada, [8]Department of Neurology, Dr.-Georges-L.-Dumont University Hospital Center, Moncton, NB, Canada

The neurological impact of COVID-19 is a rising concern among medical professionals, as patients continue to experience symptoms long after their recovery. This condition, known as neurological post-acute sequelae of COVID-19 (Neuro-PASC), can last for more than 12 weeks and includes symptoms such as attention disorders, brain fog, fatigue, and memory loss. However, researchers and health professionals face significant challenges in understanding how COVID-19 affects the brain, limiting the development of effective prevention and treatment strategies. In this mini-review, we provide readers with up-to-date information on the imaging techniques currently available for measuring the neurological impact of post-SARS-CoV-2 infection. Our search of PubMed and Google Scholar databases yielded 38 articles on various brain imaging techniques, including structural MRI (magnetic resonance imaging), functional MRI, diffusion MRI, susceptibility-weighted imaging, SPECT (single-photon emission computed tomography) imaging, and PET (positron emission tomography) imaging. We also discuss the optimal usage, limitations, and potential benefits of these techniques. Our findings show that various cerebral imaging techniques have been evaluated to identify a reliable marker for Neuro-PASC. For instance, ^{18}F-FDG-PET/CT and functional MRI have demonstrated hypometabolism in cerebral regions that are directly linked to patient symptoms. Structural MRI studies have revealed different findings, such as infarcts, white matter atrophy, and changes in gray matter volumes. One SPECT imaging study noted frontal lobe hypometabolism, while diffusion MRI showed increased diffusivity in the limbic and olfactory cortical systems. The sequence SWI showed abnormalities primarily in white matter near the gray-white matter junction. A study on ^{18}F-amyloid PET/CT found amyloid lesions in frontal and anterior cingulate cortex areas, and a study on arterial spin labeling (ASL) found hypoperfusion primarily in the frontal lobe. While accessibility and cost limit the widespread use of ^{18}F-FDG-PET/CT scans and functional MRI, they seem to be the most promising techniques. SPECT, SWI sequence, and

^{18}F-amyloid PET/CT require further investigation. Nevertheless, imaging remains a reliable tool for diagnosing Neuro-PASC and monitoring recovery.

KEYWORDS

Neuro-PASC, post-COVID, MRI, fMRI, PET/CT scan, imaging, SPECT (single-photon emission computed tomography)

1 Introduction

Since making its debut in December of 2019, COVID-19 (SARS-CoV-2) has infected nearly 750 million people around the globe, according to the World Health Organization (1). Primarily presenting as a respiratory syndrome, many have reported neurological manifestations, termed "neuro-COVID" either in the acute setting of the disease, or neurological symptoms lingering far after respiratory recovery (2). Approximately one-third of the population affected with COVID-19 and nearly two-thirds of hospitalized COVID-19 patients have experienced neurological complications from their infection (3, 4). Common acute neurological complications, lasting <4 weeks, include anosmia, dysgeusia, altered mental status, encephalopathy, peripheral neuropathy and acute cerebrovascular events (3, 4). On the other hand, nearly 10% of people affected by COVID-19 have signs or symptoms that develop during or after COVID-19 and that persist for over 3 months (5). This was classified as post-COVID syndrome. There is some discrepancy with regard to the accepted time frame to be classified as "post-COVID", ranging between 4 weeks and 12 weeks after the acute phase (6). To further distinguish the acute from the persistent or chronic post-COVID syndrome, the neurological symptoms associated with long-term post-COVID syndrome are different than those present in the acute phase, and they are referred to as Neuro PASC (Neurological manifestations of Post-Acute Sequelae of SARS-CoV-2 infection (7). Fatigue, memory loss, brain fog, anosmia, attentional disorders, subjective cognitive impairment, and headaches dominate the clinical board when it comes to prolonged coronavirus implications (4, 8). These have been seen to persist for over 6 months following onset (5).

1.1 Pathophysiology of neuro-COVID

Three main hypotheses are currently considered to explain Neuro-PASC (8). The first is by indirect mechanism, via peripheral inflammation, also known as the "cytokine storm" that is triggered by SARS-CoV-2. This systemic inflammatory response could alter the equilibrium of the brain, similar to a septic encephalopathy (9). Cytokine storms occur when the fine balance between pro-inflammatory and anti-inflammatory cytokines is lost, and a previously localized inflammation affects the entire system. This deregulation can be non-provoked, as in auto-inflammatory illnesses, or can be precipitated by an infectious agent, as is the case for COVID-19. In the latter, studies have shown an elevation of IL-1β, IL-2, IL-6, IL-10, IFN-γ, and TNF-α, amongst others, and that the degree of elevation was proportional to the severity of the illness (10). The second theory is also one of indirect mechanism, and rests on the basis of lack of perfusion, sepsis or hyperpyrexia that can accompany the respiratory infection, each with their respective toll on the brain's homeostasis. The third hypothesis is one of direct neurotropism (11). SARS-CoV-2 infects the human body by binding to ACE2 receptors, which are primarily found in type 2 alveoli of the lungs (12) and entering the cells. Particularly, ACE2 receptors are also present in the brain's vascular endothelium and smooth muscles, as well as in skeletal muscles, thus explaining why myalgia is a widely present symptom included in post-COVID syndrome. Skeletal muscle cells express ACE2 receptors, which makes them a direct target for SARS-CoV-2 invasion (8). In support of this third theory, previous studies demonstrated that SARS-CoV-2 enters the nervous system by latching onto ACE2 receptors of the olfactory mucosa, penetrating the neural-mucosal interface, the only part of the brain not protected by the dura (3), and migrating along neuronal structures, eventually leading to the centers controlling cardiorespiratory functions (11). Whether Neuro-PASC is caused by direct attack of the virus on the brain or indirectly from systemic secondary damages, or by a combination of these (2), needs to be clarified.

1.2 The need for a precise marker

Despite the immensely rapid response and development of COVID-19 management protocols, many gaps need to be filled when it comes to understanding the pathophysiology of the disease as a whole. For example, up to 55% of hospitalized COVID-19 patients have reported to have neurological manifestations 3 months after their infection (2). This is still not well investigated and studied. This article serves as a review of the radiological markers that are currently in development for the evaluation of neurological damages of COVID-19. We will discuss ^{18}F-FDG-PET/CT, SPECT, and ^{18}F-AMYLOID PET/CT imaging, as well as structural, functional, diffusion MRI, ASL, and susceptibility-weighted imaging, and their current contribution in the management of COVID-19 specifically from a neurological standpoint.

2 Methods

2.1 Search strategy

A record search was performed to identify neuro-imaging methods for tracing Neuro-PASC including ^{18}F-FDG-PET/CT, SPECT, MRI and fMRI. Databases searched were PubMed and Google Scholars for papers published between March 2020 and April 2023. Searches were divided by neuro-imaging methods for

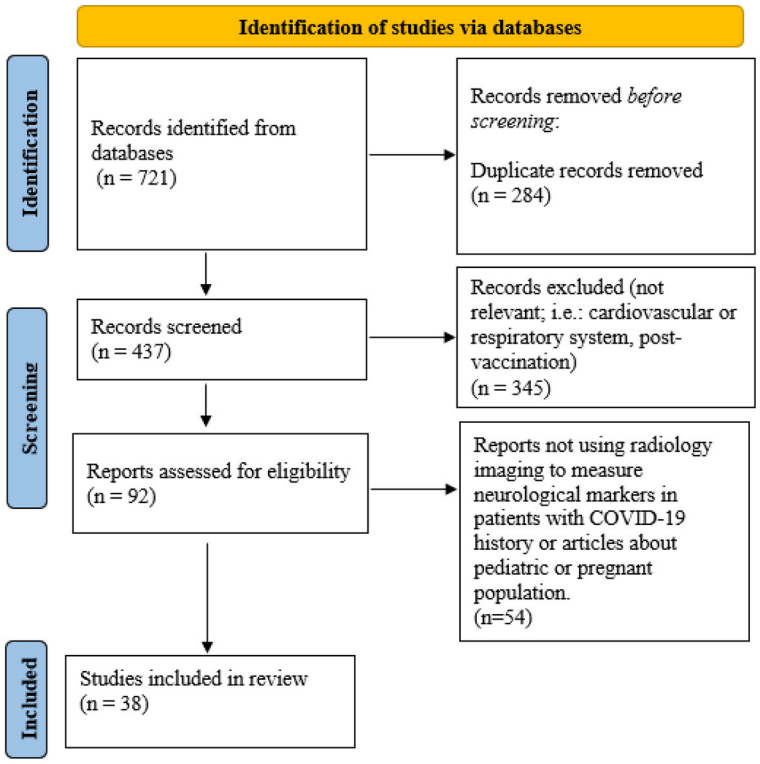


FIGURE 1
Prisma flowchart.

tracing Neuro-PASC. Studies were included if they (1) examined neurological markers, (2) used neuro-imaging modalities, (3) studied patients with a COVID-19 history and, (4) were in English. We excluded articles that examined children, adolescents and pregnant women or consisted of post-vaccination studies.

2.2 Search chains

With regards to 18 F-FDG-PET/CT imaging, the search key was ((((Neuro*) OR (brain)) AND ((Covid*) OR (coronavirus) OR (SARS-CoV-2))) AND ((long covid) OR (post covid))) AND ((PET) OR (positron)). For SPECT imaging, ((((Neuro*) OR (brain)) AND ((Covid*) OR (coronavirus) OR (SARS-CoV-2))) AND ((long covid) OR (post covid))) AND ((SPECT) OR (single photon)). For 18F-amyloid PET/CT, ((((Neuro*) OR (brain)) AND ((Covid*) OR (coronavirus) OR (SARS-CoV-2))) AND ((long covid) OR (post covid))) AND ((amyloid) OR (amyloid PET)). For structural MRI, (((((Neuro*) OR (brain)) AND ((Covid*) OR (coronavirus) OR (SARS-CoV-2))) AND ((long covid) OR (post covid))) AND ((MRI) OR (Magnetic resonance imaging)). For functional MRI, ((((Neuro*) OR (brain)) AND ((Covid*) OR (coronavirus) OR (SARS-CoV-2))) AND ((long covid) OR (post covid))) AND ((fMRI) OR (functional MRI)) yielded no results addressing our topic's subject. For ASL MRI, ((((Neuro*) OR (brain)) AND ((Covid*) OR (coronavirus) OR (SARS-CoV-2))) AND ((long covid) OR (post covid))) AND ((ASL MRI) OR (arterial spin labeling)). For diffusion MRI, ((((Neuro*) OR (brain)) AND ((Covid*) OR (coronavirus) OR (SARS-CoV-2))) AND ((long covid) OR (post covid))) AND ((diffusion MRI) OR (dMRI)). For susceptibility-weighted imaging, ((((Neuro*) OR (brain)) AND ((Covid*) OR (coronavirus) OR (SARS-CoV-2))) AND ((long covid) OR (post covid))) AND ((SWI) OR (Susceptibility-weighted imaging)). A targeted search was done on Google Scholar and PubMed for each neuro-imaging modality and post-covid (i.e.: post-covid PET neuro finding) to identify specific articles that may have been omitted.

2.3 Selection strategy

Retained articles were checked for duplicates and were selected after undergoing a title, abstract and eventually a full text screening. The screening and selection process was done by two independent authors (OC and MM). Collectively, 92 abstracts were read and 38 were used to construct this review. Specifically, 1 for SPECT imaging, 9 for advances with ^{18}F-FDG-PET/CT, 1 for ^{18}F-Amyloid-PET/CT, 10 for structural MRI, 2 for functional MRI, 1 for diffusion MRI, 2 for SWI and the remainder for additional information on Neuro-PASC. A PRISMA flowchart can be found in Figure 1.

3 Results

For each selected article, the following data was extracted and summarized in Table 1: author, journal, study design, number of

TABLE 1 Summary of the characteristics and findings of the imaging studies included in this review.

Authors	Journal	Study design	Number of subjects	Number of controls	Gender distribution male/female	Age (years)	Time since COVID-19 infection	Type of imaging	Main findings in patients
Sollini et al. (13)	Springer Nature	Prospective case-control study	13	26	8/5	54 (46–80)	132 ± 31 days	^{18}F-FDG PET/CT	^{18}F-FDG uptake in "target" and "non-target" tissues. Relative hypometabolism in the right parahippocampus and thalamus. Specific region(s) of hypometabolism in patients with persistent anosmia/ageusia, fatigue, and vascular uptake.
Karimi-Galougahi et al. (14)	Academic Radiology	Case study	1	N/A	0/1	27	6 weeks	^{18}F-FDG-PET/CT	Hypometabolism in the orbitofrontal cortex.
Donegani et al. (15)	Biomedicines	Longitudinal cross-sectional cohort study	22	61	12/10	64 ± 10.5	>1 month	^{18}F-FDG-PET/CT	Relative hypometabolism shown in bilateral parahippocampus and fusiform gyri and in left insula.
Hosp et al. (9)	Oxford University Press	Prospective cohort study	29	45	18/11	65.2 ± 14.4	1 month average	3T sMRI and ^{18}F-FDG PET/CT	MRI showed subacute infarcts. ^{18}F-FDG PET/CT showed predominant frontoparietal hypometabolism.
Guedj et al. (16)	Springer Nature	Retrospective case control study	35	44	20/15	55.06 ± 11.22	≥3 weeks	^{18}F-FDG PET/CT	Hypometabolism in olfactory gyrus and connected paralimbic/limbic regions, extended to the cerebellum and brainstem.
Dressing et al. (17)	The Journal of Nuclear Medicine	Prospective cohort study	14	45	5/9	56.3 ± 7.2	198.0 ± 63.5 days	^{18}F-FDG PET/CT	No pathological findings found on imaging.
Debs et al. (18)	American Journal of Neuroradiology	Retrospective single-center study	45	52	24/21	58 (18–87)	6.57 ± 4.85 months	^{18}F-FDG-PET/CT	Focal hypometabolism peak in cerebellum and in bilateral frontal, parietal, occipital, and posterior temporal lobes, during the first 2 months, nearly resolved at 6 months and disappeared at 12 months. Hypermetabolism in brainstem, cerebellum, limbic structures, frontal cortex, and periventricular white matter shown 2–6 months post-infection.
Jamoulle et al. (19)	Viruses	Mixed method, cohort study (Action research)	55 (32 for imaging)	N/A	15/40	42.4 (12–79)	13.3 ± 8.9 (recovered mild and severe) 18.3 ± 5.9 (still ill, very severe)	SPECT-CT	SPECT-CT showed cerebral hypoperfusion lesions consistent with the severity of the condition.

(Continued)

10.3389/fneur.2023.1233079

TABLE 1 (Continued)

Authors	Journal	Study design	Number of subjects	Number of controls	Gender distribution male/female	Age (years)	Time since COVID-19 infection	Type of imaging	Main findings in patients
Ferrucci et al. (20)	Springer Nature	Retrospective case study	7	N/A	4/3	56 ± 12.39	>12 months	^{18}F-FDG PET/CT and ^{18}F-amyloid PET/CT	^{18}F-FDG PET/CT showed various hypometabolism in the left temporal mesial, pontine, and bilateral prefrontal and parietal regions. ^{18}F-amyloid PET/CT done for the patient with the greatest extent of hypometabolism showed significant Aβ deposition in the superior and middle frontal cortex, in the posterior cingulate, and mildly in the rostral and caudal anterior cingulate regions.
Thapaliya et al. (21)	Frontiers in Neuroscience	Cross-sectional study	8	10	3/5	43.2 ±10.7	≥3 months	7T sMRI	Strong negative relationship between midbrain volume and "breathing difficulty". Greater pons and whole brainstem volumes in patients.
Cecchetti et al. (22)	Springer Nature	Longitudinal quasi-experimental study	36	36	25/11	58.5 ± 13.3	≥30 ± 15 days	3T sMRI	No significant differences in total brain, gray, or white matter volumes were found between patients and controls. Greater total of right frontal and right parieto-occipital white matter hyperintensity volumes. Interrelated cognitive, EEG and MRI alterations were observed after two months of COVID-19 resolution.
Douaud et al. (23)	Nature	Longitudinal quasi-experimental cohort study	401	384	172/229	62.1 ± 6.7	141 ± 79 days	sMRI, fMRI, dMRI	Reduced total brain size, gray matter thickness and tissue contrast in orbitofrontal cortex and parahippocampal gyrus. Greater changes in patients regarding diffusion measures in areas functionally connected to the primary olfactory cortex.
Kandemirli et al. (24)	Academic Radiology	Prospective case study	23	N/A	9/14	29 (22–41)	1–4 months	Paranasal sinus CT and 3T MRI dedicated to olfactory nerves	CT showed opacification in olfactory cleft. MRI showed olfactory bulb degeneration and changes in shape. MRI also showed diffused increase in signal intensity from the olfactory bulb, scattered hyperintense foci, and microhemorrhages.
Besteher et al. (25)	Psychiatry Research	Cross-sectional study	30	20	13/17	47.5 ± 11.5	8.65 (2–16) months	3T sMRI	Multiple clusters of significant bilateral gray matter volume enlargement in fronto-temporal regions, insula, hippocampus, amygdala, basal ganglia, and thalamus.

(Continued)

10.3389/fneur.2023.1233079

TABLE 1 (Continued)

Authors	Journal	Study design	Number of subjects	Number of controls	Gender distribution male/female	Age (years)	Time since COVID-19 infection	Type of imaging	Main findings in patients
Hellgren et al. (26)	BMJ Open	Ambidirectional observational cohort study	35	N/A	28/7	59 (51–66)	7 months	3T SWI, DWI, and sMRI	Multiple findings of white matter lesions near gray-white matter junction in frontal and parietal lobes.
Campabadal et al. (27)	Annals of Clinical and Translational Neurology	Prospective cohort study	48	N/A	10/38	48.04 ± 7.5 (normal olfaction) 51.96 ± 7.92 (olfactory dysfunction)	9.94 ± 3.83 months	3T sMRI and DWI	Reduced gray matter volume and increased mean diffusivity in olfactory-related areas explaining persistent olfactory deficits in patients. Greater radial diffusivity in the anterior corona radiata, the genu of the corpus callosum, and uncinate fasciculus in patients with deficits compared to those without.
Yus et al. (28)	Acta Neurologica Scandinavica	Cross-sectional study	82	N/A	24/58	51.74 ± 10.85	11.18 ± 3.78 months	ASL, sMRI, and DTI	Olfactory dysfunction associated with lower tissue perfusion in orbital and medial frontal areas. Absence of statistically significant findings in brain volumes and diffusion-tensor imaging.
Kiatkittikul et al. (29)	Nuclear Medicine and Molecular Imaging	Retrospective case study	13	N/A	6/7	47 (42–54)	>28 days	^{18}F-FDG PET/CT and 3 T PET/rsfMRI	^{18}F-FDG PET/CT showed uptake in many organs. ^{18}F FDG PET showed many areas of hypometabolism in the thalamus, and in parietal, temporal, frontal, and occipital lobes. rsfMRI results showed abnormal brain connectivity which is coherent with ^{18}F-FDG PET findings.
Churchill et al. (30)	Frontiers in Neurology	Cross-sectional study	51	15	17/34	41 ± 12	4–5 months average	3 T sMRI and fMRI	Lower connections in the thalamus and decreased temporal subcortical functional connectivity in patients.
Ajčević et al. (31)	Nature Portfolio	Prospective cohort study	24	22	9/15	53.0 (±14.5)	≥4 weeks	ASL MRI	Hypoperfusion predominantly in frontal, parietal, and temporal cortex.
Mishra et al. (32)	medRxiv pre-print, not peer reviewed	Prospective cohort group-level study	46	30	31/15	34.67 ± 9.51	<6 months	3T SWI and sMRI	Higher susceptibility imaging values in the frontal lobe and brainstem in patients. Observed cluster in midbrain and bilateral clusters in white matter near the orbitofrontal gyri and the gray-white matter junctions. Significant clusters negatively correlated with fatigue scores found in frontal lobe, anterior cingulate cortex, and brainstem.

^{18}F-FDG PET/CT, Positron emission tomography with 18 fluoro-D-glucose integrated with computed tomography; SPECT-CT, Single Photon Emission Tomography-Computed Tomography; sMRI, structural MRI; dMRI, diffusion MRI; SWI, susceptibility-weighted imaging; DWI, diffusion-weighted imaging; DTI, diffusion-tensor imaging; ASL, arterial spin labeling.

10.3389/fneur.2023.1233079

subjects, number of controls, gender distribution, age, time elapsed since COVID-19 infection, type of imaging and main findings.

3.1 ^{18}F-FDG-PET/CT

Positron emission tomography (PET) measures the emission of positrons from radiomarked tracer molecules, allowing localization of metabolically active processes. The most widely used radiotracer is currently ^{18}F-Fluorodeoxyglucose (^{18}F-FDG), a radiolabeled glucose molecule. This method allows localization of regions of abnormal increase or decrease glucose intake in the body to better identify hyper or hypometabolic states and is currently mainly used as part of the workup and follow-up in oncology. In the Neuro-PASC scope, the expected utility of ^{18}F-FDG-PET/CT is to identify a specific cerebral target that explains the clinical manifestations (33). This will be useful to better determine the pathophysiology, to improve the accuracy of the diagnosis, to then better develop therapeutic options and accurate follow-ups. When the intrinsic role of the hyper/hypometabolic brain loci correlates with the clinical manifestations of Neuro-PASC, while it cannot prove causality, points toward understanding the pathophysiology of COVID-19 and helps clinicians make the diagnosis of Neuro-PASC.

Sollini et al.'s case control study in 2021 evaluated post-COVID syndrome hallmarks on ^{18}F-FDG-PET/CT and showed brain hypometabolism in limbic, paralimbic, brainstem and cerebellum. In addition, none of the post-COVID patients exhibited regions of hypermetabolism compared to controls. Limbic and orbito-frontal hypometabolism correlated with the anosmia present during acute COVID-19 infection. Sollini's team also evaluated the whole-body ^{18}F-FDG-PET/CTscans. Despite the hypometabolic activity in the nervous system, they found hypermetabolic activity in different organs, independent of ACE-2 receptor activity, in other words, regions of hypermetabolism were seen in target (ACE-2 presenting) as well as non-target organs, supporting the hypothesis that systemic inflammation may be in play (13).

Verger et al.'s (34) study showed that 47% of the ^{18}F-FDG-PET/CT scans of 143 patients with suspected Neuro-PASC had hypometabolism in limbic/paralimbic and fronto-orbital olfactory regions, as well as in the brainstem and cerebellum.

Several other studies have been conducted using ^{18}F-FDG-PET/CT imaging to reveal potential Neuro-PASC biomarkers. A study by Karimi-Galougahi et al. (14) brought forth reduced metabolic activity in the orbitofrontal cortex using ^{18}F-FDG-PET/CT. Bilateral par hippocampal, fusiform gyri, and left insula hypometabolism were seen in an ^{18}F-FDG-PET/CT imaging study conducted by Donegani et al. (15).

A study by Hosp et al. (9) that ran its course in parallel with the Montreal Cognitive Assessment test (MoCA), a highly sensitive tool for early detection of mild cognitive impairment (MCI), correlated cognitive decline with the evident frontoparietal hypometabolism seen on scan. This study showed that while a structural MRI could not find any sign of cerebral damage, ^{18}F-FDG-PET/CT discovered cortical fronto-parietal hypometabolism.

A study by Guedj et al. (16), demonstrated that clusters of patients with hypometabolic patterns on ^{18}F-FDG-PET/CT scans, flagged by whole-brain statistical analysis performed using SPM8, were very distinct in patients with Neuro-PASC and allowed to reliably differentiate their brain from one of a control subject. The findings suggested that hypometabolism was seen in bilateral rectal/orbital gyrus, including the olfactory gyrus, right temporal lobe, bilateral pons/medulla, and the cerebellum bilaterally. These patients exhibited many functional complaints. Patients with cerebellar hypometabolism experienced hyposmia, anosmia and memory impairment. Patients with frontal cortex, brainstem and cerebellum hypometabolism presented pain and insomnia.

^{18}F-FDG-PET/CT has also proven to be useful in characterizing the timeline of damages caused by SARS-CoV-2. Post-COVID syndrome patients who had increased vascular uptake (hypermetabolism) on whole-body scan done at 1-month post-infection also showed hypometabolism in the brain, thus demonstrating the different effects of COVID-19 on different regions of the body, and the chronological sequence for brain and whole-body changes throughout the disease (13).

In contrast to these studies, Dressing et al.'s (17) study revealed that post-COVID patients reporting symptoms lasting for over 3 months after the acute infection, actually only presented mild impairment on cognitive testing (MoCA) with their distinct pathologic findings on ^{18}F-FDG-PET/CT. In this same stretch of ideas, Ferruci et al.'s review explained that not all patients who presented cognitive decline in the post-COVID timeframe showed hypometabolism on ^{18}F-FDG-PET/CT (20).

In Debs et al. (18) study, a time-dependent brain PET hypo- and hypermetabolism was observed in patients with a history of COVID-19. Hypometabolic activity, in the bilateral frontal, parietal, occipital, and posterior temporal lobes and cerebellum, reached its peak at 2 months post-infection, then nearly resolved at 6 months, followed by disappearance at 12 months. Additionally, 2–6 months after infection onset, hypermetabolism was observed in brainstem, cerebellum, limbic structures, frontal cortex, and periventricular white matter.

3.2 SPECT/CT

Single Photon Emission Computed Tomography (SPECT/CT) is a method that allows superposition of anatomical images with metabolic activity. While PET scans detect metabolism through emission of photons, SPECT scans detect gamma rays from tracers injected into the patient (35). Brain SPECT measures brain perfusion. A limited number of studies met the particular interest of this topic. Takao et al.'s (36) study on Neuro-PASC patients described observing hypoperfusion on SPECT imaging in various areas of the brain, particularly the frontal lobes, which correlates with the previous findings in 18 F-FDG-PET/CT scans. A study conducted on 32 patients with highly impaired functional status, determined by COOP/WONCA functional ability questionnaire (Cooperative Research Network/World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians), demonstrated cerebral perfusion changes on SPECT/CT in 29 patients (90%) (19). Fifteen patients then underwent a control SPECT-CT 3–9 months after their initial

imaging taken during the acute infection. The follow-up image showed marked improvement in 8 cases and worsening in 7 cases.

3.3 ^{18}F-AMYLOID PET/CT

Amyloid PET is an imaging modality that allows the visualization of amyloid plaques. A retrospective study conducted by Ferrucci et al. (20) found amyloid plaques in one Neuro-PASC patient 12 months after hospital discharge for his acute COVID-19 infection using an ^{18}F-amyloid PET/CT. The plaques were found in the superior and middle frontal cortex, in the posterior cingulate cortex and in the rostral and caudal areas of the anterior cingulate cortex in a lower quantity. ^{18}F- FDG PET/CT also detected hypometabolism in the left mesial temporal cortex of this patient (20). To our knowledge, this is the only published article that examined Amyloid PET.

3.4 Structural MRI

The anatomy of the brain can be studied using an MRI, an imaging modality that allows the visualization of soft tissues using a magnetic field (37). Results by Hosp et al. (9) suggest that ^{18}F-FDG-PET/CT seems to be more effective in detecting anomalies than 3T MRI. Specifically, ^{18}F-FDG-PET/was able to detect frontoparietal hypometabolism, whereas 3T MRI found no relevant structural or vascular anomalies. The sequences used in this article were as follow: sagittal 3D-T1 rapid gradient echo (MP-RAGE) before and after contrast infusion, sagittal 3D FLAIR SPACE (sampling perfection with application-optimized contrasts using different flip angle evolutions), SWI and diffusion mesoscopic imaging (DMI). Nonetheless, 3T MRI allowed to localize a few subacute infarcts (9).

However, in a pilot study conducted by Thapaliya et al. (21), T_1-weighted 7T MRI showed an increased volume of the superior cerebella peduncle, pons, and entire brainstem in Neuro-PASC patients compared to controls. These biomarkers were also found in patients with myalgic encephalomyelitis/chronic fatigue syndrome which could explain the similarity in symptoms between these two conditions (21).

On another hand, Cecchetti et al. (22) found that COVID-19 patients showed interrelated cognitive, EEG and 3T T2-weighted structural MRI abnormalities 2 months after being discharged from the hospital. A UK Biobank longitudinal imaging study of 785 patients having been scanned by structural MRI (T1, T2 fluid attenuation inversion recovery (FLAIR) and susceptibility-weighted MRI) before, through indications for scans unrelated to COVID-19, and approximately 141 days after testing positive for COVID-19, showed statistically significant atrophy of gray matter in limbic cortical areas, directly linked to olfactory and gustatory systems 6 (23).

Another application for 3T T2-space structural MRI in post-COVID syndrome is demonstrated in Kandemirli et al.'s (24) study. Out of 23 patients with persistent COVID-19 olfactory dysfunction, nearly three-quarters had olfactory cleft opacification, a reduction in olfactory bulb volumes, change in bulb shape or signal anomalies (24). These MRI studies allowed for a better understanding of the damages inflicted on the olfactory pathway in the context of COVID-19 anosmia.

In a study conducted by Besteher et al. (25), increased gray matter volume clusters were found in post-COVID patients 8 months after their acute COVID-19 infection compared to controls using voxel-based morphometry (VBM). They used VBM with CAT12 toolbox, using T1-weighted images obtained from a 3T MRI to measure gray matter volumes. The clusters were found bilaterally in the frontal lobe, temporal lobe, insula, amygdala, hippocampus, basal ganglia, and thalamus. The volume of four of these clusters was found to decrease over time. The first cluster was in the anterior insula and some regions of the frontal lobe. The second cluster was scattered in the left temporal lobe. The third cluster was in the left post-central and precentral gyrus and finally, the fourth cluster was in parts of the temporal lobe, the right fusiform gyrus, the parahippocampal gyrus, and the hippocampus. It was hypothesized that the augmentation of the gray matter volumes was caused by compensatory processes or inflammation (25).

Hellgren et al.'s (26) observational cohort study compared the MRI imaging of post-COVID patients to the neuropsychological findings of these patients. 3T MRI (T2-FLAIR, T2-FSE, T1-FSE, T1-GRE, DWI and SWI) imaging was done on patients whose neurocognitive test results seemed concerning to researchers. The neurocognitive test performed was the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Thirty-five post-COVID patients who had been hospitalized for their acute COVID-19 infection and who were discharged on average 6.5 months prior underwent a brain MRI which revealed subcortical white matter lesions in 71% of these patients. The lesions were primarily found in the frontal and parietal lobes near the gray-white matter junction. Compared to the patients with normal MRI results, the patients with white matter lesions had lower scores in the RBANS visuospatial index. It is worth noting that the functionality level of the patients with white matter lesions prior to their COVID-19 infection was lower compared to controls (26).

Campabadal et al. (27) using 3T structural MRI found a reduction in gray matter volume in the caudate nucleus, putamen, olfactory cortex, parahippocampal gyrus, straight gyrus, left amygdala, and the superior and inferior orbital gyri using voxel-based morphometry. A study by Yus et al. (28) using 3T structural MRI (3D-T1, T2-FLAIR) found no statistically significant findings in brain volumes.

3.5 Functional MRI

A functional MRI (fMRI) is able to estimate brain metabolism by using either blood-oxygen level dependant (BOLD) contrast or cerebral blood flow to measure activity in different regions of the brain. Resting-state fMRI (rsf-MRI) refers to an fMRI being performed while a patient is not performing any tasks (38). Limited studies have been published regarding functional MRI and its applicability in Neuro-PASC patients. Kiatkittikul et al. (29) showed abnormal brain connectivity on rsf-MRI which was concordant with 18 F-FDG-PET/CT findings. It was reported that one patient who had sensorineural hearing loss of the left ear as a consequence of COVID-19 showed hypometabolism of the left

temporal region on 18 F-FDG PET/CT scans and anomalies in rsf-MRI in the same region (29). Another study using rsf-MRI, led by Churchill et al. (30), demonstrated that patients who are currently experiencing a larger number of Neuro-PASC symptoms tended to have altered connectivity between parietal, temporal, occipital and subcortical regions using BOLD rsf-MRI. Additionally, distinct patterns correlated to the intensity of PASC symptoms. They elude to the fact that this could be a useful tool to differentiate between Neuro-PASC and other non-COVID-related infections (30).

Arterial spin labeling (ASL) is an MRI technique that has been used to measure brain perfusion in Neuro-PASC patients. A study by Ajčević et al. (31) found that participants who still had cognitive impairment 2 to 10 months after the beginning of their acute COVID-19 infection had cerebral hypoperfusion patterns on ASL MRI imaging. The hypoperfusion was primarily found in the frontal cortex but was also present in the temporal and parietal cortex. These findings were more significant in the right hemisphere. They also found that overall, the cerebral blood flow was lower throughout the gray matter in Neuro-PASC patients compared to healthy controls (31). Yus et al. (28) found similar results in their ASL study on post-COVID patients where they found lower perfusion in the patient's orbital and medial frontal lobes.

3.6 Diffusion MRI

Diffusion MRI (dMRI) is an imaging modality that utilizes the diffusion of water as contrast. Diffusion tensor imaging (DTI) is a type of dMRI that creates a 3D construction of diffusion (39). Diffusivity measurements are indicators of tissue microstructure integrity. Douaud et al. (23) found a greater increase in diffusivity, an indicator of tissue damage, in areas functionally connected to the piriform cortex, olfactory tubercle and anterior olfactory nucleus, in patients who were infected with SARS-CoV-2 compared to healthy controls (23). Additionally, a study by Campabadal et al. (27) found that Neuro-PASC patients presenting with olfactory dysfunction had higher mean and radial diffusivity in certain white matter regions on DTI compared to post-acute COVID-19 patients without olfactory dysfunction. The areas of increased mean diffusivity were found in the genu of the corpus callosum, forceps minor, orbitofrontal white matter tracts, and anterior thalamic radiations. Regions with augmented radial diffusivity were found in the genu of the corpus callosum, anterior corona radiata, and uncinate fasciculus (27). In contrast, a study done by Yus et al. (28) found no statistically significant findings with DTI—in patients with Neuro-PASC.

3.7 Susceptibility-weighted imaging

Susceptibility-weighted imaging was also used to try to visualize the neurological sequela of SARS-CoV-2 infection. This imaging modality is an MRI technique that uses the patient's iron, calcium, and deoxygenated blood as a source of contrast for the image. This imaging modality is useful for detecting hemorrhages, traumatic brain injury, microvasculature, and neurodegenerative diseases (40). Hellgren et al.'s (26) study using SWI found mostly subcortical abnormalities near the gray-white matter junction in frontal and parietal lobes in 8 patients out of 35 (26).

In addition, Mishra et al. (32) found regions of abnormal susceptibility bilaterally in the brain stem, the gray-white matter junction and in the white matter of the frontal lobes in patients with post-COVID condition or patients who had recovered after COVID-19 infection. The abnormalities seen in the brainstem were primarily in the midbrain and the abnormalities in the frontal lobes were located in the uncinate fasciculus tract and the inferior frontal-occipital fasciculus tracts (32). However, it is important to note that this article has not been peer-reviewed. To our knowledge, this is the only published article where the main focus was the use of susceptibility-weighted imaging to find radiological markers in post-COVID patients.

4 Discussion

Overall, different cerebral imaging techniques have been evaluated to find a reliable and reproducible marker of the Neuro-PASC footprint. ^{18}F-FDG-PET/CT and sMRI seem to be the most studied. SPECT scans, SWI, dMRI, fMRI, and ASL were not largely studied, however, deserve to be further investigated in the context of Neuro-PASC.

One current limitation of ^{18}F-FDG-PET/CT and SPECT studies is that these studies' complexity, cost and radiation exposure limit the number of research cohorts. These types of imaging require prolonged periods in a scanner which is possibly not efficient when searching for a highly available, yet reliable method.

On the other hand, the use of ionizing radiation, as seen in ^{18}F-FDG-PET/CT can only really be justified when there is high suspicion of important neurological complications. Thus, exposing patients to radiation when the benefits of such a technique remain uncertain can be perceived as questionable. Consent for such radiation exposure would be, as per usual, required.

While studies on ^{18}F-FDG-PET/CT are ample, studies on SPECT are insufficient. Despite this, current literature suggests that because ^{18}F-FDG-PET/CT has superior sensitivity, as well as better contrast and resolution than SPECT, currently, ^{18}F-FDG-PET/CT imaging, is superior to SPECT. On the other hand, the cost of ^{18}F-FDG PET/CT is significantly higher than SPECT and remains an important obstacle to its access in our healthcare system. Verger et al.'s (34) SPECT study also demonstrated that this imaging technique can be of particular interest when tracking the recovery from Neuro-PASC.

Although amyloid deposits were found in Ferrucci et al.'s study, they only conducted an amyloid PET scan on one patient. Further research is needed to conclude whether the amyloid PET scan is a useful imaging modality to visualize Neuro-PASC. A study from Sun et al. (41) showed significantly higher plasma levels of amyloid beta in participants after recovery from acute COVID-19 infection compared to controls. These results were present in participants whether they had perduring neurological symptoms or not (41). This also supports the need for further research.

With what pertains to structural MRI, findings varied depending on the strength of the MRI and the MRI technique. Structural MRI gave varying information on Neuro-PASC, such as localizing subacute infarcts and noting cortical atrophy. With a 3T MRI, some researchers were only able to localize areas of previous infarcts whilst others found atrophy of the gray matter in limbic cortical areas, a reduction in olfactory bulb volumes, or subcortical white matter lesions in the frontal and parietal lobes. On the other hand, with a 7T MRI, Thapaliya et al. found an increased volume of the brainstem in Neuro-PASC patients but the literature regarding 7T MRI in this population is limited. Clusters of increased gray matter volumes were found with voxel-based morphometry in the frontal lobe, temporal lobe, insula, amygdala, hippocampus, basal ganglia, and thalamus.

On the other hand, keeping in mind that studies are also quite limited, functional MRI shows concordant results to ^{18}F-FDG-PET/CT, meaning findings of corresponding regions of hypometabolism and their symptomatic manifestations. ASL MRI found areas of hypoperfusion primarily in the frontal cortex but also in the temporal and parietal cortex, which concorded with SPECT findings.

Overall, most diffusion MRI studies showed changes in diffusivity in areas connected to the primary olfactory cortex. Increased diffusivity was also noted in the genu of the corpus callosum, orbitofrontal white matter tracts, anterior thalamic radiation, and forceps minor. The same study found a decrease in gray matter volumes in olfactory-related regions. These findings along with the increased mean and radial diffusivity could explain the persistent olfactory deficits found in patients.

Additionally, susceptibility-weighted imaging revealed low susceptibility mainly in the frontal lobes and brain stems, which is consistent with abnormalities detected by other imaging modalities. The anomalies found in the uncinate fasciculus tract could explain the memory and mental health problems that are often present in post-COVID patients. The orbitofrontal region of the brain has a major influence on smell and taste therefore the areas of abnormal susceptibility near the orbitofrontal gyri could explain the loss of smell and taste seen in post-COVID patients.

Combining these different neuro-imaging modalities, particularly ^{18}F-FDG-PET/CT and sMRI, could be an interesting and rewarding approach in identifying neurological markers of Neuro-PASC. Starting with a structural imaging technique and then proceeding to functional or metabolic modalities could allow for a better grasp of the structural and metabolic long-term progression and ultimate impact of COVID-19 on the brain. A consideration to keep in mind is that pre-existing neurological conditions and neurocognitive disorders need to be considered when interpreting Neuro-PASC symptoms and imaging. Also, the reassurance of a proper diagnosis and management comforted many Neuro-PASC patients who had noticed psychological decline for a prolonged period after the initial infection, for no clear reason. Their memory, energy level and concentration were not restored post-infection, leaving them with great uncertainty regarding the cause of their psychological decline. The clear and visible perfusion defects on SPECT imaging provided great validation to patients living with these new post-infectious deficits and helped physicians make a positive diagnosis.

5 Conclusion

Overall, many studies have been conducted on the use of neuro-imaging in post-COVID syndrome patients with Neuro-PASC. Among these, ^{18}F-FDG-PET/CT and sMRI seem to be the most studied and the most promising neuro-imaging modalities to identify Neuro-PASC markers. Further research needs to be conducted with regard to fMRI, dMRI, SPECT, amyloid PET, ASL MRI and susceptibility-weighted imaging. Although multiple structural MRI studies revealed significant abnormalities, these findings differed considerably in location within the brain and in type of abnormality from one study to another. These gaps in our knowledge do not allow us to confidently confirm the applicability of these imaging techniques in the detection, monitoring, and response to treatment. Future research should include homogenous and larger sample sizes and longitudinal data as much as possible to better identify and understand Neuro-PASC markers.

The cumulation of preliminary results of ^{18}F-FDG-PET/CT showed that hypometabolism seen in reports could constitute a quantitative marker of cerebral damage of post-COVID syndrome. sMRI identified atrophy in white matter and changes in gray matter volumes, which could also be considered potential markers of Neuro-PASC. The possibility of having markers that allow a more accurate follow-up on brain damage, progression and response to therapy would not only allow us to better treat the increasing number of patients suffering from Neuro-PASC, but to better understand the pathophysiology of this cataclysmic disease.

Author contributions

OC and LA are the main authors of the article, doing the literature review, building the article, and sending for revisions. MM, JS, and DM helped screen the search results, with the writing and editing of the manuscript. AE and JW provided feedback and corrections, based on their expertise, in neurosurgery, and diagnostic imaging, respectively. LC-W overlooked the project and provided feedback at every stage of the article. All authors contributed to the article and approved the submitted version.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated

organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. WHO Coronavirus (COVID-19) Dashboard. Available online at: https://covid19.who.int (accessed April 27, 2023).

2. DeKosky ST, Kochanek PM, Valadka AB, Clark RSB, Chou SHY, Au AK, et al. Blood biomarkers for detection of brain injury in COVID-19 patients. *J Neurotrauma.* (2021) 38:1–43. doi: 10.1089/neu.2020.7332

3. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID 19. *Lancet Neurol.* (2020) 19:767–83. doi: 10.1016/S1474-4422(20)30221-0

4. Meyer PT, Hellwig S, Blazhenets G, Hosp JA. Molecular imaging findings on acute and long-term effects of COVID-19 on the brain: a systematic review. *J Nucl Med Off Publ Soc Nucl Med.* (2022) 63:971–80. doi: 10.2967/jnumed.121.263085

5. Premraj L, Kannapadi NV, Briggs J, Seal SM, Battaglini D, Fanning J, et al. Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: a meta-analysis. *J Neurol Sci.* (2022) 434:120162. doi: 10.1016/j.jns.2022.120162

6. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. *Nat Med.* (2020) 26:1017–32. doi: 10.1038/s41591-020-0968-3

7. Rudroff T, Workman CD, Ponto LLB. 18F-FDG-PET imaging for Post-COVID-19 brain and skeletal muscle alterations. *Viruses.* (2021) 13:2283. doi: 10.3390/v13112283

8. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature.* (2021) 594:259–64. doi: 10.1038/s41586-021-03553-9

9. Hosp JA, Dressing A, Blazhenets G, Bormann T, Rau A, Schwabenland M, et al. Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. *Brain J Neurol.* (2021) 144:1263–76. doi: 10.1093/brain/awab009

10. Zanza C, Romenskaya T, Manetti AC, Franceschi F, La Russa R, Bertozzi G, et al. Cytokine storm in COVID-19: immunopathogenesis and therapy. *Medicina.* (2022) 58:144. doi: 10.3390/medicina58020144

11. Heming M, Li X, Räuber S, Mausberg AK, Börsch AL, Hartlehnert M, et al. Neurological manifestations of COVID-19 feature T cell exhaustion and dedifferentiated monocytes in cerebrospinal fluid. *Immunity.* (2021) 54:164–175.e6. doi: 10.1016/j.immuni.2020.12.011

12. Morbelli S, Ekmekcioglu O, Barthel H, Albert NL, Boellaard R, Cecchin D, et al. COVID-19 and the brain: impact on nuclear medicine in neurology. *Eur J Nucl Med Mol Imaging.* (2020) 47:2487–92. doi: 10.1007/s00259-020-04965-x

13. Sollini M, Morbelli S, Ciccarelli M, Cecconi M, Aghemo A, Morelli P, et al. Long COVID hallmarks on [18F]FDG-PET/CT: a case-control study. *Eur J Nucl Med Mol Imaging.* (2021) 48:3187–97. doi: 10.1007/s00259-021-05294-3

14. Karimi-Galougahi M, Yousefi-Koma A, Bakhshayeshkaram M, Raad N, Haseli S. ^{18}FDG PET/CT scan reveals hypoactive orbitofrontal cortex in anosmia of COVID-19. *Acad Radiol.* (2020) 27:1042–3. doi: 10.1016/j.acra.2020.04.030

15. Donegani MI, Miceli A, Pardini M, Baucknehtt M, Chiola S, Pennone M, et al. Brain metabolic correlates of persistent olfactory dysfunction after SARS-Cov2 infection. *Biomedicines.* (2021) 9:287. doi: 10.3390/biomedicines9030287

16. Guedj E, Campion JY, Dudouet P, Kaphan E, Bregeon F, Tissot-Dupont H, et al. 18F-FDG brain PET hypometabolism in patients with long COVID. *Eur J Nucl Med Mol Imaging.* (2021) 48:2823–33. doi: 10.1007/s00259-021-05215-4

17. Dressing A, Bormann T, Blazhenets G, Schroeter N, Walter LI, Thurow J, et al. Neuropsychologic profiles and cerebral glucose metabolism in neurocognitive long COVID syndrome. *J Nucl Med.* (2022) 63:1058–63. doi: 10.2967/jnumed.121.262677

18. Debs P, Khalili N, Solnes L, Al-Zaghal A, Sair HI, Yedavalli V, et al. "Post-COVID-19 Brain [18F] FDG-PET findings: a retrospective single-center study in the United States. *AJNR Am J Neuroradiol.* (2023) 44:517–22. doi: 10.3174/ajnr.A7863

19. Jamoulle M, Kazeneza-Mugisha G, Zayane A. Follow-up of a cohort of patients with post-acute COVID-19 syndrome in a Belgian family practice. *Viruses.* (2022) 14:2000. doi: 10.3390/v14092000

20. Ferrucci R, Cuffaro L, Capozza A, Rosci C, Maiorana N, Groppo E, et al. Brain positron emission tomography (PET) and cognitive abnormalities one year after COVID-19. *J Neurol.* (2023) 270:1823–34. doi: 10.1007/s00415-022-11543-8

21. Thapaliya K, Marshall-Gradisnik S, Barth M, Eaton-Fitch N, Barnden L. Brainstem volume changes in myalgic encephalomyelitis/chronic fatigue syndrome and long COVID patients. *Front. Neurosci.* (2023) 17:1125208. doi: 10.3389/fnins.2023.1125208

22. Cecchetti G, Agosta F, Canu E, Basaia S, Barbieri A, Cardamone R, et al. Cognitive, EEG, and MRI features of COVID-19 survivors: a 10-month study. *J Neurol.* (2022) 269:3400–12. doi: 10.1007/s00415-022-11047-5

23. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature.* (2022) 604:697–707. doi: 10.1038/s41586-022-04569-5

24. Kandemirli SG, Altundag A, Yildirim D, Sanli DET, Saatci O. Olfactory bulb MRI and paranasal sinus CT findings in persistent COVID-19 anosmia. *Acad Radiol.* (2021) 28:28–35. doi: 10.1016/j.acra.2020.10.006

25. Besteher B, Machnik M, Troll M, Toepffer A, Zerekidze A, Rocktäschel T, et al. Larger gray matter volumes in neuropsychiatric long-COVID syndrome. *Psychiatry Res.* (2022) 317:114836. doi: 10.1016/j.psychres.2022.114836

26. Hellgren L, Birberg Thornberg U, Samuelsson K, Levi R, Divanoglou A, Blystad I. Brain MRI and neuropsychological findings at long-term follow-up after COVID-19 hospitalisation: an observational cohort study. *BMJ Open.* (2021) 11:e055164. doi: 10.1136/bmjopen-2021-055164

27. Campabadal A, Oltra J, Junqué C, Guillen N, Botí MÁ, Sala-Llonch R, et al. Structural brain changes in post-acute COVID-19 patients with persistent olfactory dysfunction. *Ann Clin Transl Neurol.* (2023) 10:195–203. doi: 10.1002/acn3.51710

28. Yus M, Matias-Guiu JA, Gil-Martínez L, Gómez-Ruiz N, Polidura C, Jorquera M, et al. Persistent olfactory dysfunction after COVID-19 is associated with reduced perfusion in the frontal lobe. *Acta Neurol Scand.* (2022) 146:194–8. doi: 10.1111/ane.13627

29. Kiatkittikul P, Promteangtrong C, Kunawudhi A, Siripongsatian D, Siripongboonsitti T, Ruckpanich P, et al. Abnormality pattern of F-18 FDG PET whole body with functional MRI brain in post-acute COVID 19. *Nucl Med Mol Imaging.* (2022) 56:29–41. doi: 10.1007/s13139-021-00730-6

30. Churchill NW, Roudaia E, Chen JJ, Gilboa A, Sekuler A, Ji X, et al. Effects of post-acute COVID-19 syndrome on the functional brain networks of non-hospitalized individuals. *Front Neurol.* (2023) 14:1136408. doi: 10.3389/fneur.2023.1136408

31. Ajčević M, Iscra K, Furlanis G, Michelutti M, Miladinović A, Buoite Stella A, et al. Cerebral hypoperfusion in post-COVID-19 cognitively impaired subjects revealed by arterial spin labeling MRI. *Sci Rep.* (2023) 13:5808. doi: 10.1038/s41598-023-32275-3

32. Mishra SS, Hafiz R, Misra R, Gandhi TK, Prasad A, Mahajan V, et al. Brain alterations in Covid recovered revealed by susceptibility-weighted magnetic resonance imaging. *medRxiv.* (2022). doi: 10.1101/2022.11.21.22282600

33. Unterrainer M, Eze C, Ilhan H, Marschner S, Roengvoraphoj O, Schmidt-Hegemann NS, et al. Recent 274 advances of PET imaging in clinical radiation oncology. *Radiat Oncol.* (2020) 15:88. doi: 10.1186/s13014-020-01519-1

34. Verger A, Kas A, Dudouet P, Goehringer F, Salmon-Ceron D, Guedj E. Visual interpretation of brain hypometabolism related to neurological long COVID: a French multicentric experience. *Eur J Nucl Med Mol Imaging.* (2022) 49:3197–202. doi: 10.1007/s00259-022-05753-5

35. Nuclear Medicine. *National Institute of Biomedical Imaging and Bioengineering.* Available online at: https://www.nibib.nih.gov/science-education/science-topics/nuclear-medicine (accessed April 30, 2023).

36. Takao M, Ohira M. Neurological post-acute sequelae of SARS-CoV-2 infection. *Psychiatry Clin Neurosci.* (2023) 77:72–83. doi: 10.1111/pcn.13481

37. National Institute of Biomedical Imaging and Bioengineering. *Magnetic Resonance Imaging (MRI).* Available online at: https://www.nibib.nih.gov/science-education/science-topics/magnetic-resonance-imaging-mri (accessed September 23, 2023).

38. Glover GH. Overview of functional magnetic resonance imaging. *Neurosurg Clin N Am.* (2011) 22:133–9. doi: 10.1016/j.nec.2010.11.001

39. Le Bihan D. Diffusion MRI: what water tells us about the brain. *EMBO Mol Med.* (2014) 6:569–73. doi: 10.1002/emmm.201404055

40. Halefoglu AM, Yousem DM. Susceptibility weighted imaging: clinical applications and future directions. *World J Radiol.* (2018) 10:30–45. doi: 10.4329/wjr.v10.i4.30

41. Sun B, Tang N, Peluso MJ, Iyer NS, Torres L, Donatelli JL, et al. Characterization and biomarker analyses of Post-COVID-19 complications and neurological manifestations. *Cells.* (2021) 10:386. doi: 10.3390/cells10020386

frontiers | Frontiers in Aging Neuroscience

TYPE Review
PUBLISHED 08 January 2024
DOI 10.3389/fnagi.2023.1274452

OPEN ACCESS

EDITED BY
Urszula Wojda,
Polish Academy of Sciences, Poland

REVIEWED BY
Ludivine Chamard-Witkowski,
Université de Sherbrooke, Canada
Fatemeh Sodeifian,
Shahid Beheshti University of Medical Sciences, Iran

*CORRESPONDENCE
Muhammad Danial Che Ramli
✉ muhddanial_cheramli@msu.edu.my
Suresh Kumar
✉ sureshkumar@msu.edu.my

RECEIVED 08 August 2023
ACCEPTED 14 December 2023
PUBLISHED 08 January 2024

CITATION
Shajahan SR, Kumar S and Ramli MDC (2024) Unravelling the connection between COVID-19 and Alzheimer's disease: a comprehensive review.
Front. Aging Neurosci. 15:1274452.
doi: 10.3389/fnagi.2023.1274452

Unravelling the connection between COVID-19 and Alzheimer's disease: a comprehensive review

Shah Rezlan Shajahan[1], Suresh Kumar[2]* and Muhammad Danial Che Ramli[2]*

[1]School of Graduate Studies, Management and Science University, Shah Alam, Selangor, Malaysia, [2]Faculty of Health and Life Sciences, Management and Science University, Shah Alam, Selangor, Malaysia

Currently, there exists a limited comprehension regarding the correlation between COVID-19 and Alzheimer's disease (AD). To elucidate the interrelationship and its impact on outcomes, a comprehensive investigation was carried out utilising time-unrestricted searches of reputable databases such as Scopus, PubMed, Web of Science, and Google Scholar. Our objective was to evaluate the impact of various medical conditions on severe COVID-19-related events. We focused on identifying and analysing articles that discussed the clinical characteristics of COVID-19 patients, particularly those pertaining to severe events such as ICU admission, mechanical ventilation, pneumonia, mortality and acute respiratory distress syndrome (ARDS) a serious lung condition that causes low blood oxygen. Through careful data analysis and information gathering, we tried to figure out how likely it was that people with conditions, like AD, would have serious events. Our research investigated potential mechanisms that link AD and COVID-19. The ability of the virus to directly invade the central nervous system and the role of ACE-2 receptors were investigated. Furthermore, the OAS1 gene served as the genetic link between AD and COVID-19. In the context of COVID-19, our findings suggest that individuals with AD may be more susceptible to experiencing severe outcomes. Consequently, it is crucial to provide personalised care and management for this demographic. Further investigation is required to attain a comprehensive comprehension of the intricate correlation between Alzheimer's disease and COVID-19, as well as its ramifications for patient outcomes.

KEYWORDS

Alzheimer's disease, dementia, cognition, COVID-19, SARS-CoV-2

1 Introduction

The World Health Organisation (WHO) recorded more than 6.9 million fatalities as of June 26, 2023, and there were more than 768 million confirmed COVID-19 infections worldwide (Crook et al., 2021). In December 2019, an outbreak of pneumonia with an unknown origin was initially reported in Wuhan, Hubei Province, China (Sharma, 2021). Angiotensin-converting enzyme 2 (ACE-2) receptors are a route by which the virus that causes COVID-19, severe acute respiratory syndrome coronavirus 2 (SARSCoV-2), enters cells (Kumar et al., 2021). SARS-CoV-2 is a positive-strand RNA virus that is exceedingly contagious and calls for exceptional care to stop transmission (Sharma, 2021). Once inside the body, the virus replicates and matures,

causing an inflammatory response in some patients, including the activation and infiltration of immune cells by various cytokines (Crook et al., 2021). The ACE-2 receptor is present in many cell types throughout the human body, including the brain, liver, kidneys, spleen, lungs, oral and nasal mucosa, heart, gastrointestinal tract, and arterial and venous endothelial cells (Crook et al., 2021). This indicates how SARS-CoV-2 can harm various organs.

Alzheimer's disease (AD) is one of the world's most serious public health challenges, with nearly 10 million new cases diagnosed each year and approximately 50 million people affected worldwide (Esandi et al., 2021). Alzheimer's disease, in its advanced stages, can also impair a person's ability to walk and swallow due to widespread brain damage and functional decline. It is also a degenerative condition that decline the patient's condition on advances stages (Wee and Kumar, n.d.). Alzheimer's disease is believed to begin at least 20 years before symptoms appear (Alzheimer's Association, 2021). Individuals only notice symptoms like memory loss and language difficulties after years of brain changes (Che Ramli et al., 2022). Symptoms occur because of nerve cell (neurons) damage or destruction in areas of the brain involved in thinking, learning, and memory (cognitive function; Che Ramli et al., 2022). Neurons in other brain areas are also damaged or destroyed as the disease progresses (Alzheimer's Association, 2021). Neurons in areas of the brain that allow a person to walk, and swallow are eventually affected (Alzheimer's Association, 2021).

Multi-system organ failure affecting not just the pulmonary but also the cardiovascular, neurological, and other systems occur in COVID-19 patients (Reiken et al., 2022). According to recent research, COVID-19 may be related to neurodegenerative illnesses (Li et al., 2022). However, it is unclear whether a causal connection exists and how the effect will go (Li et al., 2022). The symptoms of acute cerebrovascular illness were caused by the virus's direct invasion of the CNS and involuntary SARS-CoV-2 increase in protein and angiotensin-converting enzyme 2 (ACE-2; Ciaccio et al., 2021). These symptoms include confusion, headache, hypogeusia/ageusia, hyposmia/anosmia, dizziness, epilepsy, and acute cerebrovascular illness. During post-mortem examinations, Patients with COVID-19 have SARS-CoV-2 RNA and antigens inside their brain tissue. In COVID-19 pathogenesis, ACE-2 expression is essential. ACE-2 is expressed in neurons, glial cells, endothelial cells, and smooth muscle cells of the arteries in the brain. The temporal lobe and the hippocampus, two cerebral areas involved in the aetiology of Alzheimer's disease, both express ACE-2 (Ciaccio et al., 2021).

2 COVID-19 and Alzheimer's disease related

Alzheimer's disease (AD) is acknowledged by the World Health Organisation (WHO) as a global public health concern (Lane et al., 2018). According to Zhang X. X. et al. (2021), AD is the primary cause of dementia and accounts for 50–70% of cases. The virus responsible for the global COVID-19 pandemic is the Severe Acute Respiratory Syndrome Coronavirus 2, commonly referred to as SARS-CoV-2 (Ciaccio et al., 2021). Recent research has demonstrated how COVID-19 affects the CNS and results in neurological problems (Fotuhi et al., 2020). As amyloid beta and neurofibrillary tangles (NFT) are accumulated, the hippocampus, which oversees memory and learning, deteriorates (Rahman et al., 2020). Patients with AD rely on their loved ones and carers to meet their requirements. Managing both Alzheimer's disease (AD) patients and their caregivers during the COVID-19 pandemic poses significant challenges. The protocols and measures required to manage COVID-19, such as isolation and social distancing, contradict the principles of Alzheimer's disease management. This incongruence between the two creates complex difficulties for individuals with AD and their caregivers (Rahman et al., 2020).

Additionally, Patients who recovered from severe COVID-19 infection are more likely to acquire stable neuropsychiatric and neurocognitive conditions like depression, obsessive-compulsive disorder, psychosis, Parkinson's disease, and Alzheimer's disease. The CNS may be harmed by SARS-CoV-2 directly by the release of neurotoxins or concomitantly through activation of the immune system, which may result in cellular senescence, neurodegeneration, and demyelination (Kumar, 2022). Additionally, research has demonstrated that SARS-CoV-2-infected AD patients had a higher mortality rate. In a study from the Department of Neuroscience at the University of Madrid, 204 participants with Frontotemporal Dementia (FTD) and Alzheimer's disease (AD) were enrolled. According to the study, 15.2% of these individuals had COVID-19 infection, and sadly, 41.9% of those who had the virus died as a result of their illness (Matias-Guiu et al., 2020).

Based on a recent study, the OAS1 gene is the genetic link between AD and catastrophic COVID-19 results. The study indicates the way oligoadenylate synthetase 1 (OSA1) contributes to a risk factor for AD by enhancing transcriptional networks, which are produced by the microglia (Magusali et al., 2021). By using both animal and human test subjects, they were able to determine that the OSA1 variant, rs1131435, increases the likelihood of acquiring AD (Magusali et al., 2021). Interestingly, this same genetic locus of OAS1 has also been found to have a connection with SARS-CoV-2, the virus causing COVID-19 (Magusali et al., 2021). According to the study, the single nucleotide polymorphism rs1131454(A) and rs4766676(T) are associated with AD, whereas rs10735079(A) and rs6489867(T) are associated with SARS-CoV-2 infections (Magusali et al., 2021). The study shows rs1131454 is inside linkage disequilibrium with newly identified single nucleotide polymorphisms associated with acute COVID-19 infections, suggesting that the spot controls of COVID-19 and AD risk (Magusali et al., 2021). The same study's functional experiment with human iPSC-derived microglia demonstrated how OSA1 levels control myeloid cells' pro-inflammatory response to increased interferon levels (Magusali et al., 2021). Therefore, individuals with lowered or impaired levels of OSA1 due to expressive quantitative trait loci (eQTL) variants could demonstrate an inflammatory response to COVID-19 as well as AD-associated pathology, which can trigger a 'cytokine storm' and potentially cause cell death and damage to neighbouring cells such as of the alveoli and neurons (Magusali et al., 2021).

In another study, researchers attempt to determine the neurochemical crosstalk between AD and COVID-19. According to studies, during the invasion, SARS-CoV-2 stimulates a neuroinflammatory cascade, astrogliosis, and microglia activation (Rahman et al., 2020). This causes the blood–brain barrier (BBB) to have cooperated due to the inflammation and disrupted homeostasis of the brain (Rahman et al., 2020). Inflammatory mediators are released due to infection of SARS-CoV-2, which is related to a higher

BBB permeability and heightened hypoxia (Wu et al., 2020). Acute encephalitis, infectious, toxic encephalopathy, and cerebrovascular attacks (CVAs) occur when the central nervous system (CNS) lacks histocompatibility antigen and predominantly depends on cytotoxic T lymphocytes (Wu et al., 2020). Acute encephalitis symptoms consist of headache and seizures, infectious, toxic encephalopathy symptoms include delirium and coma, as well as a greater risk of CAV caused by a cytokine storm generated by SARS-CoV-2 and coagulation problems (Wu et al., 2020). Additionally, this study examines and demonstrates the relationships between AD and COVID-19 with inflammatory signals such as interleukin 6 (IL-6), interleukin 1 (IL-1), and cytoskeleton-associated protein 4 (CKAP4).

Another link found between AD and COVID-19 is anosmia. The AD symptoms will become more obvious in old age (60 years or more; Mohammad Azizur et al., 2020). However, If AD's management is managed from an early-stage of Alzheimer's disease, the progression of these symptoms may be decreased (Mohammad Azizur et al., 2020). Moreover, the "anosmia" novel was an approach to diagnosing AD pathogenesis (Mohammad Azizur et al., 2020). People who carry the e4 allele of apo-lipoprotein E4 (Apo E4) have a higher risk of developing AD and anosmia (Manzo et al., 2021). Anosmia has become one of the most prevalent symptoms of people infected with SARS-CoV-2 (Mohammad Azizur et al., 2020). SARS-CoV-2 uses the ACE2 receptor on the cell's membrane to enter the cell, and the olfactory tissue has an abundance of ACE2 receptors (Mohammad Azizur et al., 2020). The loss of smell is an early indicator of COVID-19, and for AD, this proves that anosmia is the connection between AD and COVID-19 (Mohammad Azizur et al., 2020).

3 Biomarkers of cognition in COVID-19 and Alzheimer's disease

Restrictions on research due to the recency of COVID-19 have led to the discovery of various cytokines correlating with Alzheimer's disease. Through genome-wide association studies, it was discovered that ACE2 expression increased in the brain tissue of severely affected Alzheimer's Disease patients and posed a potential risk for Covid transmission (Ciaccio et al., 2021). This is because increased levels of ACE-2 will constitute an increase the risk of viral entry (Toniolo et al., 2021). Generally, ACE-2 is not just expressed in glial cells, neurons, and arterial and endothelial smooth muscle cells. Still, it is also indicated in the hippocampus and temporal lobe, which are the regions involved in the pathogenesis of AD (Ciaccio et al., 2021). Other than this biomarker, the apolipoprotein E ε4 genotype is also another important association between AD and Covid-19, as it is both a biomarker for Covid-19 increased severity and a genetic risk factor for late-onset AD (Frontera et al., 2022). Polymorphism APOE ε4 will also increase the risk of AD when the homozygous genotype of ε4 is associated with a 14-fold (Ciaccio et al., 2021). Those who are homozygous for APOE 4 have also demonstrated a greater prevalence of SARS-CoV-2 infection. According to Kuo (2020), APOE ε4 can increase the vulnerability to neurodegeneration and viral infection in our body. So, this will postulate SARS-CoV-2 infection in individuals with susceptible genetic variants (Ciaccio et al., 2021). The recent study done by UK-Biobank which has shown that APOE ε4 homozygotes have a 2.2-fold increased risk for the infection of Covid-19, and if it is a 4.3-fold case, it could turn into a fatal case (Toniolo et al., 2021).

Furthermore, systemic inflammation will activate astrocytes and microglia, which will then help to secrete pro-inflammatory cytokines, including IL-6, IL-1β, IL-12, and TNF-α. These biomarkers can cause synaptic dysfunction, potentially leading to AD, and inflammatory biomarkers like IL-6, galectin-3 (Gal-3), and IL-1 have been showing a linkage between AD and Covid-19 (Ciaccio et al., 2021). IL-6 represents not just a prognostic biomarker that is reliable in SARS-CoV-2 infection but also in AD. When the levels of IL-6 are increased, it will progress to AD and lead to worse cognitive performance, and this will cause a higher risk of developing severe Covid-19 and mortality (Ciaccio et al., 2021). When IL-6 interacts with IL-6R to exert biological effects, it could be soluble or expressed in the epithelial cells, immune membrane, and liver cells (Ciaccio et al., 2021). In the same way, glial cells and neurons produce the pro-inflammatory cytokine IL-1 (Ciaccio et al., 2021). In the brains of individuals affected by both Alzheimer's disease (AD) and COVID-19, there is an observed increase in the levels of IL-1 (Interleukin-1; Ciaccio et al., 2021). Since it is involved in the regulation of memory processes physiologically and physiologically regulation of hippocampal plasticity, Covid-19 patients may enhance cognitive decline, and this will lead them to develop AD in the future (Ciaccio et al., 2021).

In addition to these biomarkers, transforming the growth factor of beta 1 (TGFB1), a vascular cell adhesion protein 1 (VCAM1), and ras-related protein Rab-7a (RAB7A) are the additional biomarkers that have demonstrated a connection between AD and Covid-19 (Zhou et al., 2021). The blood expression level of an individual is favourably correlated with their performance on the high memory test, making RAB7A a potential biomarker for AD (Zhou et al., 2021). It is also a top host factor in SARS-CoV-2 datasets based on the CRISPR-Cas9 and a direct target of SARS-CoV-2's non-structural protein 7 (nsp7), which will aid in lowering SARS-CoV-2 entry into cells. VCAM1 is a target for treating age-related neurodegeneration since it is connected to changes in the white matter's structure and the severity of dementia (Zhou et al., 2021). In contrast to moderate individuals, significantly increased serum levels of VCAM were found in patients with severe COVID-19. Then there is TGFB1, a cytokine that regulates cell differentiation and growth. Through the analysis of a substantial dataset of RNA sequencing data obtained from peripheral blood mononuclear cells of individuals diagnosed with COVID-19, researchers discovered a noteworthy observation. The expression of TGFB1 (Transforming Growth Factor Beta 1) was found to be significantly reduced in patients with mild COVID-19 symptoms as well as those who required intensive care unit (ICU) level care, in comparison to individuals who were not affected by COVID-19 (Zhou et al., 2021). The infection of SARS-CoV-2 led to alterations in various Alzheimer's disease (AD) markers within peripheral blood mononuclear cells (PBMCs). These changes affected several proteins, including SERTA domain-containing protein 3 (SERTAD3), TGFB1, kinase D-interacting substrate of 220 kDa (KIDINS220), glutathione S-transferase M3 (GSTM3), arylsulfatase B (ARSB), insulin-like growth factor 1 (IGF1), and natural killer tumour recognition (Zhou et al., 2021). Among both Alzheimer's disease (AD) and COVID-19 patients, certain biomarkers exhibited changes in a similar direction, while others displayed alterations in a different direction. Notably, the expression of TNF receptor superfamily member 1B (TNFRSF1B) consistently showed changes in cerebrospinal fluid (CSF) samples

obtained from patients affected by both COVID-19 and AD (Zhou et al., 2021). In a recent study, researchers have identified and chosen three cerebrospinal fluid (CSF) markers, TNFRSF1B, CXCL10, and SPP1, along with three blood markers associated with Alzheimer's disease (AD), which are GSTM3, TGFB1, and NKTR. These markers have been specifically selected for their relevance and potential implications in understanding AD (Zhou et al., 2021). The findings of the recent study reveal that NKTR exhibits interactions with several host factors involved in SARS-CoV-1 and SARS-CoV-2, such as zinc finger CCCH-type containing 18 (ZC3H18), MERS-CoV, as well as casein kinase II subunit alpha (CSNK2A2). This highlights the potential significance of NKTR in the context of these viral infections (Zhou et al., 2021). These have demonstrated that SARS-CoV-2 infection would change some of the expression for the chosen AD markers, impacting various immune-related genes and perhaps causing the patients to experience neurologic impairment resembling AD (Zhou et al., 2021).

Besides, evidence suggests that Aβ peptides are one of the factors that increase the risks in Covid-19 patients to get diagnosed with AD, which these peptides act as antimicrobial peptides (Ciaccio et al., 2021). Loss of pericytes and endothelial dysfunction will reduce the cerebral metabolites' clearance, including Aβ peptides (Ciaccio et al., 2021). As a result, there will be an accumulation and excess of Aβ protein in the senile plaques, especially in the hippocampus, representing the main pathophysiological mechanism underlying AD (Ciaccio et al., 2021). To diagnose of AD depends on the detection that we get from the CSF biomarker profile, which are the ratio Aβ 1–42/1–40, decrease in amyloid beta 1–42 (Aβ 1–42), and the increase of p-Tau and t-Tau levels (Ciaccio et al., 2021). T-tau protein is a biomarker of neuronal damage or death, and according to Ciaccio et al., some of the authors have found that there was an increase of CSF t-Tau levels in COVID-19 patients, in which the increased levels of this biomarker will cause several neurodegenerative diseases, including AD (See Figure 1; Ciaccio et al., 2021). Furthermore, in severe COVID-19 patients, it is found to have increased levels of Gal-3, and this will progress COVID-19 due to lung fibrosis and hyper-inflammation reaction (Ciaccio et al., 2021). In AD patients' serum, it has also been found to have increased levels of Gal-3 (Ciaccio et al., 2021). Gal-3, a lectin-family member that binds carbohydrates, is crucial for pathological and physiological processes like fibrosis and inflammation (Ciaccio et al., 2021). Gal-3 is thought to be involved in aggregation and the production of amyloid plaques. Therefore, the elevated levels in Covid-19 patients may harm them and eventually result in the development of AD (Ciaccio et al., 2021).

4 Prevention and treatment

According to the World Health Organisation (WHO), the second-highest neurological disorder that affects people worldwide happens to be Alzheimer's disease (AD). Due to this, many of these Alzheimer's patients may face various conditions or complications if they get affected by the COVID-19 coronavirus. In terms of prevention and treatment, no outright cure is known for AD. Still, there are several ways to slow down the progression of Alzheimer's in patients affected by COVID-19 since it is known to speed up AD progression. There are also ways to reduce the risk of an elderly patient with COVID-19 from developing Alzheimer's. Firstly, anti-inflammatory therapy can be carried out. According to Wang et al. (2021), Systemic inflammation from COVID-19 and AD is brought on by a rise in TNF- and other pro-inflammatory chemicals. Studies on anti-inflammatory treatments conducted in mice, rats, and monkeys demonstrate favourable outcomes (Wang et al., 2021). It has been demonstrated that using TNF inhibitors as a treatment reduces neurofibrillary tangles, amyloid precursor protein, and amyloid beta (A) plaques and functions as an important immune modulator that aids in the prevention of AD (Wang et al., 2021). In addition to TNF inhibitors, a different study discovered that long-term usage of non-steroidal anti-inflammatory medicines could suppress the microglial activation brought on by A oligomers that cause neuronal ectopic cell cycle events, which will aid in preventing the onset of AD (Wang et al., 2021).

Next, another method that can be used is antioxidant therapy. Antioxidant therapies can help Alzheimer's patients with COVID-19 as both these diseases are known to increase oxidative stress on the human body (Wang et al., 2021). Certain antioxidants, such as vitamin E and its derivatives, were shown to mitigate oxidative stress and mitochondrial dysfunction in brain cells (Wang et al., 2021).

Anticholinesterase Inhibitors and Memantine are frequently used in COVID-19 Infected Alzheimer's Patients (Brown et al., 2020). Anticholinesterase inhibitors, which are also known as cholinesterase inhibitors, are a type of drug that will reduce the breakdown of acetylcholine, which is a neurotransmitter that is found in the brain and the nervous system. As for memantine, it is a medication that helps to slow down the progression of AD. For dementia (BPSD), behavioural and psychological symptoms that could compromise isolation efforts, such as motor agitation, intrusiveness, or wandering, medications such as antidepressants, antiepileptics, and other psychotropic medications are commonly used as well (Brown et al., 2020). For COVID-19, some potential drugs such as hydroxychloroquine (HCQ) and chloroquine (CQ) could interact with the cholinesterase inhibitors, which could lead to the alteration of the pharmacological function of the cholinesterase functions (Xia et al., 2021). It can increase the chance of toxic side effects and adverse events such as bradycardia, gastrointestinal issues, falls, fractures, heart attacks, or strokes (Balli et al., 2020).

Nutritional intervention is also another method that was also recently found to be useful in slowing down AD progression and prevention as well. Nutritional interventions were shown to reduce the rate of occurrence and severity of AD through modulation of the flora of the gut and cerebral Aβ production (Wang et al., 2021). Prebiotics, like wheat bran, has been shown to reduce neuroinflammation, encourage the growth of commensal bacteria, positively influence the gut-brain axis, and delay the onset and progression of AD (Wang et al., 2021). Other than nutritional interventions, physical exercise is also a viable option as it is shown to prevent several AD risk factors. Physical exercise's main benefit will be the anti-inflammatory and antioxidative effects and greater cerebral blood flow (Wang et al., 2021).

Another method that may be effective may be controlling blood glucose levels. Both AD and diabetes mellitus have the same pathophysiological factors, such as severe inflammation, oxidative stress, and dysfunction of the mitochondria (Wang et al., 2021). COVID-19 can cause the development of dysglycemia and possibly type 1 Diabetes Mellitus (Wang et al., 2021). As a result, AD may subsequently develop because of this. Fiore et al. (2019) demonstrate how hyperglycemia and hypoglycemia can result in cognitive

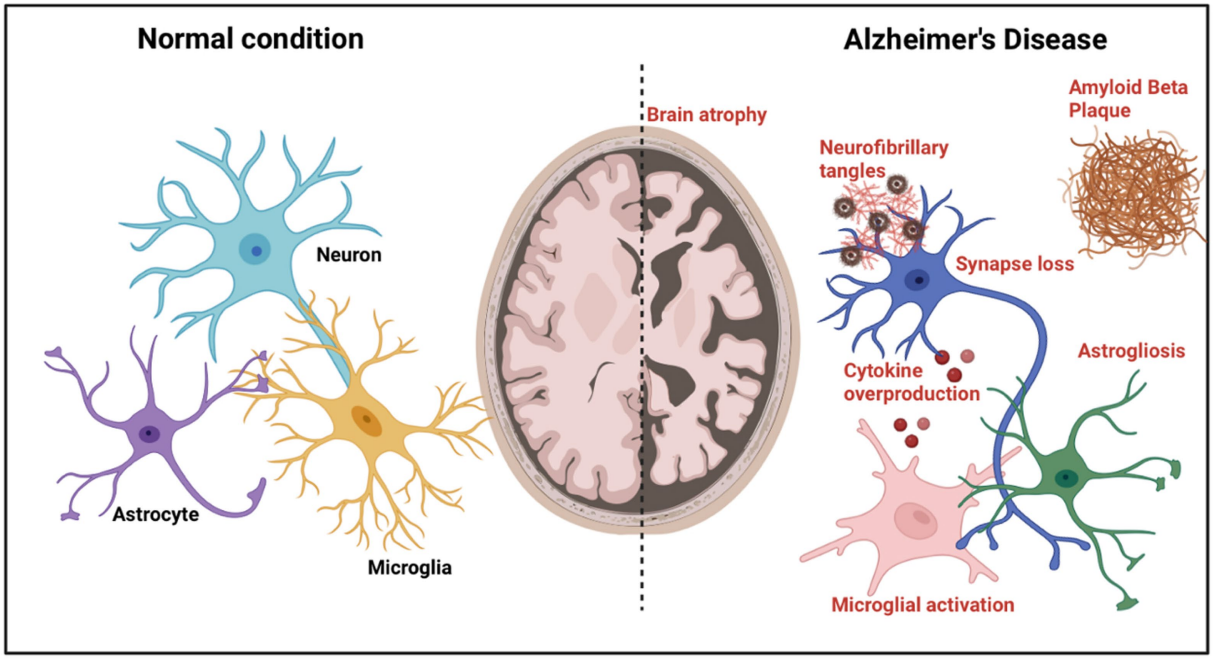


FIGURE 1
Alzheimer's disease pathological features. A diagram depicting the pathogenic alterations in AD brains compared to normal brains. Brain atrophy caused by neuronal loss is visible at the gross anatomical level. At the microscopic level, toxic amyloid-β, intraneuronal neurofibrillary tangle development, synaptic loss, activation of microglia, astrogliosis, cytokine overproduction, and neurite dystrophy are detected.

impairment and AD. Hence, methods for controlling blood glucose levels may positively benefit Alzheimer's patients with COVID-19 by minimising the risk of AD or slowing down its progression.

5 COVID-19 long-term effects on Alzheimer's disease patient

Elderly people with Alzheimer's disease and other dementias are more vulnerable to the COVID-19 pandemic (Palmieri et al., 2020). Research by Luigi et al. has carried out a study to examine symptoms and pre-existing comorbidities by analysing clinical reports of COVID-19 deaths. The results suggested comorbidities are related to a higher mortality risk and negative consequences in COVID-19 patients (Palmieri et al., 2020). Moreover, it is shown that SARS-CoV-2 can damage the peripheral and the central nervous system through both direct and indirect pathways, potentially leaving COVID-19 patients at higher risks for neurological difficulties, including depression, Parkinson's disease, AD, etc., after recovering from severe symptoms (Palmieri et al., 2020). Severe symptoms of COVID-19 in patients with pre-existing dementia can be explained through several reasons (Mok et al., 2020). Firstly, demented patients are prone to have a high viral load as it is comparatively more difficult for them to understand the importance of standard operating procedures (SOPs) and to comply with public health measures (Mok et al., 2020). Second, the important population of AD patients takes residence in care homes where the infection is likely to spread (Mok et al., 2020). Lastly, COVID-19 causes a secondary effect on underlying brain pathologies as SARS-CoV-2 has been shown to trigger or accelerate neurodegeneration processes that possibly explain long-term neurodegenerative effects in the elderly population (Vincent).

5.1 Non-neurological effects of COVID-19 on AD patients

In response to the impact of COVID-19 in 2020, governments worldwide acted promptly by implementing various public health measures. These measures included the enforcement of movement restriction orders, mandatory wearing of face masks in public settings, and the promotion of social distancing to mitigate the spread of the virus (Vincent, 2020). During this period, people with cognitive impairments such as dementia or AD may experience greater stress and anxiety due to sudden changes in the environment and people's behaviour (Vincent, 2020). Movement controls during quarantine cause AD patients to be restricted to confined spaces which can further lead to depression or apathy (Palmieri et al., 2020). The pandemic and quarantine also cause AD patients to be isolated in hospital environments or care homes, away from their family and friends, increasing the risk for further dementia-related decline (Palmieri et al., 2020). It is also significantly harder for AD patients to comprehend and execute defensive measures such as wearing face masks and sanitising frequently (Mok et al., 2020). Patients with agitation and wandering conditions are exposed to higher risks of infection (Mok et al., 2020).

Furthermore, physical distancing does not apply to AD patients as they depend on caregivers to carry out daily tasks such as bathing. In contrast, some patients reside in care houses where patients live close to other people (Mok et al., 2020). This makes them more

vulnerable to infection than non-demented people (Palmieri et al., 2020). AD patients are usually diagnosed with age-related sensory deficits and perceptual troubles (Gil and Arroyo-Anlló, 2021). This leads to prosopagnosia, commonly known as face blindness or the inability to recognise other people through their morphological structures of faces (Gil and Arroyo-Anlló, 2021). Wearing face masks during the pandemic has become a common practice. Still, it increases the difficulty for AD patients to recognise their family members and friends as the face is partially concealed (Gil and Arroyo-Anlló, 2021). Fragmented perception of the face also reduces the ability of AD patients to discriminate facial emotions (Gil and Arroyo-Anlló, 2021).

5.2 Neurological effects of COVID-19 on AD patients

Studies have shown that COVID-19 will likely leave long-term neurological complications in patients who survive and recover from the infection (Chen et al., 2022). Meanwhile, neuroinflammation is suggested to be the underlying cause of neurological complications and the important bridge between COVID-19 and AD (Finelli, 2021; Chen et al., 2022). There are a few potential mechanisms that increase the risk of developing long-term neurological consequences, leading to the acceleration of pre-existing AD progression or initiating AD development in COVID-19 patients (Iodice et al., 2021). These potential mechanisms include Renin-angiotensin system (RAS) hyperactivation, systemic inflammation, and damage to the CNS by direct viral infection (Heneka et al., 2020).

COVID-19 neurological effects research has highlighted a need for a better knowledge of how the virus may damage brain health and may contribute to the advancement of Alzheimer's disease. Table 1 shows recent clinical investigations reveal that people with Alzheimer's disease may be more likely to have serious problems if they contract COVID-19.

TABLE 1 Clinical findings between alzheimer's disease and COVID-19.

Type of COVID-19 sample	Clinical findings	References
A study conducted among the UK Biobank community.	-Delirium being a leading symptom -Mortality rate was higher among patients	Rudnicka-Drożak et al. (2023)
COVID-19 patients with ARDS and neurological manifestations admitted to an ICU.	-Prevalence of cognitive impairment: 100%	Chaumont et al. (2020)
Patients admitted to an ICU with ARDS due to COVID-19.	-Prevalence of dysexecutive syndrome at discharge: 36%	Helms et al. (2020)
COVID-19 hospitalised patients admitted to a neurology unit or with neurological symptoms.	-Prevalence of short-term memory loss: 24%	Pinna et al. (2020)
CoroNerve Platform COVID-19 hospitalised patients with neurological manifestations.	-Prevalence of neurocognitive disorder: 4.8%	Varatharaj et al. (2020)

ARDS, Acute respiratory distress syndrome; ICU, Intensive care unit; UK, United Kingdom.

5.2.1 Renin-angiotensin system hyperactivation

The renin-angiotensin system (RAS) remains a hormone system that regulates blood pressure, electrolyte balance, and vascular resistance (Wang et al., 2021). The RAS contained in the pathogenicity of COVID-19 is angiotensin-converting enzyme 2 (ACE2), which acts as a critical point for SARS-CoV-2 and belongs to part of this system (Sarzani et al). Within the RAS, ACE2 regulates blood pressure by converting angiotensin 2 (Ang-II) into angiotensin (Ang), thus inhibiting the RAS pathway (Wang et al., 2021). During an infection, ACE2 binds to the protein of spike from SARS-CoV-2, causing a reduction in enzymatic function (Wang et al., 2021). As a result, Ang-II levels are increased, disturbing the signalling pathway in RAS and promoting brain degeneration (Wang et al., 2021). Moreover, the binding of the SARS-CoV-2 and ACE2 triggers the formation of a cytokine storm, characterised by increasing stages of IL-1, IL-6, and TNF (El-Arif et al., 2021). Another way through which SARS-CoV-2 can cause RAS hyperactivity in the brain through stimulating the production of neurotoxins and proinflammatory factors (Wang et al., 2021). RAS hyperactivation caused by elevated Ang-II leads to microglial inflammatory response and oxidative stress, favouring AD development (Wang et al., 2021). Ang-II activates NLRP3 inflammasome, which, as mentioned, is a key mediator in AD (Miners et al., 2020). Meanwhile, RAS hyperactivation also impairs Aβ clearance (Miners et al., 2020). These factors altogether contribute to AD development (Miners et al., 2020). However, ACE2 expression and the consequence on AD pathology remains controversial and requires support from further studies (Chen et al., 2022).

5.2.2 Systemic inflammation

Severe systemic inflammation caused by SARS-CoV-2 is predicted to have long-term negative consequences like cognitive impairment (Finelli, 2021). SARS-CoV-2 infection causes immune system dysfunction, which can lead to suppression of neurogenesis, synaptic damage, and neuronal death, all of which are associated with the aetiology of Alzheimer's disease (Chen et al., 2022).

5.2.2.1 Cytokine storm

Cytokines are messenger molecules immune cells produce (Rahman et al., 2020). It alters the function of proteins and changes the gene expression of receptor molecules (Ragab et al., 2020). Proinflammatory cytokines endorse inflammation, while anti-inflammatory cytokines decrease inflammation (Ragab et al., 2020). Further, cytokines are categorised based on their functions into 4 major groups, which are Interleukins (IL), Tumour Necrosis Factor (TNF), and Interferons and Colony Stimulating factors (CSF; Ragab et al., 2020).

During an infection, the invasion of SARS-CoV-2 stimulates humoral and cell-mediated immunity to battle infection (Hu et al., 2021). However, a deadly and uncontrolled inflammatory response known as the 'cytokine storm' can lead to the fast secretion of pro-inflammatory cytokines, creating an inequity between pro-inflammatory cytokines and anti-inflammatory cytokines (Ragab et al., 2020). The cytokine storm increases vascular

permeability and abnormal blood coagulation. It explains the multi-organ damage found in COVID-19 patients (Wang et al., 2020), as the effects of SARS-CoV-2 in CNS also explained as the cytokines can attack brain regions, resulting in harm to healthy neurons (Hardan et al., 2021). Moreover, Proinflammatory cytokines like interleukin (IL)-1β, IL-17, IL-6, also tumour necrosis factor-α (TNF-α) that are involved in AD development are significantly elevated in cerebrospinal fluid of COVID-19 patients (Finelli, 2021; Wang et al., 2021). High levels of IL-1β decrease hippocampal neurogenesis and increase apoptosis (Boldrini et al., 2021) IL-17 targets neutrophils, promoting inflammation and brain tissue damage (Wang et al., 2021). TNF-α links peripheral and central inflammation and modulates neuropathological mechanisms in AD. In contrast, higher stages in COVID-19 individuals are associated with a higher percentage of cognitive impairment months after infection (Finelli, 2021). Elevated levels of IL-6 are related to hippocampus shrinkage and decreased human cognitive performance, one of the early symptoms of AD (Mohammad Azizur et al., 2020). Acknowledge a nucleic acid, which contains amyloid fibrils, Type I interferons (IFN) mediate inflammation, ultimately leading to synaptic loss, an effect that is strongly related to cognitive decline (Hardan et al., 2021). Through these mechanisms, proinflammatory cytokines play a significant part in AD progression (Wang et al., 2021).

5.2.2.2 NLRP3

Inflammasomes are multiprotein complexes that build or activate cytokines during an inflammatory response. An inflammasome called NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) controls inflammatory signalling and the release of proinflammatory cytokines IL-1 and IL-18 (Wang et al., 2021). Initiating caspase-1 self-cleavage to create active caspase-1 when NLRP3 is activated is crucial for the maturation of IL-1 and IL-18 (Wang et al., 2021). Inflammasome activation may occasionally result in cell death (Mark et al., 2021). Although inflammasomes are beneficial immune responses to infections, at the same time, they might also cause collateral damage to recipient cells due to hyperinflammatory responses and are also known to be the key mediator of AD development. (Ding et al., 2018; Mark et al., 2021) In a COVID-19 patient, overstimulation in the NLRP3 inflammasome pathway leads to a systemic inflammatory response during infection (Wang et al., 2021). Consequently, the impairment of useful immune functions in the brain is caused by the NLRP3 inflammasome-driven inflammation and aberrant accumulations of peptides linked to neurodegeneration, such as fibrillar amyloid (Finelli, 2021). A work by Ising et al. (2019) showing that NLRP3 inflammasome produces hyperphosphorylation and aggregation and is crucial for the emergence and advancement of beta-amyloid pathology in mice supports this. Additionally, it has been demonstrated that NLRP3 inflammasome activation encourages tau pathology, which speeds up the development of AD (Chen et al., 2022).

Through both direct and indirect processes, including ARDS, hypercapnia, and ORF3a protein-mediated activation, SARS-CoV-2 has been exposed to raise NLRP3 levels (Ren et al., 2020). In the study by Ren et al. (2020), NLRP3 inflammasome was discovered for the first time in similarly stimulated epithelial cells infected with SARS-CoV-2. Furthermore, the SARS-CoV genome encodes three ion channel proteins, namely ORF3a, ORF8a, and E (Ren et al., 2020). It is noteworthy that ORF3a plays a role in virus-host interactions. The secretion of the proinflammatory cytokine IL-1 and the activation of the NLRP3 inflammasome by the SARS-CoV-2 ORF3a protein leads to the demise of respiratory tract epithelial cells (Xu et al., 2022). This conclusion is further supported by the observation that lung alveolar epithelial cells obtained from autopsy samples of COVID-19 patients who passed away exhibit significant activity of the NLRP3 inflammasomes (Toldo et al., 2021).

Acute respiratory distress syndrome is a common complication in severe COVID-19 patients, and it is caused by dysregulated hyperinflammation caused by SARS-CoV-2 (Wang et al., 2021). Invasion of the virus stimulates innate immune response and activates NLRP3 inflammasome (Wang et al., 2021). The NLRP3 inflammasome then functions to mediate lung inflammation in SARS-CoV-2 infection. As stated, SARS-CoV-2 targets ACE2 receptors found on type II alveolar epithelial cells, causing them to undergo cell apoptosis (Mark et al., 2021). Signals of cellular damage or stress released can lead to NLRP3 inflammasome activation (Mark et al., 2021). Activation stimuli of NLRP3 inflammasome include foreign matter, extracellular adenosine triphosphate (ATP), toxins, and mitochondrial processes (Mark et al., 2021). During an infection, alveolar macrophages initiate a proinflammatory response which triggers the secretion of cytokines like TNF-α and IL-1β (Freeman and Swartz, 2020). Secretion of these cytokines induces a widespread NLRP3 activation to form a proinflammatory positive feedback cascade (Freeman and Swartz, 2020). Hypercapnia, defined by high levels of arterial carbon dioxide, is a side effect caused by protective lung ventilatory strategies used to treat severe ARDS patients (Freeman and Swartz, 2020). However, it is shown that hypercapnia can also activate NLRP3 inflammasomes to induce IL-1β overproduction, which is linked to neuroinflammation, increased neuronal cell death, and contributes to the pathogenesis of cognitive impairments (Freeman and Swartz, 2020).

5.2.2.3 Oxidative stress

Reactive oxygen species (ROS) encompass a group of chemically reactive oxygen-containing molecules, including peroxides, superoxide, hydroxyl radicals, and more, that are produced during instances of inflammation (Ionescu-Tucker and Cotman, 2021). The existence of an unpaired valence electron makes ROS free radicals attack the different cells and damage DNA, proteins, and lipids (Ionescu-Tucker and Cotman, 2021). In contrast, antioxidants are chemicals that lessen the effect of free radicals (Wang et al., 2021). An imbalance in the amount of ROS and antioxidants within the human body causes oxidative stress, which plays a part in both the pathogenesis of SARS-CoV-2 infection and AD (Wang et al., 2021). This suggests that SARS-CoV-2 might contribute to AD through an oxidative stress mechanism (Wang et al., 2021).

During SARS-CoV-2 infection, angiotensin-converting enzyme 2 (ACE2) binds its viral protein, increasing Ang-II (Kumar et al., 2022). As Ang II acts as an oxidative stress enhancer, the increased presence of Ang-II promotes the presence of ROS and creates oxidative stress in the body (Meinhardt et al., 2021). In comparison, decreased ACE2 is also related to the production of ROS in CNS (Meinhardt et al., 2021). ROS are harmful as they can cause lipid peroxidation and mitochondrial dysfunction (Meinhardt et al., 2021). To gain stability, ROS can donate an electron to a nearby lipid molecule from the phospholipid bilayer (Butterfield, 2020). This

causes the lipid molecules to become reactive and initiate a chain reaction that results in cell membrane damage and lysis (Butterfield, 2020). In addition, oxidative damage is a major character in the brain of AD patients. At the same time, studies suggest that lipid peroxidation is the first type of oxidative damage associated with amyloid β (Aβ). This amino acid is critical to the pathophysiology of AD (Butterfield, 2020).

In the mitochondria, superoxide radicals are created by-products of the electron transport chain (Ionescu-Tucker and Cotman, 2021) naturally. Excessive mitochondrial ROS can cause damage to the electron transport chain, subsequent in increased generation of superoxide radicals in a positive feedback cycle (Ionescu-Tucker and Cotman, 2021). Frequent damage to the mitochondria eventually results in degradation (Ionescu-Tucker and Cotman, 2021). Significantly, dysfunctional mitochondria are one of the first markers and a vital cause of Alzheimer's disease (Ionescu-Tucker and Cotman, 2021). Loss of mitochondrial function interferes with the expression and processing of amyloid precursor protein (APP) and facilitates the formation of beta-amyloid plaques (Ionescu-Tucker and Cotman, 2021). This relationship further demonstrates the possible role of the virus in the expansion of AD and other associated neurodegenerative diseases (Ionescu-Tucker and Cotman, 2021).

5.2.3 Damage to the CNS by a direct viral infection

According to studies, SARS-CoV-2 can penetrate the CNS and cause neuroinflammation and neuronal damage, which aids in the emergence of neurodegenerative disorders like Alzheimer's disease (Wang et al., 2020). The blood–brain barrier (BBB), olfactory nerve channels, and trans-synaptic routes are possible routes by which SARS-CoV-2 could enter the brain (Zhang Q. et al., 2021).

A complex system called the Blood–Brain Barrier (BBB) encircles most of the brain's blood vessels (kadry et al). By serving as a barrier between the bloodstream and the brain's extracellular space, it regulates the flow of substances between them (Zhang Q. et al., 2021). The BBB protects most blood vessels in the brain, except for blood vessels in circumventricular organs (CVO), as their function requires access to the bloodstream (Zhang Q. et al., 2021). Recent research has shown that SARS-CoV-2 can infect ACE2 receptors on the vascular endothelium of the BBB, allowing blood material to reach the brain (Zhang Q. et al., 2021). By causing instability or by way of monocytes, the activation of inflammatory cytokines might raise the BBB's permeability and allow the entry of cytokines and SARS-CoV-2 into the brain parenchyma (Zhang Q. et al., 2021) as shown in Figure 2.

Reactive astrogliosis, microglial activation, and a neuroinflammatory cascade are brought on by SARS-CoV-2 upon invasion (Iodice et al., 2021). Disruption of brain homeostasis and neuronal death damages the function of BBB, leading to long-term neuropsychiatric consequences (Iodice et al., 2021). Furthermore, the virus can reach brain tissue via CVOs and has been found in brain vascular endothelium (Boldrini et al., 2021). CVO and brain stem viral infection explains COVID symptoms such as ageusia, nausea, and vomiting, as also autonomic abnormalities, and anxiety (Boldrini et al., 2021). Due to the penetration of blood content, viral particles can enter and damage neurons directly as ACE2 receptors are present (Majid et al., 2021). In addition, recent studies have shown that immune cells that express ACE2 receptors, such as lymphocytes, granulocytes, monocytes, and monocyte derivatives, provide another pathway for entering through the BBB through a trojan horse mechanism (Wang et al., 2020). The SARS-CoV-2 will enter the cytoplasm of these immune cells and cross the BBB to access the CNS for replication (Pezzini and Padovani, 2020).

Several types of research have shown trans-synaptic transfer through peripheral nerve terminals (Pezzini and Padovani, 2020). By binding to ACE2 receptors on peripheral neurons, it can spread through the axonal endoplasmic reticulum over large distances (Fenrich et al., 2020). Additionally, SARS-CoV-2 can penetrate the CNS via the olfactory route, which explains the loss of smell in COVID-19 patients (Meinhardt et al., 2021; Chen et al., 2022). As a part of the respiratory system, the olfactory mucosa is in the upper region of the nasal cavity (Wang et al., 2020). The olfactory epithelium consists of 10–20 million olfactory receptor neurons that detect the sense of smell (Wang et al., 2020). Unsurprisingly, the entry proteins ACE2 and TMPRSS2 involved in the binding of SARS-CoV-2 are found in abundance in these olfactory receptor neurons (Wang et al., 2020). Following infection, the virus binds to ACE2 receptors on olfactory receptor neurons, spreads through the olfactory bulb, and eventually reaches the hippocampus and other brain structures (Pezzini and Padovani, 2020). Notably, the hippocampus is one of the brain areas affected during the early stages of AD progression (Iodice et al., 2021).

Regardless of the pathway used by SARS-CoV-2, it enters the CNS and initiates viral replication, resulting in neuronal cell death and immune system activation in the brain, which may explain the acute symptoms of COVID-19 and long-term complications of SARS-CoV-2 infection in Alzheimer's disease patients (Wang et al., 2020).

5.3 The comparison of AD patients with COVID-19 and AD patients without COVID-19

Based on the selected reviews, we have compiled a table (Table 2) that compares AD patients with COVID-19 to AD patients without COVID-19. According to a study by Frontera et al. (2022), hospitalised COVID-19 patients exhibited greater levels of neurodegenerative biomarkers than non-COVID subjects with normal cognition, mild cognitive impairment, or Alzheimer's dementia. The results showed that various neurodegenerative biomarkers, including t-tau, p-tau181, UCHL1, GFAP, and NfL, were raised in hospitalised COVID-19 patients. The Table 2 provides an overview of various biomarkers and pathological features in Alzheimer's disease (AD) patients with and without COVID-19 infection. The findings suggest that COVID-19 infection has a significant impact on the pathogenesis of AD, leading to alterations in inflammatory responses, oxidative stress, ACE2 functions, and neurodegenerative biomarkers. Notably, the presence of COVID-19 in AD patients appears to exacerbate some of the AD-related pathological changes, such as increased proinflammatory cytokines, NLRP3 activation, and oxidative stress. Additionally, direct viral infection in AD patients with COVID-19 leads to damage to the central nervous system, which can accelerate AD progression. These observations highlight the importance of monitoring AD patients who contract COVID-19 and considering potential implications for disease management and intervention

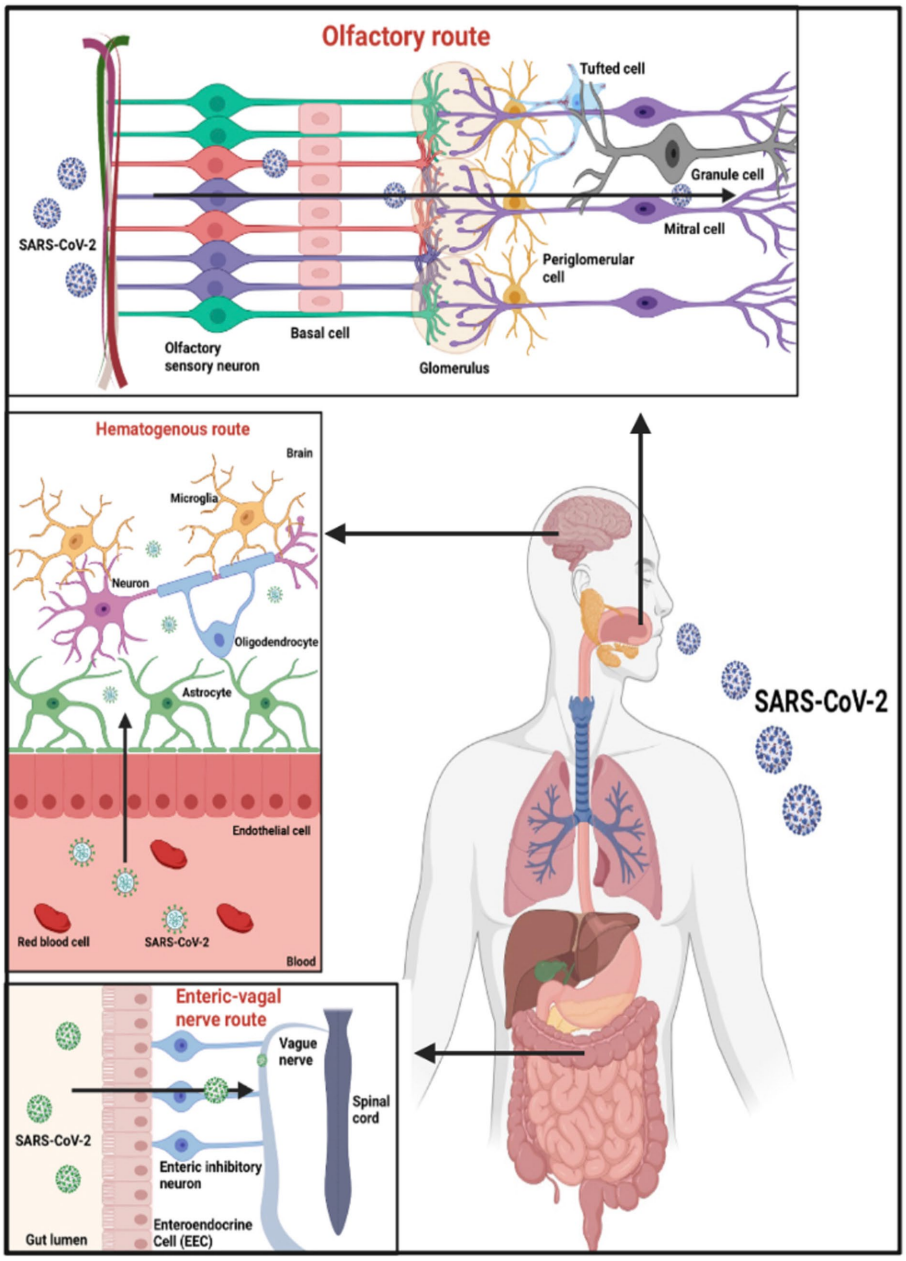


FIGURE 2
Potential entry points for SARS-CoV-2 entering the CNS. Based on the tissue/cell expression patterns of the viral binding receptor ACE2 and cell entry-associated proteases TMPRSS2 on the olfactory epithelium, myelin-forming cells, enteric neurons, and vascular endothelium, it is possible that SARS-CoV-2 enters the human blood–brain barrier through the neural route of myeline sheaths of olfactory, enteric, and vagal nerves, as well as the hematogen.

strategies. Further research is needed to elucidate the underlying mechanisms and long-term consequences of COVID-19 on AD pathology.

6 Conclusion

In conclusion, COVID-19 has generated a worldwide outbreak, resulting in a slew of issues for humans, particularly those suffering from Alzheimer's disease. Its ability to invade the central nervous system through the hematogenous and neural routes, besides attacking the respiratory system, has the potential to worsen cognitive decline in Alzheimer's disease patients. Apart from that, the impact of Covid-19 on the brain can be concluded to be like the impact given by Alzheimer's Disease, as these both cause inflammation. This inflammation, if left untreated, could surely predispose someone who had Covid-19 before to develop Alzheimer's later, especially if they were seriously infected and experienced long-covid symptoms. Hence, Covid-19 worsens the cognitive decline or impairment in patients with Alzheimer's and increases the risk of those who had a Covid-19 infection towards developing Alzheimer's later in life. The severity of this issue must be highlighted.

TABLE 2 Comparison of AD patients with and without COVID-19 based on relevant biomarkers and pathological features.

	AD patients with COVID-19	AD patients without COVID-19	
Proinflammatory cytokines	Cytokine storm greatly increases number of proinflammatory cytokines such as IL-6 and TNF-alpha.	no significant difference in cytokine levels	Frontera et al. (2022)
NLRP3	SARS-CoV-2 induces activation of NLRP3, increasing NLRP3 levels.	no significant difference in NLRP3 levels	Ding et al. (2018)
ACE2	ACE2 enzymatic functions is reduced.	Functions and number of ACE2 unaffected	Ding et al. (2018)
Oxidative stress	Higher	Lower	Suhail et al. (2020)
Damage to the CNS	Direct viral infection damages the blood–brain barrier and damages brain tissue, accelerating AD progression.	Neurological complications contributing to AD progression at normal pace.	Kadry et al. (2020)
Neurodegenerative biomarkers	t-tau, p-tau181, GFAP, and NfL significantly increased after COVID-19 infection	Lower when compared to AD patients with COVID-19 (same-age group)	Kadry et al. (2020)

Moreover, being the most common and prominent type of dementia, Alzheimer's damage to our cognitive system is beyond our knowledge, and Covid-19 infections further worsen it. Though many research papers are looking at the effects of COVID-19 concerning neurological diseases, such as Alzheimer's, a definite conclusion has yet to be proven. In this paper, the possible effects of COVID-19 concerning AD, as well as the effects of COVID-19 on AD patients, have been explored. A correlation between the two ailments can be hypothesised. However, still, no finalised answer can be made as to whether one of the aftermath conditions of COVID-19 is a neurological disorder such as Alzheimer's disease.

Author contributions

SS: Writing – original draft, Resources. MR: Writing –review & editing, Supervision. SK: Writing – review & editing, Software.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. Funding by Management & Science University (MSU) SEEDS Grant Number: MPCG-007-022023-FHLS.

Acknowledgments

Authors would like to thank support of research management centre, Management and Science University, Shah Alam, Malaysia.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Alzheimer's Association (2021). 2021 Alzheimer's disease facts and figures. *Alzheimers Dement* 17, 327–406. doi: 10.1002/alz.12328

Balli, N., Kara, E., and Demirkan, K. (2020). Another side of COVID-19 in Alzheimer's disease patients: drug-drug interactions. *Int J Clin Pract* 74:e13596. doi: 10.1111/ijcp.13596

Boldrini, M., Canoll, P. D., and Klein, R. S. (2021). How COVID-19 affects the brain. *JAMA Psychiatry* 78, 682–683. doi: 10.1001/jamapsychiatry.2021.0500

Brown, E. E., Kumar, S., Rajji, T. K., Pollock, B. G., and Mulsant, B. H. (2020). Anticipating and mitigating the impact of the COVID-19 pandemic on Alzheimer's disease and related dementias. *Am J Geriatr Psychiatry* 28, 712–721. doi: 10.1016/j.jagp.2020.04.010

Butterfield, D. A. (2020). Brain lipid peroxidation and alzheimer disease: synergy between the Butterfield and Mattson laboratories. *Ageing Res Rev* 64:101049. doi: 10.1016/j.arr.2020.101049

Chaumont, H., San-Galli, A., Martino, F., Couratier, C., Joguet, G., Carles, M., et al. (2020). Mixed central and peripheral nervous system disorders in severe SARS-CoV-2 infection. *J Neurol* 267, 3121–3127. doi: 10.1007/s00415-020-09986-

Che Ramli, M. D. B., Md Nazrey, N. A. S. B., Mohd Uzid, M. B., Weinheimer, A. Z., Nizam, N. B. B., Mazlan, N. N. B., et al. (2022). The effects of *Clitoria ternatea* extract on zebrafish model of Alzheimer's disease: a Neurobehavioural study. *Sains Malaysiana* 51, 803–814. doi: 10.17576/jsm-2022-5103-14

Chen, F., Chen, Y., Wang, Y., Ke, Q., and Cui, L. (2022). The COVID-19 pandemic and Alzheimer's disease: mutual risks and mechanisms. *Translational neurodegeneration* 11:40. doi: 10.1186/s40035-022-00316-y

Ciaccio, M., Lo Sasso, B., Scazzone, C., Gambino, C. M., Ciaccio, A. M., Bivona, G., et al. (2021). COVID-19 and Alzheimer's disease. *Brain Sci* 11:305. doi: 10.3390/brainsci11030305

Crook, H., Raza, S., Nowell, J., Young, M., and Edison, P. (2021). Long covid—mechanisms, risk factors, and management. *BMJ* 374:648. doi: 10.1136/bmj.n1648

Ding, H. G., Deng, Y. Y., Yang, R. Q., Wang, Q. S., Jiang, W. Q., Han, Y. L., et al. (2018). Hypercapnia induces IL-1beta overproduction via activation of NLRP3 inflammasome: implication in cognitive impairment in hypoxemic adult rats. *J Neuroinflammation* 15:4. doi: 10.1186/s12974-017-1051-y

El-Arif, G., Farhat, A., Khazaal, S., Annweiler, C., Kovacic, H., Wu, Y., et al. (2021). The renin-angiotensin system: a key role in SARS-CoV-2-induced COVID-19. *Molecules (Basel, Switzerland)* 26:6945. doi: 10.3390/molecules26226945

Esandi, N., Nolan, M., Canga-Armayor, N., Pardavila-Belio, M. I., and Canga-Armayor, A. (2021). Family dynamics and the Alzheimer's disease experience. *J Fam Nurs* 27, 124–135. doi: 10.1177/1074840720986611

Fenrich, M., Mrdenovic, S., Balog, M., Tomic, S., Zjalic, M., Roncevic, A., et al. (2020). SARS-CoV-2 dissemination through peripheral nerves explains multiple organ injury. *Front Cell Neurosci* 14:229. doi: 10.3389/fncel.2020.00229

Finelli, C. (2021). Metabolic syndrome, Alzheimer's disease, and covid 19: a possible correlation. *Curr Alzheimer Res* 18, 915–924. doi: 10.2174/1567205018666211209095652

Fiore, V., de Rosa, A., Falasca, P., Marci, M., Guastamacchia, E., Licchelli, B., et al. (2019). Focus on the correlations between Alzheimer's disease and type 2 diabetes. *Endocr Metab Immune Disord Drug Targets* 19, 571–579. doi: 10.2174/1871530319666190311141855

Fotuhi, M., Mian, A., Meysami, S., and Raji, C. A. (2020). Neurobiology of COVID-19. *J Alzheimers Dis* 76, 3–19. doi: 10.3233/jad-200581

Freeman, T. L., and Swartz, T. H. (2020). Targeting the NLRP3 inflammasome in severe COVID-19. *Front Immunol, Sec Viral Immunology* 11:518. doi: 10.3389/fimmu.2020.01518

Frontera, J. A., Boutajangout, A., Masurkar, A. V., Betensky, R. A., Ge, Y., Vedvyas, A., et al. (2022). Comparison of serum neurodegenerative biomarkers among hospitalized COVID-19 patients versus non-COVID subjects with normal cognition, mild cognitive impairment, or Alzheimer's dementia. *Alzheimers Dement* 18, 899–910. doi: 10.1002/alz.12556

Gil, R., and Arroyo-Anlló, E. M. (2021). Alzheimer's disease and face masks in times of COVID-19. *J Alzheimer's Dis: JAD* 79, 9–14. doi: 10.3233/JAD-201233

Hardan, L., Filtchev, D., Kassem, R., Bourgi, R., Lukomska-Szymanska, M., Tarhini, H., et al. (2021). COVID-19 and Alzheimer's disease: a literature review. *Medicina (Kaunas)* 57:1159. doi: 10.3390/medicina57111159

Helms, J., Kremer, S., Merdji, H., Clere-Jehl, R., Schenck, M., Kummerlen, C., et al. (2020). Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med* 382, 2268–2270. doi: 10.1056/nejmc2008597

Heneka, M. T., Golenbock, D., Latz, E., Morgan, D., and Brown, R. (2020). Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimers Res Ther* 12:69. doi: 10.1186/s13195-020-00640-3

Hu, B., Huang, S., and Yin, L. (2021). The cytokine storm and COVID-19. *J Med Virol* 93, 250–256. doi: 10.1002/jmv.26232

Iodice, F., Cassano, V., and Rossini, P. M. (2021). Direct and indirect neurological, cognitive, and behavioral effects of COVID-19 on the healthy elderly, mild-cognitive-impairment, and Alzheimer's disease populations. *Neurol Sci* 42, 455–465. doi: 10.1007/s10072-020-04902-8

Ionescu-Tucker, A., and Cotman, C. W. (2021). Emerging roles of oxidative stress in brain aging and Alzheimer's disease. *Neurobiol Aging* 107, 86–95. doi: 10.1016/j.neurobiolaging.2021.07.014

Ising, C., Venegas, C., Zhang, S., Scheiblich, H., Schmidt, S. V., Vieira-Saecker, A., et al. (2019). NLRP3 inflammasome activation drives tau pathology. *Nature* 575, 669–673. doi: 10.1038/s41586-019-1769-z

Kadry, H., Noorani, B., and Cucullo, L. (2020). A blood-brain barrier overview on structure, function, impairment, and biomarkers of integrity. *Fluids and barriers of the CNS* 17:69. doi: 10.1186/s12987-020-00230-3

Kumar, S. (2022). In silico drug repositioning for COVID-19: Progress and challenges. *Front COVID-19*. 24, 487–504. doi: 10.1007/978-3-031-08045-6_24

Kumar, S., Karuppanan, K., and Subramaniam, G. (2022). Omicron (BA.1) and sub-variants (BA.1.1, BA.2, and BA.3) of SARS-CoV-2 spike infectivity and pathogenicity: a comparative sequence and structural-based computational assessment. *J Med Virol* 94, 4780–4791. doi: 10.1002/jmv.27927

Kumar, S., Thambiraja, T. S., Karuppanan, K., and Subramaniam, G. (2021). Omicron and Delta variant of SARS-CoV-2: a comparative computational study of spike protein. *J Med Virol* 94, 1641–1649. doi: 10.1002/jmv.27526

Kuo, I., and O'Brien, T. P. (2020). COVID-19 and ophthalmology: An environmental work hazard. *J. Occup. Health.* doi: 10.1002/1348-9585.12124

Lane, C. A., Hardy, J., and Schott, J. M. (2018). Alzheimer's disease. *Eur J Neurol* 25, 59–70. doi: 10.1111/ene.13439

Li, C., Liu, J., Lin, J., and Shang, H. (2022). COVID-19 and risk of neurodegenerative disorders: a mendelian randomization study. *Transl Psychiatry* 12:283. doi: 10.1038/s41398-022-02052-3

Magusali, N., Graham, A. C., Piers, T. M., Panichnantakul, P., Yaman, U., Shoai, M., et al. (2021). A genetic link between risk for Alzheimer's disease and severe COVID-19 outcomes via the OAS1 gene. *Brain* 144, 3727–3741. doi: 10.1093/brain/awab337

Manzo, C., Serra-Mestres, J., Isetta, M., and Castagna, A. (2021). Could COVID-19 anosmia and olfactory dysfunction trigger an increased risk of future dementia in patients with apo E4? *Med Hypotheses* 147:110479. doi: 10.1016/j.mehy.2020.110479

Mark, J. M., Benjamin, E. S., and Neil, M. G. (2021). (2020) inflammasome activation in acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 320, L165–L178. doi: 10.1152/ajplung.00303.2020

Matias-Guiu, J., Pytel, V., and Matias-Guiu, J. (2020). Death rate due to COVID-19 in Alzheimer's disease and frontotemporal dementia. *J Alzheimers Dis* 78, 537–541. doi: 10.3233/jad-200940

Meinhardt, J., Radke, J., Dittmayer, C., Franz, J., Thomas, C., Mothes, R., et al. (2021). Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat Neurosci* 24, 168–175. doi: 10.1038/s41593-020-00758-5

Miners, S., Kehoe, P. G., and Love, S. (2020). Cognitive impact of COVID-19: looking beyond the short term. *Alzheimers Res Ther* 12:170. doi: 10.1186/s13195-020-00744-w

Mohammad Azizur, R., Mohammad Saidur, R., and Nur, A. (2020). Heightened vulnerability of Alzheimer's disease in COVID-19 cataclysm and putative management strategies. *Annals of Alzheimer's and Dementia Care.* 5, 027–029. doi: 10.17352/aadc.000015

Mok, V. C. T., Pendlebury, S., Wong, A., Alladi, S., Au, L., Bath, P. M., et al. (2020). Tackling challenges in care of Alzheimer's disease and other dementias amid the COVID-19 pandemic, now and in the future. *Alzheimers Dement*. 16, 1571–1581. doi: 10.1002/alz.12143

Palmieri, L., Vanacore, N., Donfrancesco, C., Lo Noce, C., Canevelli, M., Punzo, O., et al. (2020). Italian National Institute of health COVID-19 mortality group, clinical characteristics of hospitalized individuals dying with COVID-19 by age group in Italy. *J Gerontol: Series A* 75, 1796–1800. doi: 10.1093/gerona/glaa146

Pezzini, A., and Padovani, A. (2020). Lifting the mask on neurological manifestations of COVID-19. *Nat Rev Neurol* 16, 636–644. doi: 10.1038/s41582-020-0398-3

Pinna, P., Grewal, P., Hall, J. P., Tavarez, T., Dafer, R. M., and Garg, R. (2020). Neurological manifestations and COVID-19: experiences from a tertiary care center at the frontline. *J Neurol Sci* 415:116969. doi: 10.1016/j.jns.2020.116969

Ragab, D., Salah Eldin, H., Taeimah, M., Khattab, R., and Salem, R. (2020). The COVID-19 cytokine storm; what we know so far. *Front Immunol* 11:1446. doi: 10.3389/fimmu.2020.01446

Rahman, M. A., Islam, K., Rahman, S., and Alamin, M. (2020). Neurobiochemical cross-talk between COVID-19 and Alzheimer's disease. *Mol Neurobiol* 58, 1017–1023. doi: 10.1007/s12035-020-02177-w

Reiken, S., Sittenfeld, L., Dridi, H., Liu, Y., Liu, X., and Marks, A. R. (2022). Alzheimer's-like signaling in brains of COVID-19 patients. *Alzheimers Dement* 18, 955–965. doi: 10.1002/alz.12558

Ren, Y., Shu, T., Wu, D., Mu, J., Wang, C., Huang, M., et al. (2020). The ORF3a protein of SARS-CoV-2 induces apoptosis in cells. *Cell Mol Immunol* 17, 881–883. doi: 10.1038/s41423-020-0485-9

Rudnicka-Drożak, E., Drożak, P., Mizerski, G., Zaborowski, T., Ślusarska, B., Nowicki, G., et al. (2023). Links between COVID-19 and Alzheimer's disease—what do we already know? *Int J Environ Res Public Health* 20:2146. doi: 10.3390/ijerph20032146

Sharma, S. K. (2021). COVID-19 and dementia. *Ann Neurosci* 28, 101–104. doi: 10.1177/09727531211009420

Suhail, S., Zajac, J., Fossum, C., Lowater, H., McCracken, C., Severson, N., et al. (2020). Role of oxidative stress on SARS-CoV (SARS) and SARS-CoV-2 (COVID-19) infection: a review. *Protein J* 39, 644–656. doi: 10.1007/s10930-020-09935-8

Toldo, S., Bussani, R., Nuzzi, V., Bonaventura, A., Mauro, A. G., Cannatà, A., et al. (2021). Inflammasome formation in the lungs of patients with fatal COVID-19. *Inflammation Res: Official J European Histamine Res Society* 70, 7–10. doi: 10.1007/s00011-020-01413-2

Toniolo, S., Scarioni, M., Di Lorenzo, F., Hort, J., Georges, J., Tomic, S., et al. (2021). Dementia and COVID-19, a bidirectional liaison: risk factors, biomarkers, and optimal health care. *J Alzheimer's Dis: JAD* 82, 883–898. doi: 10.3233/JAD-210335

Varatharaj, A., Thomas, N., Ellul, M. A., Davies, N. W. S., Pollak, T. A., and Tenorio, E. L. (2020). Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psychiatry* 7, 875–882. doi: 10.1016/S2215-0366(20)30287-X

Vincent, J. L., and Créteur, J. (2020). Ethical aspects of the COVID-19 crisis: How to deal with an overwhelming shortage of acute beds. *Eur Heart J Acute Cardiovasc Care*. doi: 10.1177/2048872620922788

Wang, F., Kream, R. M., and Stefano, G. B. (2020). Long-term respiratory and neurological sequelae of COVID-19. *Medical Sci Monitor: Int Med J Experimental and Clinical Res* 26:e928996. doi: 10.12659/MSM.928996

Wang, H., Lu, J., Zhao, X., Qin, R., Song, K., Xu, Y., et al. (2021). Alzheimer's disease in elderly COVID-19 patients: potential mechanisms and preventive measures. *Neurol Sci* 42, 4913–4920. doi: 10.1007/s10072-021-05616-1

Wee, J. J., and Kumar, S. (n.d.). Prediction of hub genes of Alzheimer's disease using a protein interaction network and functional enrichment analysis. *Genomics Inform* 18:e39. doi: 10.5808/GI.2020.18.4.e39

Wu, Y., Xu, X., Chen, Z., Duan, J., Hashimoto, K., Yang, L., et al. (2020). Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun* 87, 18–22. doi: 10.1016/j.bbi.2020.03.031

Xia, X., Wang, Y., and Zheng, J. (2021). COVID-19 and Alzheimer's disease: how one crisis worsens the other. *Translational Neurodegeneration* 10:15. doi: 10.1186/s40035-021-00237-2

Xu, H., Akinyemi, I. A., Chitre, S. A., Loeb, J. C., Lednicky, J. A., McIntosh, M. T., et al. (2022). SARS-CoV-2 viroporin encoded by ORF3a triggers the NLRP3 inflammatory pathway. *Virology* 568, 13–22. doi: 10.1016/j.virol.2022.01.003

Zhang, Q., Schultz, J. L., Aldridge, G. M., Simmering, J. E., Kim, Y., Ogilvie, A. C., et al. (2021). COVID-19 case fatality and Alzheimer's disease. *J Alzheimer's Dis: JAD* 84, 1447–1452. doi: 10.3233/JAD-215161

Zhang, X. X., Tian, Y., Wang, Z. T., Ma, Y. H., Tan, L., and Yu, J. T. (2021). The epidemiology of Alzheimer's disease modifiable risk factors and prevention. *J Prev Alzheimers Dis*. 8, 1–9. doi: 10.14283/jpad.2021.15

Zhou, Y., Xu, J., Hou, Y., Leverenz, J. B., Kallianpur, A., Mehra, R., et al. (2021). Network medicine links SARS-CoV-2/COVID-19 infection to brain microvascular injury and neuroinflammation in dementia-like cognitive impairment. *Alzheimers Res Ther* 13:110. doi: 10.1186/s13195-021-00850-3

frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 07 February 2024
DOI 10.3389/fneur.2024.1345787

OPEN ACCESS

EDITED BY
Pankaj Seth,
National Brain Research Centre (NBRC), India

REVIEWED BY
Penghui Wei,
Qilu Hospital of Shandong University (Qingdao), China
Samir Abu Rumeileh,
Martin Luther University of Halle-Wittenberg, Germany
Jolanta B. Zawilska,
Medical University of Lodz, Poland

*CORRESPONDENCE
Lise Beier Havdal
✉ lise.beier.havdal@ahus.no

RECEIVED 21 December 2023
ACCEPTED 24 January 2024
PUBLISHED 07 February 2024

CITATION
Havdal LB, Selvakumar J, Lund Berven L, Stiansen-Sonerud T, Zetterberg H, Blennow K, Holmøy T and Wyller VBB (2024) Neurological involvement among non-hospitalized adolescents and young adults 6 months after acute COVID-19. *Front. Neurol.* 15:1345787. doi: 10.3389/fneur.2024.1345787

Neurological involvement among non-hospitalized adolescents and young adults 6 months after acute COVID-19

Lise Beier Havdal[1]*, Joel Selvakumar[1,2], Lise Lund Berven[1], Tonje Stiansen-Sonerud[1,3], Henrik Zetterberg[4,5,6,7,8], Kaj Blennow[4,5], Trygve Holmøy[2,9] and Vegard Bruun Bratholm Wyller[1,2]

[1]Department of Paediatrics and Adolescent Health, Akershus University Hospital, Lørenskog, Norway, [2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [3]Department of Clinical Molecular Biology (EpiGen), University of Oslo and Akershus University Hospital, Lørenskog, Norway, [4]Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, Sahlgrenska Academy, University of Gothenburg, Mölndal, Sweden, [5]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, [6]UCL Institute of Neurology, Department of Neurodegenerative Disease, Queen Square, London, United Kingdom, [7]UK Dementia Research Institute, London, United Kingdom, [8]Hong Kong Center for Neurodegenerative Diseases, Kowloon, Hong Kong SAR, China, [9]Department of Neurology, Akershus University Hospital, Lørenskog, Norway

Introduction: The post-COVID-19 condition (PCC) is characterized by debilitating persistent symptoms, including symptoms suggesting neurological aberrations such as concentration difficulties, impaired memory, pain, and sleep disturbances. The underlying mechanisms remain elusive. This study aimed to investigate brain injury biomarkers, neurocognitive test performance, and self-reported neurological and neuropsychological symptoms in young people with PCC.

Methods: A total of 404 non-hospitalized adolescents and young adults aged 12–25 years who tested positive for SARS-CoV-2, along with 105 matched SARS-CoV-2 negative individuals, were prospectively enrolled and followed-up for 6 months (Clinical Trials ID: NCT04686734). All participants underwent comprehensive assessment encompassing clinical examinations, questionnaires, neurocognitive testing and blood sampling. Serum samples were immunoassayed for the brain injury biomarkers neurofilament light chain (Nfl) and glial fibrillary acidic protein (GFAp). At 6 months, cross-sectional analyses of serum Nfl/GFAp, neurocognitive test results and symptom scores were performed across groups based on adherence to PCC criteria as well as initial SARS-CoV-2 test results. Also, associations between Nfl/GFAp, neurocognitive test results, and symptom scores were explored.

Results: A total of 381 SARS-CoV-2 positive and 85 SARS-CoV-2 negative were included in the final analysis at 6 months, of whom 48% and 47%, respectively, adhered to the PCC criteria. Serum levels of Nfl and GFAp were almost equal across groups and did not differ from reference values in healthy populations. Also, neurocognitive test results were not different across groups, whereas symptom scores were significantly higher in patients fulfilling PCC criteria (independent of initial SARS-CoV-2 status). No significant associations between Nfl/GFAp, neurocognitive test results, and symptom scores were found.

Conclusion: Normal brain injury biomarkers and neurocognitive performance 6 months after mild COVID-19 implies that the persistent symptoms associated

with PCC are not concurrent with ongoing central nervous system damage or permanent disruption of cognitive functions. This finding contradicts the notion of neuroinflammation as a likely explanation for the persistent symptoms.

KEYWORDS

COVID-19, neurofilament, glial fibrillary acidic protein, post-COVID-19 condition, adolescents, cognitive functions, fatigue

Introduction

The majority of individuals infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus that causes Corona Virus Disease of 2019 (COVID-19), typically recover to their baseline health status within a few weeks after the acute infection. However, a substantial portion of individuals experience persistent post-infective symptoms (1–3). Persisting symptoms have been reported in patients regardless of the severity of the acute COVID-19 infection (4), and even children and young adults who experienced predominantly mild cases of acute COVID-19 may endure prolonged symptoms (5). These enduring health issues commonly include various neurological complaints such as fatigue, post-exertional malaise, headache, memory difficulties, and sleep disturbances (6–8). The World Health organization (WHO) has defined these long-lasting symptoms following confirmed or suspected COVID-19 infection, with no alternative diagnosis to explain them, as Post-COVID-19 condition (PCC) (9). PCC exhibits significant clinical overlap with post-infective fatigue syndrome (PIFS) (10), and numerous queries concerning the underlying mechanisms of disease and its natural progression still lack definite answers. Further, it is still to be established whether the subjective experience of neurological and neuropsychological symptoms in PCC correspond with objectively measurable deficits (8, 11–13).

Multiple mechanisms have been suggested as potential underlying mechanisms of neurobiological aberrations in COVID-19 and PCC. In the acute and subacute stages, CNS involvement may be due to immune activation triggered by systemic inflammation, microvascular damage, thromboembolic events, or non-specific hypoxic effects resulting from severe illness (14, 15). One mechanism proposed to account for the manifestations of PCC revolves around activation of the neuroimmune system (16, 17). Alternatively, the symptoms of PCC may be explained from functional CNS alterations (18), analogous to common mechanisms of chronic pain conditions (19). This latter explanation acknowledges that symptoms may arise independently of neuronal damage and/or interoceptive afferent signals, and resonates with previous published evidence of psychosocial factors as important predictors of persistent symptoms (20, 21).

The intra-axonal protein neurofilament light chain (Nfl) is a validated biomarker for neuroaxonal injury and neuroinflammation regardless of cause (22–24). Numerous studies have demonstrated a strong correlation between levels of Nfl in cerebrospinal fluid (CSF) and blood serum samples (25, 26) rendering it widely applicable as a biomarker for neuroinflammation and neurodegeneration. Glial fibrillary acidic protein (GFAp) is an astrocytic cytoskeletal protein upregulated in activated astrocytes, recognized for its swift elevation in both CSF and serum in response to acute brain injuries. Studies have evidenced a robust correlation between the levels of GFAp detected in CSF and blood serum samples (27–30). Elevated serum levels of these biomarkers in the acute phase of COVID-19 infection provides evidence of astrocytic and neuroaxonal damage in patients undergoing a severe course of SARS-CoV-2 infection (13, 31–34). We have previously reported these biomarkers to be slightly elevated in the subacute phase of SARS-CoV-2 infection in adolescents and young adults with mildly symptomatic disease (11). Studies examining neuroinflammatory biomarkers during follow-up after COVID-19 infection yield varied outcomes, even when they are limited to mild initial cases (35, 36).

In the current study we report serum levels of NfL and GFAp at 6-This study aimed to investigate brain injury biomarkers, neurocognitive test performance, and self-reported neurological and neuropsychological symptoms in young people with PCC. We examined cross-sectional data from 6-month follow-up of a large prospective cohort of adolescents and young adults with and without COVID-19.

Methods

Study design

The long-term effects of COVID-19 in Adolescents (LoTECA) project is a longitudinal observational cohort study of non-hospitalized adolescents and young adults. Participants testing positive and negative for SARS-CoV-2 were included, with follow-up at 6 and 12 months (Clinical Trials ID: NCT04686734). Details of the study design have been described previously (20). This study reports results from the 6-month follow-up visit.

Ethical approval for this project was granted by The Regional Committee for Ethics in Medical Research. Written informed consent was obtained from each participant at study inclusion.

Participants

Between 24 December 2020 and 18 May 2021, a consecutive cohort of adolescents and young adults undergoing SARS-CoV-2 testing with reverse transcription-polymerase chain reaction (RT-PCR) were enrolled. All participants were recruited from one of two microbiological laboratories, Fürst Medical Laboratory or Department of Microbiology and Infection Control at Akershus University Hospital, both located in Southeast Norway. The prevailing strain of SARS-CoV-2 in this geographical area during most of the recruitment period was B.1.1.7 (Alpha). Any SARS-CoV-2 positive individuals were considered eligible for enrolment after fulfilling a 10-day quarantine. Concurrently, a SARS-CoV-2 negative control

group was recruited among individuals exhibiting a similar distribution of sex and age as the SARS-CoV-2 infected cases. Within the SARS-CoV-2 negative group, some individuals had undergone testing due to acute infectious symptoms, while others were asymptomatic close contacts of confirmed cases.

Exclusion criteria at baseline encompassed the following: (1) A duration of more than 28 days since onset of symptoms; (2) Hospitalization due to COVID-19; (3) Pregnancy; and (4) Serological evidence of SARS-CoV-2 infection (in the SARS-CoV-2-negative group).

Investigational program

At enrolment and each follow-up assessment, all participants attended a comprehensive assessment program at the study center at Akershus University Hospital, Norway. This program encompassed clinical interview, physical examination, blood sample collection, vital sign recording, functional and neurocognitive testing, and completion of questionnaires. The complete investigational program of the LoTECA project has been published previously (20).

Laboratory assays

Blood samples were collected via antecubital venepuncture as the first part of the 6-month follow-up visit. Samples were subjected to analysis for routine clinical markers. To identify previous infection with COVID-19, serum samples were analyzed for SARS-CoV-2 nucleocapsid and receptor binding antibodies.

Serum samples for measurement of GFAp and Nfl was collected in 3.5 mL Vacuette R (Greiner bio-one GmbH) with gel. Samples underwent clotting for a minimum of 30 min. Within 2 h, they were processed by centrifugation at 2,200 g for 10 min. The aliquots were stored immediately at −80°C until analysis. Serum GFAp and Nfl measurement was conducted at the Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Sweden, by certified laboratory technicians blinded to clinical data. The analysis was performed utilizing commercially available Single Molecule Array (Simoa) assays on an HD-X analyzer (Human Neuro 2-plex B assay), as instructed by the manufacturer (Quanterix, Billerica, MA). Calibrators were run in duplicates, while the samples were diluted four-fold and run as singlicates. To monitor assay performance, two quality control (QC) samples, with different concentration levels, were run in duplicates at the beginning and end of each analytical run. For the QC sample with a Nfl concentration of 14.1 pg./mL, repeatability and intermediate precision were both 6.2%, and for QC samples with a concentration of 77.3 pg./mL, both repeatability and intermediate precision was 5.9%. For GFAp CQ samples with concentration 99.4 pg./mL, repeatability was 4.4% and intermediate precision was 8.3%. For GFAp QC samples with concentration 281 pg./mL, repeatability was 5.6% and intermediate precision was 6.3%.

Neurocognitive testing

During the 6-month follow-up visit, all study participants underwent neurocognitive assessment with two standardized tests: the Digit-Span Test from the Wechsler Intelligence Scale for Children, 4th edition (WISC) (37), and the Hopkins Verbal Learning Test-Revised (HVLT-R) (38).

The Digit-Span Test is a tool for evaluating verbal and auditory working memory. An examiner presents a series of random digits verbally. The initial digit sequence comprises two random numbers, and with each subsequent sequence, an additional digit is included. During the digit span forward mode, the participant is tasked with repeating the digits in the same order as they were presented, while in the digit span backward mode, the digits are to be repeated in reverse order. A score of one point is assigned for each correctly recalled digit sequence. The test is discontinued when the participant provides incorrect responses for two sequences of equal length. Results are reported in the form of sum scores for digit span forward and backward, as well as a total sum score.

The HVLT-R test is designed to assess verbal learning, delayed recall, and recognition. A standardized procedure is followed, where the examiner orally presents a list of 12 words, and the participant is tasked with repeating as many of these words as possible in three consecutive trials. The cumulative score for verbal learning memory is determined by summing the total number of words remembered across the three trials, with a possible range of scores ranging from 0 to 36. To evaluate delayed verbal memory, the number of words successfully recalled after a 20-min interval is recorded; score ranges from 0 to 12. Subsequently, a list of 24 words is presented, of which 12 words are identical to those from the initial list. The number of correctly recognized words and falsely recognized words are recorded separately; scores range from 0 to 12.

Questionnaires

A questionnaire was employed to gather information regarding comorbidities, family medical history, current medication, smoking habits, substance abuse, physical activity and parental occupation. Parental occupation was used to gauge socioeconomic status.

Sleep problems and pain were recorded through the Karolinska Sleep Inventory and the Brief Pain Inventory, respectively (39, 40). In the Karolinska Sleep Inventory, a total of 12 items addressed frequency of sleep disturbances on 6-point Likert scales, where 1 is "never" and 6 is "all the time"; then, the scoring was reversed, and total sum score was computed across all items ranging from 12 to 72, where *lower* scores indicate more sleep disturbances. Accordingly, indexes for insomnia, awakening problems, and sleepiness were computed as sum scores across relevant items. In the Brief Pain Inventory, a total of four items addressed different aspects of pain on 10-point Likert scales, where 1 is "no pain" and 10 is "worst pain imaginable"; total sum score was computed across all items ranging from 4 to 40, where higher scores indicate more pain.

In addition, five neurological/neurocognitive symptoms were assessed: Concentration difficulty, difficulty making decisions, memory difficulty, feeling confused or disoriented, and headache. The frequency of these symptoms were assessed using five-point Likert scales, ranging from 1 to 5, with options spanning from "never" to "each day/always."

SARS-CoV-2 immunization

Data pertaining to vaccination status was acquired through linkage with the Norwegian Immunization Register (41).

Case definitions

The WHO definition of Post COVID-19 Condition (PCC) (9) and the modified Fukuda-case definition of Post-Infective Fatigue Syndrome (PIFS) (42) were applied and operationalized at 6-month follow-up, as thoroughly described previously (20). In brief, all participants were categorized as either case or non-case in accordance with both definitions. To enhance accuracy, a distinction was drawn between definite and uncertain classifications, considering concurrent medical and psychiatric comorbidities that could potentially account for the reported symptoms. Both clinical findings, laboratory reports and questionnaire data from baseline and at 6-month follow-up were considered in the identification of PCC and PIFS cases. Two medical doctors blinded to the participants' initial SARS-CoV-2 status conducted the assessment independently.

Participants were stratified into four groups based on COVID status and adherence to PCC criteria as follows: (1) COVID-19 positive individuals who adhered to PCC criteria (COVID+PCC+); (2) COVID-19 positive individuals who did not adhere to PCC criteria (COVID+PCC-); (3) COVID-19 negative individuals who adhered to PCC criteria (COVID-PCC+); and (4) COVID-19 negative individuals who did not adhere to PCC criteria (COVID-PCC-). A similar categorization was undertaken based on adherence to PIFS criteria (PIFS+ or PIFS-).

Statistical analysis

For cross-sectional comparisons between COVID-19 positive and COVID-19 negative cases, chi-square test and Wilcoxon rank-sum test were applied as appropriate based on distribution of the data. For comparison across the four groups according to COVID status and PCC/PIFS adherence, one-way ANOVA or Kruskal-Wallis tests were used as appropriate. Post-hoc analyses were conducted to investigate differences between groups that exhibited statistically significant results.

Associations between symptoms, neurocognitive test results, neurological findings and the two brain injury biomarkers Nfl and GFAp were investigated using the non-parametrical Spearman's rho test.

Statistical analyses were executed using Stata Statistical Software: Release 16 (Statacorp LLC, College Station, TX). A significance threshold of $p < 0.05$ was adopted (two-sided test). Bonferroni correction was incorporated in the spearman's rho test to account for test multiplicity.

Results

At baseline 509 (404 SARS-CoV-2 positive, 105 SARS-CoV-2 negative) children and young adults were included in the study. A total of 26 participants were lost to follow-up (22 COVID-19 cases and 4 COVID-19 negative controls). Of the COVID-19 negative controls, 16 were excluded from analyses at 6 months due to SARS-CoV-2 infection during the follow-up period, either self-reported or diagnosed from the appearance of plasma SARS-CoV-2 nucleocapsid antibodies. In addition, one COVID-19 case suffering from multiple sclerosis was excluded from the current analysis of neurological involvement. A total of 466 participants (381 SARS-CoV-2 positive, 85 SARS-CoV-2 negative) were included in the final analysis of the present paper.

The median time from baseline visit to follow-up was 193 days for both the SARS-CoV-2 positive and SARS-CoV-2 negative group. An overview of demographics and background characteristics are reported in Table 1.

As previously reported (20), there was no difference in adherence to the WHO post-COVID-19 condition nor in adherence to the criteria of post infectious fatigue syndrome based on previous COVID-19 exposure.

Comparison according to COVID-19 status and PCC adherence

Results from comparison across the four groups according to COVID status and PCC adherence are presented in Table 2. Significant differences between groups were found for all symptoms of neurocognitive dysfunction, as well as pain and sleep difficulties. *Post-hoc* test results are reported in Supplementary Table 1. Generally, the *post-hoc* tests of reported symptoms showed significant differences between groups that differed in PCC adherence, but not between groups with differences in COVID status and similar PCC adherence.

Brain injury biomarkers, neurocognitive test performance, and clinical neurological findings did not differ across the four groups (Table 2; Figure 1). Similarly, there were no differences across four groups stratified according to COVID-19 status and adherence to PIFS criteria (Figure 2; Supplementary Tables 2, 3).

Associations to PCC within the SARS-CoV-2 positive cohort

Associations between PCC, PIFS, as well as subjectively reported symptoms, brain injury biomarkers, and neurocognitive test results are presented in Figure 3. Neither of the biomarkers, Nfl or GFAp, demonstrated any association with PCC nor PIFS, nor were they associated with the reported symptoms or neurocognitive test results. In contrast, both PCC and PIFS exhibited significant association with any subjective symptoms of pain, sleep disturbances, memory issues, difficulty concentrating, decision-making challenges and feeling confused or disorientated. However, none of the subjective symptoms was associated with neurocognitive test results. Complete overview of correlation coefficients and significance levels from the spearman's rho test are provided in Supplementary Table 4.

Discussion

In the present study of a large group of young, non-hospitalized COVID-19 convalescents, the main findings were: (a) That brain injury biomarkers were normalized 6 months after acute infection; (b) That neither brain injury biomarkers, neurocognitive test performance nor clinical neurological finding were associated with PCC or PIFS; and (c) That the burden of subjective neurological and/or neuropsychological symptoms is high in both PCC and PIFS.

TABLE 1 Cohort characteristics at 6-month follow-up by SARS-CoV-2 status on inclusion.

Characteristic	Participants, No. (%)		
	SARS-CoV-2 Positive group	SARS-CoV-2 Negative group	*p*-value[1]
	N = 381	*N* = 85	
Background			
Sex			
Female-N (%)	229 (60)	31 (64)	
Male	152 (40)	54 (36)	0.559[2]
Age at baseline, median (iqr)	17.5 (14.8–21.3)	17.7 (15.3–20.0)	0.655[3]
Days since baseline visit, median (iqr)	193 (188–199)	193 (188–205)	0.473[3]
Immunization against COVID-19	278 (73%)	78 (92%)	<0.001[2]
BMI kg/m2, mean (SD)	23.2 (4.70)	23.2 (4.3)	0.489[2]
Ethnicity			
Caucasian, No. (%)	286 (75%)	83 (98%)	
Other, No. (%)	95 (25%)	2 (2.4%)	<0.001[2]
Chronic disease, self[4], No. (%)	65 (17%)	17 (20%)	0.541[2]
Chronic disease, family member[4], No. (%)	122 (33%)	30 (36%)	0.677[2]
ISEI-08 Index of socioeconomy—median (iqr)	60.3 (36.4–75.5)	62.4 (47.3–73.4)	0.517[3]
Biomarkers			
B-Hemoglobin g/dL, mean (SD)	13.6 (1.18)	13.6 (1.03)	0.437
B-Leukocytes*10^9/L, mean (SD)	6.1 (1.76)	5.9 (1.51)	0.878
B-Platelets*10^9/L, mean (SD)	270 (59)	276 (58)	0.180
S-CRP[5]mg/L, no (%)			
<5	354 (95%)	76 (92%)	
>5	19 (5%)	7 (8%)	0.235
P-Ferritin µg/L, median (iqr)	45 (30–76.5)	44 (33–63)	0.809
S-Sodium mmol/L, mean (SD)	139 (1.76)	139 (1.82)	0.676
S-Potassium mmol/L, mean (SD)	4.0 (0.24)	4.1 (0.28)	0.051
P-Creatinine, mean (SD)	67 (13.3)	68 (11.7)	0.384
P-LD U/L, mean (SD)	161 (31.6)	158 (34.1)	0.759
P-ALAT, median (iqr)	17 (13–23)	16 (13–20)	0.146[3]
S-Neurofilament light chain, pg./mL, median (iqr)	4.7(2.1)	4.6(1.8)	0.374[3]
S-Glial fibrillary acidic protein, pg./mL, median (iqr)	65.1(34.8)	70.1(33.8)	0.381[3]
Caseness			
PCC cases-no. of cases (%)	184 (48%)	40 (47%)	0.837[2]
PIFS cases-no. of cases (%)	53 (14%)	7 (8%)	0.158[2]

[1]T-test unless otherwise stated. [2]Chi2 test. [3]Wilcoxon-rank test. [4]Self-reported, from questionnaires. [5]Serum CRP levels are low in the majority of cases. The participants are therefore reported as frequencies within categories, maximum observation of 118 mg/L in COVID-19 positive group.

In baseline data from our cohort, we observed a slight increase in Nfl and GFAp levels in the sub-acute phase of COVID-19 (11). Our current finding of these brain injury biomarkers returning to normal levels 6-months after mild COVID-19 infection aligns with the findings of others. Kanberg et al. found that Nfl and GFAp serum concentrations were normalized 6 months post-infection in a cohort of mild, moderate and severe COVID-19 cases (43), and Rogatzki et al. found normalization of serum levels of Nfl/GFAp as early as 1 month following mild COVID-19 infection in young adults (35).

Both Nfl and GFAp has previously been suggested as useful biomarkers for identification of patient suffering from neurological sequelae following COVID-19 infection (44). In a study of critically ill COVID-19-patients investigated 3 to 6 months after discharge from the intensive care unit, GFAp and Nfl were found to be associated with neurocognitive dysfunction and neuropsychiatric outcome (45). Contrary, in our cohort of young individuals with mild disease course, there were no association between GFAp/Nfl and neurocognitive symptoms or post-COVID-19 symptomatology. This corroborates with previous reports on milder cases. De Boni et al. reported lower

TABLE 2 Cross-sectional comparison of symptoms, clinical and laboratory findings, and neurocognitive test results among COVID-19 cases and non-COVID controls for participants with and without post-COVID-19 Condition (PCC) at 6 months follow-up.

Reported symptoms	COVID-19 cases		Non-COVID controls		
	COVID + PCC+	COVID + PCC-	COVID-PCC+	COVID-PCC-	*p*-value[a]
Symptoms suggesting neurocognitive aberrations					
Concentration difficulty, score-mean (SD)	3.3 (1.2)	1.9 (1.1)	3.3(1.1)	2.1 (1.0)	<0.001
Confidence interval	*3.2–3.5*	*1.7–2.0*	*2.9–3.6*	*1.8–2.4*	
Difficulty making decisions, score-mean (SD)	2.7 (1.3)	1.6 (0.9)	2.3 (1.1)	1.6 (0.9)	<0.001
Confidence interval	*2.5–2.8*	*1.4–1.7*	*2.0–2.7*	*1.3–1.9*	
Memory difficulty, score-mean (SD)	2.9 (1.3)	1.7 (1.0)	2.6 (1.3)	1.8 (1.2)	<0.001
Confidence interval	*2.7–3.1*	*1.6–1.8*	*1.2–3.0*	*1.4–2.1*	
Feeling confused or disoriented, score-mean (SD)	1.8 (1.1)	1.2 (0.6)	1.5 (0.7)	1.2 (0.7)	<0.001
Confidence interval	*1.7–2.0*	*1.1–1.3*	*1.3–1.8*	*1.0–1.5*	
Sleep					
Karolinska sleep questionnaire, total score-mean (SD)	40.7 (11.1)	55.0 (10.4)	42.8 (8.2)	51.4 (10.0)	<0.001
Confidence interval	*39.1–42.3*	*53.5–56.5*	*40.1–45.4*	*48.4–54.4*	
Insomnia subscore, −mean (SD)	14.6 (4.5)	18.7 (3.9)	15.1 (4.0)	17.7 (4.0)	<0.001
Confidence interval	*14.0–15.3*	*18.2–19.3*	*13.8–16.4*	*16.5–18.9*	
Awakening problems subscore-mean (SD)	8.9 (3.7)	13.3 (3.6)	9.3 (3.0)	12.2 (3.2)	<0.001
Confidence interval	*8.3–9.4*	*12.8–13.8*	*8.3–10.3*	*11.3–13.1*	
Sleepiness subscore, −mean (SD)	14.2 (3.8)	18.8 (3.6)	15.1 (3.0)	17.6 (3.6)	<0.001
Confidence interval	*13.6–14.8*	*18.2–19.3*	*14.2–16.1*	*16.5–18.7*	
Pain					
Headache, score-mean (SD)	2.6 (1.0)	1.6 (0.8)	2.3 (1.0)	2.0 (0.9)	<0.001
Confidence interval	*2.4–2.7*	*1.5–1.8*	*2.0–2.6*	*1.7–2.3*	
Brief pain inventory total score, mean (SD)	11.5 (5.5)	7.7(3.8)	11.7(4.5)	9.7(4.5)	<0.001
Confidence interval	*10.8–12.4*	*7.2–8.3*	*10.3–13.1*	*8.4–11.1*	
Worst pain in 24 h, mean (SD)	4.4 (2.3)	3.0 (2.1)	5.2 (2.3)	4.0 (2.3)	<0.001
Confidence interval	*4.1–4.8*	*2.7–3.2*	*4.5–5.9*	*3.4–4.7*	
Least pain in 24 h, mean (SD)	1.9 (1.5)	1.4 (1.1)	1.4 (0.7)	1.8 (1.8)	<0.001
Confidence interval	*1.7–2.1*	*1.3–1.6*	*1.2–1.6*	*1.2–2.3*	
Pain on average, mean (SD)	3.2 (1.8)	1.9 (1.2)	3.0 (1.4)	2.5 (2.0)	<0.001
Confidence interval	*2.9–3.4*	*1.8–2.1*	*2.6–3.5*	*1.9–3.1*	
Pain right now, mean (SD)	2.1 (1.6)	1.4 (1.2)	2.1 (1.3)	1.4 (0.6)	<0.001
Confidence interval	*1.9–2.3*	*1.2–1.6*	*1.7–2.5*	*1.2–1.5*	
Neurological findings and brain injury biomarkers					
Neurological examination, any findings -No. (%)	5 (2.7%)	8 (4%)	2(5%)	3(6.7%)	0.625
Neurofilament light chain, pg./mL, median (iqr)	4.5 (1.9)	4.9 (2.5)	4.4 (1.9)	4.6 (1.9)	0.156[b]
Confidence interval	*4.2–4.8*	*4.6–5.1*	*4.1–5.0*	*4.4–5.1*	
Glial fibrillary acidic protein, pg./mL, median (iqr)	64.9 (30.3)	65.8 (40.4)	62.2 (30.4)	71.8 (35.9)	0.607[b]
Confidence interval	*60.2–68.8*	*61.1–72.8*	*57.9–77.7*	*59.8–86.7*	
Neurocognitive test results					
Digit span forward, total sum score -mean (SD)	10.0 (2.5)	9.9 (2.5)	9.7 (2.2)	9.3 (2.4)	0.344
Confidence interval	*9.6–10.4*	*9.6–10.3*	*9.0–10.4*	*8.6–10.0*	

(Continued)

TABLE 2 (Continued)

Reported symptoms	COVID-19 cases		Non-COVID controls		
	COVID + PCC+	COVID + PCC-	COVID-PCC+	COVID-PCC-	*p*-value[a]
Digit span backward, total sum score -mean (SD)	6.0 (2.4)	6.1 (2.2)	6.0 (3.1)	5.6 (1.8)	0.670
Confidence interval	*5.7–6.4*	*5.7–6.4*	*5.0–6.9*	*5.0–6.1*	
Digit span summary score, −mean (SD)	16.0 (4.3)	16.0 (4.0)	16.0 (4.0)	14.8 (3.8)	0.368
Confidence interval	*15.4–16.6*	*15.4–16.5*	*14.2–17.2*	*13.7–16.0*	
HVLT-R immediate recall, total sum score -mean (SD)	23.4 (4.8)	23.9 (4.4)	22.9 (5.2)	23.0 (4.6)	0.401
Confidence interval	*22.7–24.1*	*23.3–24.5*	*21.2–24.6*	*21.6–24.3*	
HVLT-R delayed recall, total sum score -mean (SD)	8.3 (2.3)	8.3 (2.2)	7.9 (2.5)	7.9 (2.5)	0.521
Confidence interval	*8.0–8.7*	*8.0–8.6*	*7.1–8.7*	*7.2–8.7*	
HVLT-R correct recognition, mean (SD)	11.4 (1.1)	11.4 (0.9)	11.4 (0.8)	11.4 (1.0)	0.941
Confidence interval	*11.3–11.6*	*11.3–11.6*	*11.3–11.6*	*11.1–11.7*	
HVLT-R false recognition, mean (SD)	0.3 (0.7)	0.3 (0.6)	0.4 (0.7)	0.5 (0.9)	0.349
Confidence interval	*0.2–0.4*	*0.2–0.4*	*0.1–0.6*	*0.2–0.8*	

[a]One-way ANOVA unless otherwise stated. [b]Kruskal-Wallis.

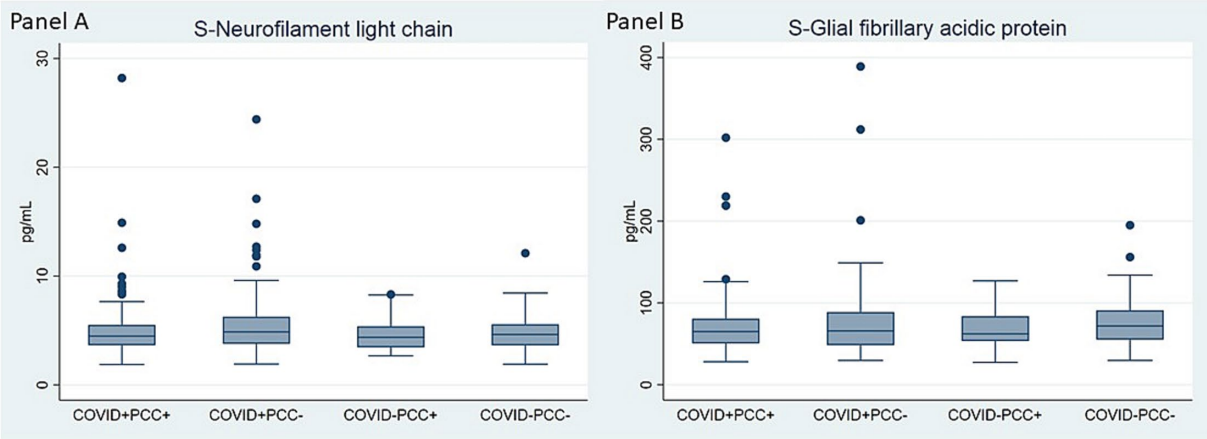


FIGURE 1
Comparison of serum levels of neurofilament light chain **(A)** and glial fibrillary acidic protein **(B)** at 6-months follow-up within groups of COVID-19 status and PCC adherence. Kruskal-Wallis test was conducted to examine the differences between groups. Panel **(A)**: Chi square = 5.22, $p = 0.156$, df = 3; Panel **(B)**: Chi square = 1.84, $p = 0.607$, df = 3.

levels of Nfl and GFAp in patients with persistent post-COVID-19 headache compared to patients with severe COVID-19 (46). Lennol et al. evidenced normalization of plasma GFAp and Nfl within 2 months following acute infection in patients with or without symptoms of fatigue, headache and memory loss (47), and Farhadian et al. found no evidence of neuroinflammation or blood–brain barrier dysfunction in a cohort of adults with self-reported PCC (48).

Our results are in contrast to those of Telser et al. (36) who reported higher GFAp levels among participants adhering to PCC criteria compared to those without PCC adherence. However, the study by Telser et al. is limited by the rather small sample size of 146 COVID-19 positive participants and the lack of a COVID-19 negative control group. Additionally, the patients' COVID-19 status was determined retrospectively based on the presence of antibodies, and differences in time span to the acute infection were not accounted for.

In line with previous reports, the present data confirm a high burden of neurological and/or neuropsychiatric symptoms among patients with PCC and PIFS (49, 50). However, these previous reports do not include measures of neuronal damage nor objective testing of neurocognitive performance. A striking result from the present study is the discrepancy between subjective symptoms and objective findings. This resonates with findings from PIFS in the aftermath of other infections (51, 52).

Various hypotheses have been suggested to explain the pathogenesis of PCC. These include systemic chronic inflammation (53), as well as neuroinflammation and autoimmunity (54). In severe cases of acute COVID-19 there is evidence that the neuroinflammation is linked to cytokine storms, as elevated serum Nfl and GFAp are associated with elevations in pro-inflammatory cytokines (55, 56). Elevated levels of Nfl have even been found to have prognostic value

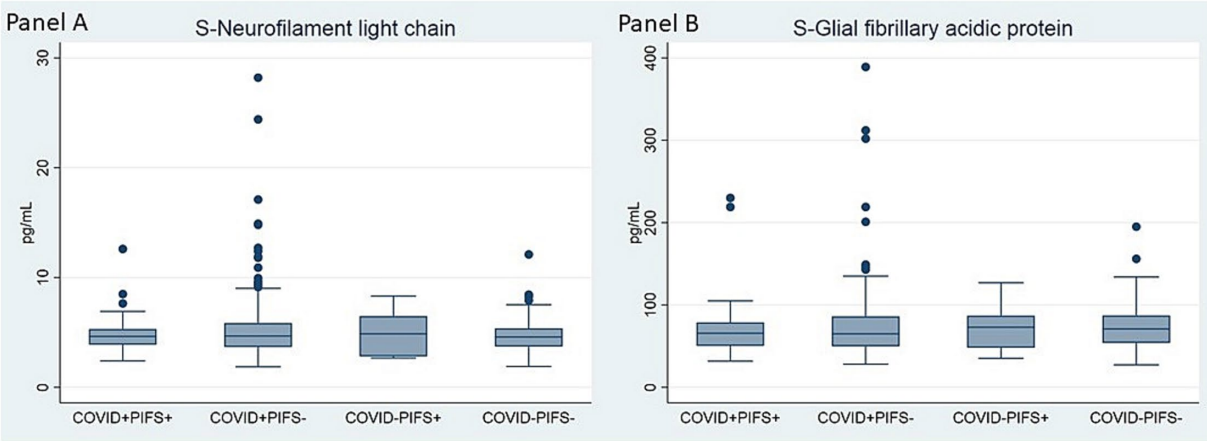


FIGURE 2
Comparison of serum levels of neurofilament light chain **(A)** and glial fibrillary acidic protein **(B)** at 6-months follow-up within groups of COVID-19 status and PIFS adherence. Kruskal-Wallis test was conducted to examine the differences between groups Panel **(A)**: Chi square = 0.89, p = 0.827, df = 3; Panel **(B)**: Chi square = 0.87, p = 0.834, df = 3.

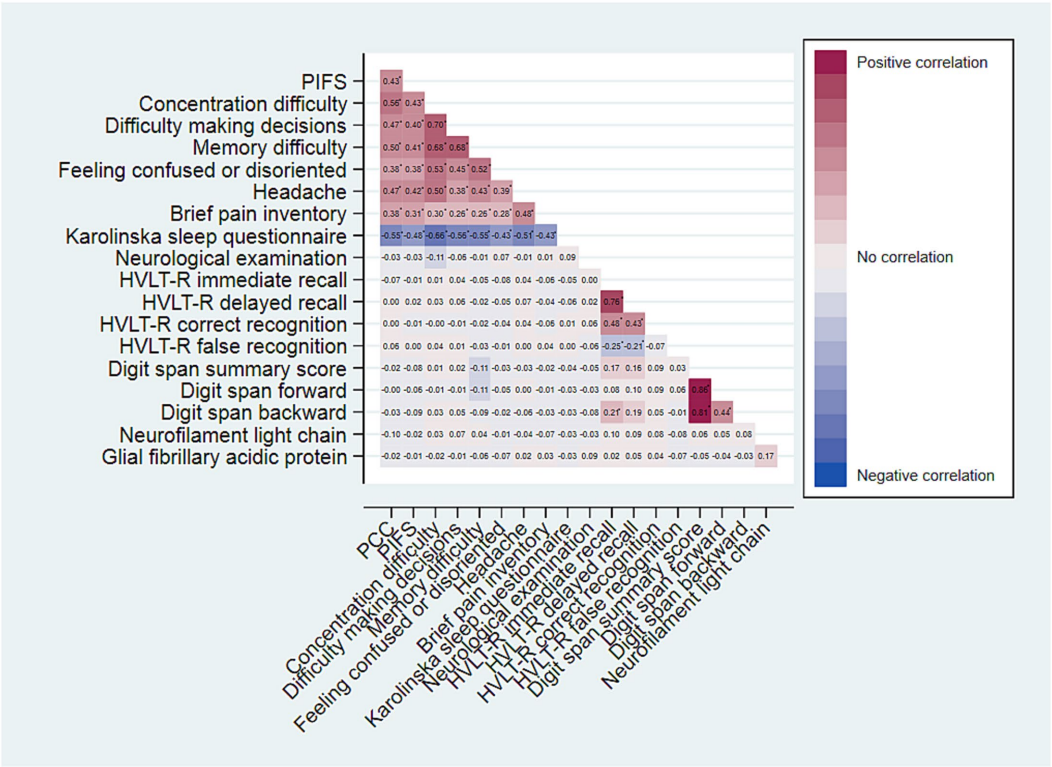


FIGURE 3
Heatplot of Spearman's Rho correlation coefficients for variables of neurocognitive symptoms, neurocognitive test results and adherence to PCC and PIFS, respectively. Coefficients marked with *, are significant at a Bonferroni adjusted significance level of $\alpha = 0.05/162 = 0.0003$.

in acute, severe cases of COVID-19 (57). The normalization of brain injury biomarkers 6 months after mild COVID-19 infection found in the current study, suggests that the neurological symptoms associated with PCC do not align with enduring or ongoing CNS injury. This argue against the notion of neuroinflammation as an explanation for the persisting symptoms. In a previous publication (58), we reported a distinct immune signature associated with COVID-19 at 6-month follow-up. However, this did not appear to be connected to PCC symptomatology. In the current study, we found no evidence of ongoing neuroinflammation, and neither brain injury biomarkers nor neurocognitive test results were associated with subjective reported symptomatology. Hence, the findings from the present study adds to

a growing body of evidence suggesting that PCC may be associated with functional CNS alterations and have origins more related to a combination of biological, psychological and social factors, rather than being solely biomedical in nature (59).

The small number of COVID-19 negative controls is a limitation to the study. Further, controls were recruited following SARS-CoV-2 testing for either infectious symptoms, or suspected SARS-CoV-2 exposure. Other viral diseases could have caused the symptoms leading to testing. Considering the established role of Epstein–Barr virus (EBV) as a trigger for post-infectious fatigue syndrome (60), individuals with recent EBV infection were not included in the analysis. To further strengthen the quality of the control group, SARS-CoV-2 antibody testing was conducted both at inclusion, and 6 months follow-up. Participant displaying antibodies indicative of prior COVID-19 infection were excluded from the control group.

The external validity of the study is limited by the potential for self-selection bias. It is plausible that our participants exhibited a higher prevalence of symptoms compared to the general population. This selection bias might be even more relevant in the control group. Further, the current study only focused on a cohort of young individuals, mostly infected with the B1.1.7 variant of SARS-CoV-2. Therefore, the generalizability of our findings to other viral strains, and to older age groups, who could exhibit increased vulnerability to both COVID-19 and PCC remains uncertain.

Conclusion

In the current study, we found that brain injury biomarkers were normalized 6 months after acute COVID-19 and that the post-COVID-19 condition, despite high symptom burden, was not associated with brain injury biomarkers, neurocognitive test performance or clinical neurological symptoms. Hence, among adolescents and young adults, neurological symptoms linked to post-COVID-19 condition do not align with continuous CNS damage, thereby challenging the notion of neuroinflammation as an underlying cause of the enduring symptoms.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Regional Committee for Ethics in Medical Research. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

LH: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. JS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. LL: Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. TS-S: Data curation, Investigation, Methodology, Writing – review & editing. HZ: Writing – review & editing. KB: Data curation, Writing – review & editing. TH: Conceptualization, Writing – review & editing, Data curation. VW: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Norwegian Research Council (grant #302079).

Acknowledgments

The authors thank Helene Larssen Mathiesen, Jeanette Dulsrud, Ann Cathrin Pettersen, Siri H. Sletner, Lene Andersen, Birute Stankuniene, and Line Sletner at the Department of Paediatrics and Adolescent Medicine, Akershus University Hospital, Truls Leegaard at the Department of Microbiology and Infection Control, Akershus University Hospital, David Hui and the Unit for Research Support at the Department of Internal Medicine, Akershus University Hospital, for invaluable practical assistance; Trygve Tjade and Sigve Fossum Grande at Fürst Medical Laboratory, Oslo, for laboratory analyses, Kirsten Haugland at Akershus University Hospital and Helge Røsjø and Torbjørn Omland at the University of Oslo and Akershus University Hospital for institutional support; and finally, all the study participants.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1345787/full#supplementary-material

References

1. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. (2021) 397:220–32. doi: 10.1016/S0140-6736(20)32656-8

2. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet*. (2021) 398:747–58. doi: 10.1016/S0140-6736(21)01755-4

3. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*. (2021) 594:259–64. doi: 10.1038/s41586-021-03553-9

4. Logue JK, Franko NM, McCulloch DJ, McDonald D, Magedson A, Wolf CR, et al. Sequelae in adults at 6 months after COVID-19 infection. *JAMA Netw Open*. (2021) 4:e210830. doi: 10.1001/jamanetworkopen.2021.0830

5. Haddad A, Janda A, Renk H, Stich M, Frieh P, Kaier K, et al. Long COVID symptoms in exposed and infected children, adolescents and their parents one year after SARS-CoV-2 infection: a prospective observational cohort study. *EBioMedicine*. (2022) 84:104245. doi: 10.1016/j.ebiom.2022.104245

6. Premraj L, Kannapadi NV, Briggs J, Seal SM, Battaglini D, Fanning J, et al. Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: a meta-analysis. *J Neurol Sci*. (2022) 434:120162. doi: 10.1016/j.jns.2022.120162

7. Molteni E, Sudre CH, Canas LS, Bhopal SS, Hughes RC, Antonelli M, et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. *Lancet Child Adolesc Health*. (2021) 5:708–18. doi: 10.1016/S2352-4642(21)00198-X

8. Pinzon RT, Wijaya VO, Jody AA, Nunsio PN, Buana RB. Persistent neurological manifestations in long COVID-19 syndrome: a systematic review and meta-analysis. *J Infect Public Health*. (2022) 15:856–69. doi: 10.1016/j.jiph.2022.06.013

9. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JVWHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*. (2022) 22:e102–7. doi: 10.1016/S1473-3099(21)00703-9

10. Wong TL, Weitzer DJ. Long COVID and Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)—a systemic review and comparison of clinical presentation and symptomatology. *Medicina*. (2021) 57:418. doi: 10.3390/medicina57050418

11. Havdal LB, Berven LL, Selvakumar J, Stiansen-Sonerud T, Leegaard TM, Tjade T, et al. Neurological involvement in COVID-19 among non-hospitalized adolescents and young adults. *Front Neurol*. (2022) 13:915712. doi: 10.3389/fneur.2022.915712

12. Virhammar J, Nääs A, Fällmar D, Cunningham JL, Klang A, Ashton NJ, et al. Biomarkers for central nervous system injury in cerebrospinal fluid are elevated in COVID-19 and associated with neurological symptoms and disease severity. *Eur J Neurol*. (2021) 28:3324–31. doi: 10.1111/ene.14703

13. Kanberg N, Ashton NJ, Andersson LM, Yilmaz A, Lindh M, Nilsson S, et al. Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. *Neurology*. (2020) 95:e1754–9. doi: 10.1212/WNL.0000000000010111

14. Franke C, Ferse C, Kreye J, Reincke SM, Sanchez-Sendin E, Rocco A, et al. High frequency of cerebrospinal fluid autoantibodies in COVID-19 patients with neurological symptoms. *Brain Behav Immun*. (2021) 93:415–9. doi: 10.1016/j.bbi.2020.12.022

15. Solomon T. Neurological infection with SARS-CoV-2 — the story so far. *Nat Rev Neurol*. (2021) 17:65–6. doi: 10.1038/s41582-020-00453-w

16. Hanson BA, Visvabharathy L, Ali ST, Kang AK, Patel TR, Clark JR, et al. Plasma biomarkers of Neuropathogenesis in hospitalized patients with COVID-19 and those with Postacute sequelae of SARS-CoV-2 infection. *Neurol Neuroimmunol Neuroinflamm*. (2022) 9:e1151. doi: 10.1212/NXI.0000000000001151

17. Pröbstel AK, Schirmer L. SARS-CoV-2-specific neuropathology: fact or fiction? *Trends Neurosci*. (2021) 44:933–5. doi: 10.1016/j.tins.2021.10.006

18. Van den Bergh O, Witthöft M, Petersen S, Brown RJ. Symptoms and the body: taking the inferential leap. *Neurosci Biobehav Rev*. (2017) 74:185–203. doi: 10.1016/j.neubiorev.2017.01.015

19. Barrett LF, Simmons WK. Interoceptive predictions in the brain. *Nat Rev Neurosci*. (2015) 16:419–29. doi: 10.1038/nrn3950

20. Selvakumar J, Havdal LB, Drevvatne M, Brodwall EM, Lund Berven L, Stiansen-Sonerud T, et al. Prevalence and characteristics associated with post-COVID-19 condition among nonhospitalized adolescents and young adults. *JAMA Netw Open*. (2023) 6:e235763. doi: 10.1001/jamanetworkopen.2023.5763

21. Wang S, Quan L, Chavarro JE, Slopen N, Kubzansky LD, Koenen KC, et al. Associations of depression, anxiety, worry, perceived stress, and loneliness prior to infection with risk of post–COVID-19 conditions. *JAMA Psychiatry*. (2022) 79:1081–91. doi: 10.1001/jamapsychiatry.2022.2640

22. Fyfe I. Neurofilament light chain — new potential for prediction and prognosis. *Nat Rev Neurol*. (2019) 15:557–7. doi: 10.1038/s41582-019-0265-2

23. Zetterberg H. Is there a value of Neurofilament light as a biomarker for neurodegeneration in Parkinson's disease? *Mov Disord*. (2020) 35:1111–2. doi: 10.1002/mds.28101

24. Abu-Rumeileh S, Abdelhak A, Foschi M, D'Anna L, Russo M, Steinacker P, et al. The multifaceted role of neurofilament light chain protein in non-primary neurological diseases. *Brain*. (2023) 146:421–37. doi: 10.1093/brain/awac328

25. Hendricks R, Baker D, Brumm J, Davancaze T, Harp C, Herman A, et al. Establishment of neurofilament light chain Simoa assay in cerebrospinal fluid and blood. *Bioanalysis*. (2019) 11:1405–18. doi: 10.4155/bio-2019-0163

26. Lee Y, Lee BH, Yip W, Chou P, Yip BS. Neurofilament proteins as prognostic biomarkers in neurological disorders. *Curr Pharm Des*. (2020) 25:4560–9. doi: 10.2174/1381612825666191210154535

27. Cabezas JA, Bustamante A, Giannini N, Pecharroman E, Katsanos AH, Tsivgoulis G, et al. Discriminative value of glial fibrillar acidic protein (GFAP) as a diagnostic tool in acute stroke. Individual patient data meta-analysis. *J Investig Med*. (2020) 68:1379–85. doi: 10.1136/jim-2020-001432

28. Laverse E, Guo T, Zimmerman K, Foiani MS, Velani B, Morrow P, et al. Plasma glial fibrillary acidic protein and neurofilament light chain, but not tau, are biomarkers of sports-related mild traumatic brain injury. *Brain Commun*. (2020) 2:fcaa137. doi: 10.1093/braincomms/fcaa137

29. Watanabe M, Nakamura Y, Michalak Z, Isobe N, Barro C, Leppert D, et al. Serum GFAP and neurofilament light as biomarkers of disease activity and disability in NMOSD. *Neurology*. (2019) 93:e1299–311. doi: 10.1212/WNL.0000000000008160

30. Abdelhak A, Foschi M, Abu-Rumeileh S, Yue JK, D'Anna L, Huss A, et al. Blood GFAP as an emerging biomarker in brain and spinal cord disorders. *Nat Rev Neurol*. (2022) 18:158–72. doi: 10.1038/s41582-021-00616-3

31. Sutter R, Hert L, de Marchis GM, Twerenbold R, Kappos L, Naegelin Y, et al. Serum Neurofilament light chain levels in the intensive care unit: comparison between severely ill patients with and without coronavirus disease 2019. *Ann Neurol*. (2021) 89:610–6. doi: 10.1002/ana.26004

32. Aamodt AH, Høgestøl EA, Popperud TH, Holter JC, Dyrhol-Riise AM, Tonby K, et al. Blood neurofilament light concentration at admittance: a potential prognostic marker in COVID-19. *J Neurol*. (2021) 268:3574–83. doi: 10.1007/s00415-021-10517-6

33. Sahin BE, Celikbilek A, Kocak Y, Saltoglu GT, Konar NM, Hizmali L. Plasma biomarkers of brain injury in COVID-19 patients with neurological symptoms. *J Neurol Sci*. (2022) 439:120324. doi: 10.1016/j.jns.2022.120324

34. Abdelhak A, Barba L, Romoli M, Benkert P, Conversi F, D'Anna L, et al. Prognostic performance of blood neurofilament light chain protein in hospitalized COVID-19 patients without major central nervous system manifestations: an individual participant data meta-analysis. *J Neurol*. (2023) 270:3315–28. doi: 10.1007/s00415-023-11768-1

35. Rogatzki MJ, Szeghy RE, Stute NL, Province VM, Augenreich MA, Stickford JL, et al. Plasma UCHL1, GFAP, tau, and NfL are not different in young healthy persons with mild COVID-19 symptoms early in the pandemic: a pilot study. *Neurotrauma Rep*. (2023) 4:330–41. doi: 10.1089/neur.2023.0014

36. Telser J, Grossmann K, Weideli OC, Hillmann D, Aeschbacher S, Wohlwend N, et al. Concentrations of serum brain injury biomarkers following SARS-CoV-2 infection in individuals with and without long-COVID-results from the prospective population-based COVI-GAPP study. *Diagnostics*. (2023) 13:2167. doi: 10.3390/diagnostics13132167

37. Grizzle R. Wechsler intelligence scale for children In: Goldstein, S., Naglieri, J.A. (eds) *Encyclopedia of Child Behavior and Development*. 4th ed Springer, Boston, MA. (2011). 1553–5. https://doi.org/10.1007/978-0-387-79061-9_3066

38. Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins verbal learning test – revised: normative data and analysis of inter-form and test-retest reliability. *Clin Neuropsychol*. (2010) 12:43–55. doi: 10.1076/clin.12.1.43.1726

39. Klepstad P, Loge JH, Borchgrevink PC, Mendoza TR, Cleeland CS, Kaasa S. The Norwegian brief pain inventory questionnaire. *J Pain Symptom Manag*. (2002) 24:517–25. doi: 10.1016/S0885-3924(02)00526-2

40. Åkerstedt T, Ingre M, Kecklund G, Folkard S, Axelsson J. Accounting for partial sleep deprivation and cumulative sleepiness in the three-process model of alertness regulation. *Chronobiol Int*. (2009) 25:309–19. doi: 10.1080/07420520802110613

41. Norwegian Institute of Public Health, *Norwegian immunisation registry SYSVAK*. (n.d.). Available online at: https://www.fhi.no/en/hn/health-registries/norwegian-immunisation-registry-sysvak/ (Accessed ongoing at time of follow-up visits)

42. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International chronic fatigue syndrome study group. *Ann Intern Med*. (1994) 121:953–9. doi: 10.7326/0003-4819-121-12-199412150-00009

43. Kanberg N, Simrén J, Edén A, Andersson LM, Nilsson S, Ashton NJ, et al. Neurochemical signs of astrocytic and neuronal injury in acute COVID-19 normalizes during long-term follow-up. *EBioMedicine*. (2021) 70:103512. doi: 10.1016/j.ebiom.2021.103512

44. Comeau D, Martin M, Robichaud GA, Chamard-Witkowski L. Neurological manifestations of post-acute sequelae of COVID-19: which liquid biomarker should we use? *Front Neurol*. (2023) 14:1233192. doi: 10.3389/fneur.2023.1233192

45. Bark L, Larsson IM, Wallin E, Simrén J, Zetterberg H, Lipcsey M, et al. Central nervous system biomarkers GFAp and NfL associate with post-acute cognitive impairment and fatigue following critical COVID-19. *Sci Rep*. (2023) 13:13144. doi: 10.1038/s41598-023-39698-y

46. de Boni L, Odainic A, Gancarczyk N, Kaluza L, Strassburg CP, Kersting XAK, et al. No serological evidence for neuronal damage or reactive gliosis in neuro-COVID-19 patients with long-term persistent headache. *Neurol Res Pract*. (2022) 4:53. doi: 10.1186/s42466-022-00217-5

47. Lennol MP, Ashton NJ, Moreno-Pérez O, García-Ayllón MS, Ramos-Rincon JM, Andrés M, et al. Transient changes in the plasma of astrocytic and neuronal injury biomarkers in COVID-19 patients without neurological syndromes. *Int J Mol Sci*. (2023) 24:2715. doi: 10.3390/ijms24032715

48. Farhadian SF, Reisert HD, McAlpine L, Chiarella J, Kosana P, Yoon J, et al. Self-reported neuropsychiatric post–COVID-19 condition and CSF markers of Neuroinflammation. *JAMA Netw Open*. (2023) 6:e2342741–1. doi: 10.1001/jamanetworkopen.2023.42741

49. Søraas A, Bø R, Kalleberg KT, Støer NC, Ellingjord-Dale M, Landrø NI. Self-reported memory problems 8 months after COVID-19 infection. *JAMA Netw Open*. (2021) 4:e2118717. doi: 10.1001/jamanetworkopen.2021.18717

50. Brunvoll SH, Nygaard AB, Fagerland MW, Holland P, Ellingjord-Dale M, Dahl JA, et al. Post-acute symptoms 3-15 months after COVID-19 among unvaccinated and vaccinated individuals with a breakthrough infection. *Int J Infect Dis*. (2023) 126:10–3. doi: 10.1016/j.ijid.2022.11.009

51. Øie MG, Rødø ASB, Bølgen MS, Pedersen M, Asprusten TT, Wyller VBB. Subjective and objective cognitive function in adolescent with chronic fatigue following Epstein-Barr virus infection. *J Psychosom Res*. (2022) 163:111063. doi: 10.1016/j.jpsychores.2022.111063

52. Sandler C, Cvejic E, Valencia BM, Li H, Hickie IB, Lloyd AR. Predictors of chronic fatigue syndrome and mood disturbance after acute infection. *Front Neurol*. (2022) 13:935442. doi: 10.3389/fneur.2022.935442

53. Su Y, Yuan D, Chen DG, Ng RH, Wang K, Choi J, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*. (2022) 185:881–895.e20. doi: 10.1016/j.cell.2022.01.014

54. Monje M, Iwasaki A. The neurobiology of long COVID. *Neuron*. (2022) 110:3484–96. doi: 10.1016/j.neuron.2022.10.006

55. Needham EJ, Ren AL, Digby RJ, Norton EJ, Ebrahimi S, Outtrim JG, et al. Brain injury in COVID-19 is associated with dysregulated innate and adaptive immune responses. *Brain*. (2022) 145:4097–107. doi: 10.1093/brain/awac321

56. Tsagkaris C, Bilal M, Aktar I, Aboufandi Y, Tas A, Aborode AT, et al. Cytokine storm and neuropathological alterations in patients with neurological manifestations of COVID-19. *Curr Alzheimer Res*. (2022) 19:641–57. doi: 10.2174/1567205019666220908084559

57. De Lorenzo R, Loré NI, Finardi A, Mandelli A, Cirillo DM, Tresoldi C, et al. Blood neurofilament light chain and total tau levels at admission predict death in COVID-19 patients. *J Neurol*. (2021) 268:4436–42. doi: 10.1007/s00415-021-10595-6

58. Sommen SL, Havdal LB, Selvakumar J, Einvik G, Leegaard TM. Inflammatory markers and pulmonary function in adolescents and young adults 6 months after mild COVID-19. *Front Immunol*. (2022) 13:1081718. doi: 10.3389/fimmu.2022.1081718

59. Saunders C, Sperling S, Bendstrup E. A new paradigm is needed to explain long COVID. *Lancet Respir Med*. (2023) 11:e12–3. doi: 10.1016/S2213-2600(22)00501-X

60. Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, et al. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ*. (2006) 333:575. doi: 10.1136/bmj.38933.585764.AE

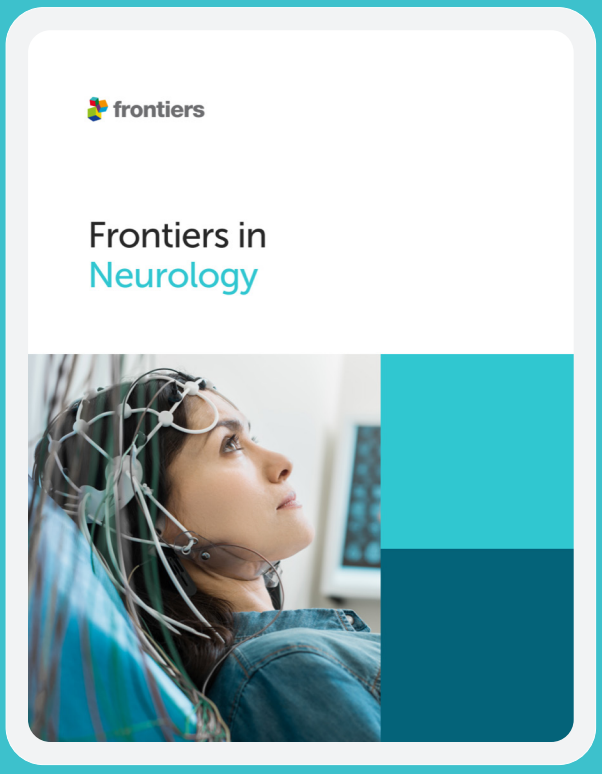
Frontiers in Neurology

Explores neurological illness to improve patient care

The third most-cited clinical neurology journal explores the diagnosis, causes, treatment, and public health aspects of neurological illnesses. Its ultimate aim is to inform improvements in patient care.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact