SN Comprehensive Clinical Medicine (2023) 5:9
https://doi.org/10.1007/s42399-022-01352-5

REVIEW

Brain fog as a Long-term Sequela of COVID-19

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Accepted: 17 November 2022 / Published online: 24 November 2022

Abstract
Increasing data indicate that people infected with COVID-19 are at high risk for developing long-term neurological complications, such as "brain fog" or cognitive impairment. However, little is known about the long-term outcomes of COVID-19 survivors. This also applies to the prevalence, risk factors, and pathobiological findings associated with these consequences. Although cognitive complications are anticipated in patients who require a long-lasting hospital stay or intubation, milder cases of COVID-19 with no record of hospitalization have also been shown to experience assessable cognitive challenges. Cognitive impairment can have a devastating impact on daily functioning. Understanding the long-term effect of COVID-19 on cognitive function is vital for applying specific schemes to those who wish to return to their jobs productively.

Keywords SARS-CoV-2 · COVID-19 · Long COVID · Virus infection · Cognitive impairment · Brain fog · Pathophysiology · Systemic inflammation

Introduction

Acute neurological complexities of hospitalized patients with the coronavirus disease 2019 (COVID-19) have globally been reported in numerous studies, but incomplete data are present about long-standing cognitive and functional outcomes [1]. This is also the case for the prevalence, risk factors, and pathophysiology of these complications [1].

In accordance with the Centers for Disease Control and Prevention (CDC), "long COVID" is described as a disease with a group of symptoms affecting different organs that develops throughout or following a confirmed or suspected case of COVID-19 and persists for more than 28 days [2–8].

Major features of "long COVID" consist of breathing difficulty, headache, pain in the chest, gastrointestinal symptoms, myalgia, fatigue, cognitive impairment, anxiety, and depression [6, 8–12]. The chance of "long COVID" manifestations was shown to be higher in cases who had more severe COVID-19 sickness, while white and non-white patients were found to be similarly involved [8].

Therefore, there is mounting warning concerning probable long-standing consequences of COVID-19, with statements of "long COVID" symptoms prolonging into the chronic stage, which include "brain fog" [7]. Although cognitive complications are anticipated in those patients who require a long-lasting hospital stay or intubation [13], milder cases of COVID-19 with no record of hospitalization have also been shown to experience assessable cognitive challenges [7].

As a result, since there are a wide range of manifestations in patients with "long COVID," multi-disciplinary teams are crucial to work together in order to develop preventive measures, rehabilitation techniques, and clinical management methods with whole-patient perspectives designed to deal with "long COVID" care. In addition, given the worldwide impact of COVID-19 and its indecisive long-term sequelae, a better understanding of the prevalence, risk factors, and pathophysiology of the condition is of primary importance.

Prevalence of Neuropsychiatric Symptoms of "Long COVID"

A systematic review and meta-analysis identified a total of 18,251 publications, which included 47,910 patients (aged 17–87 years), on the long-term effects of COVID-19 and found that 80% of the infected patients with "severe acute

This article is part of the Topical Collection on *Covid-19*

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respiratory syndrome coronavirus 2" (SARS-CoV-2) developed one or more long-term symptoms [14]. In this study, the five most common symptoms were fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%) [14].

Neuropsychiatric symptoms of post-acute sequelae of SARS-CoV-2 infection, such as disrupted sleep, headaches, anxiety, depression, impaired attention, and memory loss can occur after severe or mild disease [15] at a frequency of 31–69% [16].

A systematic review found that 36.4% of patients with COVID-19 developed neurological symptoms after analyzing data from 67 studies [17]. Several retrospective cohort studies of COVID-19 survivors found that one-third of the patients developed neurological or psychiatric symptoms 6 months after SARS-CoV-2 infection [18, 19].

A high incidence of cognitive impairment in post-COVID-19 patients, exceeding 50% in all studies, has been reported in numerous studies, and cognitive impairment was more common in critically ill patients with COVID-19 [20–25]. Interestingly, in a cohort study of 1438 COVID-19 survivors, 10% of severe COVID-19 survivors had dementia and 26.54% had mild cognitive impairment (MCI) 6 months after discharge [26]. At 12 months, the number of dementia patients increased to 15%, whereas the number of patients with MCI remained at 26.15% [26].

Method

A literature survey was conducted using databases in order to collect data for a narrative review of published reports regarding "brain fog" among COVID-19 survivors using abovementioned keywords. In this review, based on the analysis of relevant scientific evidence from original epidemiological studies, systematic review and meta-analysis, case series, cohort studies, and databases published to date, the prevalence of "brain fog" and other neuropsychiatric symptoms of "long COVID," "brain fog" among COVID-19 survivors, the mechanisms underlying "brain fog" or cognitive dysfunction after COVID-19, neuroimaging findings of "long COVID," and risk factors for "long COVID" were summarized.

Several studies with different level of evidence were identified. They included an ongoing longitudinal study [a total of 153 non-hospitalized patients with confirmed COVID-19] [27], a case series [describing COVID-19 symptoms persisting a mean of 60 days after onset among Italian patients previously discharged from COVID-19 hospitalization] [28], a telephone interview [a random sample of adults aged ≥ 18 years with milder COVID-19 illness at an outpatient visit at one of 14 U.S. academic health care systems in 13 states] [29], a cross-sectional study [young patients 20–105 days after recovery from mild-to-moderate disease who visited an outpatient clinic for post-COVID-19 care] [30], a systematic review of the literature (six studies which documented the prevalence of cognitive impairment, and one which quantified deficits after recovery) [31], a cross-sectional study [examined rates of cognitive impairment among patients who survived COVID-19] [32], an online survey [3762 participants with confirmed or suspected COVID-19, from 56 countries, with illness lasting over 28 days] [6], a prospective study of 6-month outcomes of hospitalized COVID-19 patients [1], a prospective uncontrolled cohort study [survivors of COVID-19 who had been hospitalized in a university hospital in France, underwent a telephone assessment 4 months after discharge] [33], a prospective study [data from 4,182 incident cases of COVID-19 in which individuals self-reported their symptoms lasting ≥ 28 days] [34], an ambidirectional cohort study [patients with confirmed COVID-19 who had been discharged from Jin Yin-tan hospital so that the median follow-up time after symptom onset was 186 days] [35], a retrospective cohort study [based on linked electronic health records data from 81 million patients including 273,618 COVID-19 survivors within 6 months and in the 3 to 6 months after COVID-19 diagnosis] [8], a cross-sectional cognitive performance [data from 81,337 participants who had recovered from COVID-19, including those no longer reporting symptoms, exhibited significant cognitive deficits versus controls] [7], a cohort study [administered the Montreal Cognitive Assessment at admission to 77 patients undergoing inpatient rehabilitation for COVID-19 in a large US academic medical center] [36], a cross-sectional study [recruited 1539 COVID-19 inpatients aged over 60 years who were discharged from three COVID-19-designated hospitals versus controls] [37], a cohort study [examined self-reported memory problems 8 months after COVID-19 infection] [38], a systematic review and meta-analysis [quantified the proportion of individuals experiencing fatigue and cognitive impairment 12 or more weeks following COVID-19 diagnosis] [39], a cohort study [215 patients, who had developed COVID-19, were examined 4 months after the diagnosis by means of neurological exam and extensive cognitive evaluation, investigating general cognition, memory, verbal fluency, visuospatial abilities, and executive functions. Fifty-two of them were treated in intensive care unit (ICU patients), whereas 163 were not hospitalized (non-ICU patients)] [40], a cohort study by the full set of questionnaires after 6–9 months post-infection [none had received treatment in an intensive care unit or were seeking post-COVID care at the time the study] [41], a cross-sectional online study [478 adult volunteers who self-reported a positive test for COVID-19 (mean = 30 days since most recent test) in participants who did not require hospitalization] [42], a cohort study [recruited COVID-19 survivors 60 years and older at 6 and 12 months after patient discharge

from 3 COVID-19-designated hospitals] [26], a cohort study [investigated the frequency, pattern and severity of cognitive impairments 3–4 months after COVID-19 hospital discharge] [20], a cohort study [compared critically ill and non-critically ill patients categorized according to the presence of acute respiratory distress syndrome (ARDS)] [21], a prospective cohort study [assessed neurological and cognitive symptoms in hospitalized COVID-19 patients and aimed to determine their neuronal correlates] [22], a cross-sectional analysis of a prospective study of hospitalized COVID-19 survivors followed up for 2 months after discharge [23], an ongoing prospective cohort study [the psychopathological and cognitive status of 226 COVID-19 pneumonia survivors (149 male, mean age 58) were prospectively evaluated 1 and 3 months after hospital discharge] [24], a meta-analysis of the Montreal Cognitive Assessment (MoCA) [performed with a subgroup of 290 individuals and showed a difference in MoCA score between post-COVID-19 patients versus controls] [25].

Review articles [13, 43–47] were also included where citing to their specific points had to be made ethically.

"Brain Fog" Among COVID-19 Survivors

One of the common concerns with "long COVID" includes cognitive impairment or "brain fog." Although many people who acquire COVID-19 heal with no persistent consequences, as many as 1 in 3 persist to go through cognitive deficits for weeks or even months with an assortment of symptoms, including "brain fog" [8]. Therefore, it looks like that cognitive impairment after a person is affected by the coronavirus is much more common than most other viral diseases.

"Brain fog" is a descriptive term, which is usually used by patients to explain what they experience with a diverse collection of problems in intellectual functions. However, cognitive impairment is a neuropsychological sign that is usually used by scientists to explain the loss of intellectual functions, such as thinking, remembering, and reasoning of sufficient severity to interfere with daily functioning [48–50].

Therefore, "brain fog," as it is defined by the World Health Organization (WHO), is an informal term for a common complaint of intellectual functions among patients with post-acute COVID-19 [51]. It is an umbrella term used to explain the constellation of cognitive function impairment, such as confusion, short-term memory loss, dizziness, and inability to concentrate [51].

Numerous studies have described deficient cognitive functioning in COVID-19 survivors [1, 6–8, 13, 20–46, 50]. To emphasize on important finding of cognitive impairment in "long COVID," a few studies are summarized and commented to give the reader a better perspective of the issue.

In an approved retrospective study by the University College London (UCL) describing "long COVID" in an international cohort (3762 participants from 56 countries, with the disease lasting over 28 days), over 88% of patients complained of cognitive impairment, which the authors specified as poor attention, impaired analysis of logical reasoning, and difficulty in making a decision [6]. Only a small fraction of those (10%) had been admitted to a hospital with severe COVID-19 in the past [6]. Memory and cognitive dysfunction were experienced similarly across all age groups in this cohort [6]. In addition to other commonly recorded neuropsychiatric symptoms, memory and cognitive deficits may even spot on larger neurological complications, engaging both the central and peripheral nervous systems [6]. Lengthy, multisystem engagement and major disability were also found in patients with "long COVID" in this study so that many patients could not achieve recovery mostly from systemic and neurological/cognitive indications after 7 months [6]. As a result, they could not even return to their jobs and carried on experiencing a substantial symptom load [6]. In this study, patients who returned to their jobs noticed relapses provoked by the mental effort and stress of work, frequently requiring them to leave their jobs [6]. This calls attention to the significance of the issue in order to allow all survivors of COVID-19 having sufficient time off to gain the recovery, being able to meet the criteria for disability welfare if ongoing support is required, and earning convenient facilities at work, including homework, flexible work hours, and step-by-step returns.

In general, these outcomes prove that the morbidity of COVID-19 has been significantly disregarded, even with the fact that the occurrence of multisystem symptoms has led to major crashes on patients' lives and livelihoods, and this impact has not been counted.

However, hospitalization was found to be a key determinative element in a large-scale investigation in the United Kingdom (UK) [7]. When the results of an intelligence test were assessed in more than 81,000 people, the study identified that patients who had recovered from COVID-19 underachieved compared with the control group who never had COVID-19 [7]. The rank of underachievement was found to be related to the severity of the disease, with those patients who had been ventilated in the hospital demonstrating the greatest cognitive dysfunction [7]. In this study, detailed cognitive examination and questionnaire records from a very large cross-section of a wide range of people (81,337 participants), mainly inside the UK, were performed [7]. They then illustrated that patients who had returned from COVID-19 to a former desirable state, including those no longer complaining of symptoms, suffered from considerable cognitive impairment compared with controls [7].

These findings prove that illness with COVID-19 is related to cognitive impairment that keeps up into the recovery stage

of the disease [7]. This is in agreement with accounts of "long COVID" where "brain fog" is making problem in concentrating and identification of the accurate words [7].

The healing from COVID-19 may be correlated with noticeable difficulties in characteristics of higher cognitive or "executive" function, an observation that concurs with preliminary records of executive dysfunction in a number of patients at hospital discharge [52], as well as previous findings in ventilated patients with acute respiratory distress syndrome pre-pandemic [13].

A prospective study of 4491 hospitalized patients with COVID-19 found that 606 (14%) had new neurological problems throughout hospitalization [53]. The same research group then tracked this preliminary cohort longitudinally for 6 months to assess long-term results [1]. Thus, a prospective study was designed to look at these hospitalized people with COVID-19, and they illustrated that over half of the neurologically affected patients complained of impaired thinking and reduced capability to independently accomplish daily activities 6 months after being discharged from the hospital [1]. In addition, 59% of those patients who were working prior to COVID-19 were incapable of returning to their jobs by 6 months [1]. Interestingly, they found that both sets of patients (patients identified with new neurological consequences for the duration of hospitalization for COVID-19 illness and hospitalized COVID-19 patients without neural complexities) held high ranks of cognitive impairment exceeding or approaching 50% at 6 months [1].

The rank and intensity of functional and cognitive impairments, as well as deficits in the temporary state of mind in COVID-19 hospital survivors, with or without neurological problems, should warn authorities to employ instructive and protective procedures directed at patients with COVID-19, medical practitioners, and the general public.

Another study assessed neurological function in a set of patients (age 38 to 59 years) several months after being treated for COVID-19 in outpatient, emergency department, or inpatient hospital locations and they uncovered that as many as 24% carried on the experience of cognitive complications, such as problems with memory, multitasking, processing speed, and concentration [32]. Deficiencies in executive functioning, processing speed, category fluency, memory encoding, and recall were found to be overriding among hospitalized COVID-19 patients [32]. A similar trend was also found in another study in which dysexecutive syndrome after COVID-19 was identified [54]. These findings have substantial indications for occupational, psychological, and functional results [32]. Although it is common for older adults to be prone to cognitive impairment after critical disease [55], the result of this study indicates that younger patients with COVID-19 are also at risk [32].

The Mechanisms Underlying "Brain Fog" or Cognitive Dysfunction After COVID-19

The etiology of cognitive impairment or "brain fog" is not yet clear. However, the proposed etiologies are discussed.

Since the hippocampal distribution of microglial activation has been interrelated to virus-induced cognitive impairment [56], this finding may explain the reason why some COVID-19 survivors show neuropsychiatric symptoms, such as memory disturbances, somnolence, fatigue, and insomnia [57]. In this regard, long-standing cognitive impairment and neurodegeneration, with associated hippocampal atrophy [58], have been previously shown to cause difficulties in systemic inflammation associated with severe sepsis [59, 60]. This may also be the case in acute respiratory distress syndrome (ARDS), a common clinical observation in COVID-19 patients, as it is also associated with cognitive impairment and neurodegeneration [13, 61].

Hypoxia or vascular injury can clarify cognitive dysfunction, especially in those COVID-19 cases with severe acute illness requiring intensive care and/or respiratory help [62]. Endothelial dysfunction, which causes microvascular damage, has also been proposed [63, 64]. Nevertheless, patients with mild COVID-19 infections also experience cognitive complaints [65]. In this respect, other mechanisms, including immunological dysregulation, chronic inflammation, or dysfunction of peripheral organs, have been proposed [66]. Other investigations have associated cognitive complaints with anxiety and depression [67].

Additionally, the cerebral white matter, which is vitally imperative for cognitive function, is principally vulnerable to ischaemic injury caused by COVID-19 [68]. There is growing evidence that cerebral hypoperfusion increases speed of amyloid-beta accumulation and is coupled with tau and TDP-43 pathology [68].

Furthermore, since cerebrospinal fluid examination with RT-PCR for SARS-CoV-2 in critically ill patients with COVID-19 failed to spot the virus [54], these results may advocate the proposition that systemic inflammatory injury plays an important role in the development of neurocognitive impairment following SARS-CoV-2 infection [69]. Cohort remarks [59, 70] also advocate that persistent systemic inflammation during COVID-19 infection is connected with subsequent cognitive impairment causing persistent electroencephalography (EEG) changes and hippocampal atrophy.

Aberrations in the coagulation system caused by SARS-CoV-2 infection have also been proposed [47]. These abnormalities may increase the permeability of the blood–brain barrier and boost the entry of SARS-CoV-2 into the brain parenchyma by disturbing TJ proteins [47]. In this view, since the hippocampus, temporal lobe, and thalamus that control cognition are shown to engage in a thrombotic and inflammatory cascade

resulting in capillary occlusion in SARS-CoV-2 infection, it causes ischemia and hypoxia injury to nerve cells nourished by these capillaries, which can encourage the occurrence of vascular cognitive impairment [47].

Finally, diffuse small vessel dysfunction has been reported in patients with COVID-19 [71–73], which can explain changes in cerebral blood flow in the cerebral white matter. Therefore, one of the outcomes of white matter injury in COVID-19 is likely to be cognitive impairment in affected individuals, as the integrity of the subcortical white matter is vital for the maintenance of cognitive function [74, 75]. This was confirmed by the neuroradiological observation that cerebral white matter damage and disturbance of functional integrity in brain areas, such as the hippocampus, at the 3-month follow-up in recovered COVID-19 patients, were associated with memory loss [76].

Neuroimaging Findings of "Long COVID"

Assessment of COVID-19 patients with neurological symptoms using current medical advances, such as electroencephalograms and neuroimaging, functional MRI (fMRI), and particular neurological clinical examinations, is anticipated to spot patients with specific neurological deficits [77–82].

Neuroimaging and electroencephalogrphy (EEG) have demonstrated structural and functional abnormalities in the frontal, temporal, and limbic areas of patients with post-acute sequelae of SARS-CoV-2 infection [83].

Neuroimaging studies have shown various findings. The most common structural abnormalities in COVID-19 have been reported to be within the olfactory network, which includes the limbic and prefrontal structures, and corpus callosum, followed by involvement of the insula, temporal lobe, basal ganglia, brainstem, and cerebellum [22]. This study also reported that cognitive impairment was associated with altered cerebral glucose metabolism in the subacute stage of COVID-19 [22].

Magnetic resonance imaging taken before and after SARS-CoV-2 infection has shown a greater reduction in gray matter thickness in the orbitofrontal cortex and parahippocampal gyrus, in addition to a greater reduction in overall brain size [84].

Furthermore, neuroradiological evidence of microstructural injury and disruption of functional brain integrity at the 3-month follow-up in recovered COVID-19 subjects [76] implies possible long-term neurological complications in severely infected COVID-19 cases [85].

Magnetic resonance imaging of autopsy brains from deceased COVID-19 cases within 24 h of death also showed white matter changes including foci of hemorrhage in two cases and proof of posterior reversible encephalopathy syndrome in another [86].

Risk Factors for "Long COVID"

Elevated levels of inflammatory markers (e.g., IL-6 and TNF-alpha) [87], female sex, older age, pre-existing asthma, and severity of initial disease [88] have been reported to increase the risk of post-acute sequelae of SARS-CoV-2 infection. Premorbid cognitive risk factors, such as hypertension, sleep apnea, depression, anxiety, and mild traumatic brain injury, in addition to abnormal cerebrospinal fluid results, have also been linked to cognitive complaints of post-acute sequelae of SARS-CoV-2 infection [83].

Risk factors of vascular injury have also been emerged as important predictors in the development of COVID-19 sequelae [89].

The severity of illness [18], ICU admission [18], multisystemic inflammatory syndrome in children (MIS-C) [90], and certain medication during acute COVID-19 infection all boost the risk of neurological sequelae in the post-acute COVID-19 stage [91].

A prospective cohort study of 1013 adults and 360 children, who were previously hospitalized with laboratory confirmed SARS-CoV-2 infection, examined the 6- and 12-month prevalence of post-COVID-19 condition and reported that half of adults and one of five children had post-COVID-19 condition at 6 months follow-up [92]. They found a higher risk among adult women for post-COVID-19 condition [92], which was in agreement with other studies [34, 35, 93]. Pre-existing hypertension (adults), and pre-existing neurological comorbidities, and allergic respiratory diseases (children) were also reported to be associated with post-COVID-19 condition [92]. Others also reported that allergic diseases in children were associated with a higher risk of "long COVID" [94].

Studies also suggest that "long COVID" is prevalent in adults [18, 34, 35, 95] and an increase in age is associated with a higher risk of "long COVID" [34, 94]. This is also the case in children as age was significantly associated with persistent symptom presence at the time of follow-up, with children aged ≥ 6 years being at a higher risk [94].

Among the cohort of non-hospitalized patients infected with SARS-CoV-2, risk factors for "long COVID" were female sex, belonging to an ethnic minority, socioeconomic deprivation, smoking, obesity, and a wide range of comorbidities [96].

Discussion

Neuropsychiatric symptoms of post-acute sequelae of SARS-CoV-2 infection are common and occur in both severe and mild cases. Hospitalization is a key

determinative element. This review emphasized on important finding of cognitive impairment in "long COVID" and warned authorities to employ instructive and protective procedures directed at patients with COVID-19, medical practitioners, and the general public.

Proposed pathological pathways leading to long-term COVID-19 complications include autoimmune processes in neuro-COVID-19, generalized hypoxia raised by pulmonary exudate or pulmonary fibrosis in COVID-19, blood–brain barrier dysfunction, chemokine and cytokine storm in "long COVID," lymphocyte responses in patients with "long COVID," and endothelial dysfunction [50].

Although the pathophysiology of "brain fog" in post-acute sequelae of SARS-CoV-2 infection, which characteristically consists of impairments in attention, executive function, and memory, is only about to be understood, a number of proposed etiologies were discussed. These included the hippocampal distribution of microglial activation, hippocampal atrophy, hypoxia or vascular injury, endothelial dysfunction, immunological dysregulation, chronic inflammation, dysfunction of peripheral organs, ischaemic injury of the cerebral white matter, aberration in the coagulation system, and diffuse small vessel dysfunction.

The outline of these abnormalities combined with laboratory, neuroimaging, electroencephalographic, and neuropsychological data implies that "brain fog" may be driven by direct and indirect injury to the neural networks in patients with post-acute sequelae of SARS-CoV-2 infection.

It is imperative to carry out long-term follow-up of COVID-19 patients, which includes detailed cognitive assessment, to establish the extent and prevalence of long-standing neurological and psychiatric complications of COVID-19, especially in patients who develop cerebrovascular and neurological complications during the course of acute illness.

It is also vital to learn about risk factors for "long COVID" because it can help take precautions about daily life and events. A better understanding of potential risk factors also highlights how a medical condition could affect health and anticipate probable medical treatments to reduce the risk of severe illness by managing any condition the individual has.

In addition, it is important to remember that the medications used in acute COVID-19, such as lopinavir-ritonavir and corticosteroids have neurological side effects that can manifest and persist during the acute or post-acute phase of illness. Therefore, clinicians should reflect on the neurological effects of these medications when monitoring patients in an outpatient setting for a long time.

The results of this review revealed that the effects of COVID-19 do not stop at acute infection resolution. In all patients with COVID-19, which is known to be a multi-organ disease, interdisciplinary monitoring is needed to identify post-acute COVID-19 symptoms before long-term systemic injury happens. Interdisciplinary monitoring also assists communication between providers regarding health care strategies and progress and avoids needless duplicate examinations, thereby saving patient time and health care costs. Policies and practices also need to be established to efficiently control and optimize partnerships between medical specialties, multiple health care professionals, and patients.

Conclusion

In summary, the data emphasize cognitive impairment as an imperative concern after COVID-19 infection, which necessitates inspection and follow-up. Meanwhile, clinical facilities should be equipped and ready to deal with "long COVID" characteristics in line with the best available indication as it becomes known [50].

Acknowledgements The author would like to express his honest gratitude and high respect for the lifetime support of his father, Mohammad Nouraeinejad.

Author Contribution The work has all been done by Ali Nouraeinejad.

Declarations

Consent to Publication The author has full right to publish this manuscript.

Conflict of Interest The author declares no competing interests.

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