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COVID-19 and Its Long-Term Neurological and Cognitive Implications: A Literature Review

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Abstract
Introduction: COVID-19 is an infectious disease resulting from severe acute respiratory syndrome. Individuals with prior COVID-19 infection have had neurological complaints of impaired attention, fatigue, and "brain fog". This review seeks to summarize the associations between COVID-19 infection and the development of the neurocognitive elements of post-acute COVID syndrome (PACS) which is relevant to healthcare workers for the efficient treatment and management of the long-term effects of COVID.
Methods: Literature that examines the neurocognitive complaints caused by COVID-19 infection, including brain fog, attention deficits, psychiatric impairment, and fatigue were selected. Google Scholar and PubMed were the primary databases used to obtain relevant literature. After preliminary searching, 21 articles were analyzed as part of this review.
Results: The following symptoms of PACS were persistently reported by a large majority (approximately ⅓ to ½) of patients: breathlessness, cough, fatigue, and brain fog. PACS neurological symptoms were more prevalent in females than in males. Reported psychiatric symptoms from prior COVID-19 infection were ADHD, depression, and insomnia.
Discussion: The causes of these neurocognitive symptoms were attributed to neuroinflammation of the choroid plexus, intracerebral hemorrhagic lesions, and hypoactivity in the anterior and posterior cingulate cortex. These possible pathways were confirmed with magnetic resonance imaging (MRI) findings, computed tomography (CT) scans, and positron emission tomography (PET) scans.
Conclusion: This paper will add to the evidence regarding the association between COVID-19 and the development of neurocognitive PACS. It is hoped that future research will build on a clearer understanding of the etiology of neurocognitive issues associated with viral infection.

Keywords: PACS; brain fog; neuroinflammation; COVID-19; SARS-CoV-2; cognition; neurological impairment

Introduction

The COVID-19 pandemic developed from the rapid spread of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection [1]. SARS-CoV-2 activates antiviral immune responses and can cause uncontrolled inflammatory reactions such as pro-inflammatory cytokine release, which can lead to lymphopenia (insufficient white blood cell count), lymphocyte dysfunction, granulocyte, and monocyte abnormalities [1]. COVID-19 results in a range of respiratory symptoms [2] which often manifest less than a week after infection and include fever, cough, nasal congestion, fatigue, and other signs typical of upper respiratory tract infection [3]. Worldwide, patients have subjectively reported other noticeable symptoms long after recovery from COVID-19 infection. These include exercise intolerance, fatigue, dyspnea, muscle pain, sleep difficulty, cough, chest pain, loss of smell (anosmia), and most notably, "brain fog" [4]. These symptoms fall under a more extensive condition known as post-acute COVID syndrome (PACS) [2].

PACS is the long-term complication of COVID-19 infection that persists beyond four weeks from the onset of symptoms [5]. A recent study in the United Kingdom noted the prevalence of fatigue, psychological distress, such as post-traumatic stress disorder (PTSD), anxiety, depression, concentration, and sleep abnormalities in approximately 30% of their study participants at the time of follow-up, 8-12 weeks after hospitalization for COVID-19 [5]. The preliminary research concerning the cognitive and neurological symptoms of PACS includes subjective reports of persistent cognitive impairment and "brain fog" in which patients describe feelings of mental slowness, being "fuzzy", or spaced out [4]. In a study by Graham and colleagues, 81 % of participants reported experiencing "brain fog" after COVID-19 infection [6]. In another study, common persisting symptoms after COVID-19 infection were fatigue (80%), respiratory complaints (59%), and neurological complaints (59%) followed by subjective cognitive impairments, sleep disturbance, and other mental health symptoms [7].

To date, the term "brain fog" in relation to clinical impairment is not fully understood, and there are many terms to describe this phenomenon with different conceptualizations. For example, a patient who experiences greater than 6 months of persistent fatigue may be diagnosed with chronic fatigue syndrome (CFS), and patients with CFS subjectively explain their symptoms as a "brain fog" [8]. "Brain fog" also has a relevant association with patients undergoing chemotherapy in which this impairment is referred to as "chemofog" or "chemo-brain", with an estimated 50% of patients reporting subjective fatigue long after treatment [2]. There has been much research into the etiology of the development of chemofog and results have suggested disrupted neurogenesis, aberrant myelination, interference with prefrontal activity, and neuroinflammation with cytokine dysregulation as potential mechanisms for development [2,8]. Given the history of persistent neurological symptoms after viral infection, it is imperative to systematically examine brain fog in PACS and its associated neurological and cognitive deficits.

The pathogenesis of these neurological cognitive impairments is currently unknown. Preliminary research has primarily focused on neuroinflammation as the source of the neurocognitive and clinical implications of PACS [2]. Research has shown that SARS-CoV-2 penetrates the olfactory mucosa and causes anosmia [9]. The virus is then believed to enter and infect the brain through the olfactory tract from the cribriform plate or through vagal or trigeminal nerve pathways [9]. Patients who have had severe COVID-19 infection experience a cytokine storm, and cytokine damage increases the permeability of the blood-brain barrier which could lead to more SARS-CoV-2 viral particles entering the brain and impacting neural functioning [9].

Neuroimaging findings in relation to COVID-19-associated brain fog are mixed, with different major brain areas being the topic of discussion in various studies. Several neuroimaging methods have been used to examine COVID-19-related impairment, including positron emission tomography (PET) scans [10] and magnetic resonance imaging (MRI) [11]. These imaging modalities have investigated functional changes in neural activity that persist in patients with prior COVID-19 infection. Investigation of the complications of the central nervous system (CNS) in relation to COVID-19 through neuroimaging techniques is rare and novel; however, it would be beneficial to understanding and confirming the existence of PACS [11]. Given the notable effects of COVID-19 infection on neurological and cognitive functioning, it is imperative that research examines the complications of COVID-19 infection long-term to aid diagnosis and effective treatment of PACS. Within this domain exists a gap in the literature which is due potentially to a lack of research concerning long-COVID, COVID-19 being a novel disease, surrounding conspiracies and controversy concerning COVID-19, and the inherent subjectivity of reports such as brain fog. The empirical studies and primary research concerning COVID-19 are still early and speculative. Clinicians should be aware of this research despite the fact that the field is still emerging, as it would benefit the healthcare system as the world approaches a post-covid society. Therefore, the aim of this paper is to review the current research concerning the neurological and cognitive implications of PACS.

Methods

For this literature review, only papers from 2020 onwards were selected given papers in this publication range have the most up-to-date and relevant information concerning COVID-19. The inclusion criteria were papers written in English and published in peer-reviewed journals. Exclusion criteria were conference proceedings and preprints. Papers that used empirical research and control groups were selected over meta-analyses and literature reviews. This review focused on cognitive symptoms such as brain fog, fatigue, and depression. Therefore, additional inclusion criteria were papers that specifically detailed the neurological and cognitive impacts of COVID-19 diagnosis and infection were chosen. Qualitative research, specifically patient testimonies, was also utilized for this literature review. Databases such as Google Scholar and PubMed were the search databases used for our initial search. Within the search engines, papers examining PACS or "Long-COVID`" were searched for. The first 100 papers (50 from PubMed and 50 from google scholar) were thoroughly assessed to fit the above criteria for brevity and limited research around PACS. 8 papers appeared in both google scholar and PubMed. 66 papers (32 from PubMed, 36 from google scholar, and 3 from the papers found in both databases) were excluded either because they were not related to COVID-19 or because they were not relevant to the research question. Ultimately, 21 papers were selected and analyzed further to explore and address this literature. 10 papers were selected from PubMed, 6 from google scholar, and 5 were found in both databases.

Results

Physical Symptoms and Neuroinflammation

Song et al. proposed that coughing, the hallmark symptom of COVID-19, develops due to the invasion of vagal sensory neurons by the SARS-CoV-2 virus, or neuroinflammation that leads to hypersensitivity of cough pathways [12]. They hypothesized that the neuroinflammation leading to cough might also lead to the neuropathology of PACS [12]. There is the possibility that SARS-CoV-2, in the choroid plexus of the brain may contribute to PACS. For example, Yang et al. found that the mouse choroid plexus has been reported to express several SARS-CoV-2 entry factors [1]. Some common persisting symptoms of COVID-19 were cough, fatigue, and dyspnea [13]. Mandal et al. followed up on all positive COVID-19 admissions by phone or in-person four to six weeks after leaving the hospital [13]. The symptoms were noted as present or absent on an 11-point scale of severity. It was found that 53% of patients (treated with oxygen + continuous positive airway pressure (CPAP) + intravenous therapy (IV)) from this study noted persistent breathlessness, 34% with a persistent cough, and 69% with persistent fatigue [13]. These physical symptoms were less reported in patients who were treated with oxygen alone [13]. The study by Augustin et al. investigated symptoms such as fatigue and shortness of breath using questionnaires and olfactory or gustatory tests [14]. Anosmia and ageusia symptoms, however, were solely investigated using questionnaires without being validated by olfactory or gustatory tests [14]. PACS was found to be characterized by fatigue, anosmia, ageusia or shortness of breath, which cannot be explained by an alternative diagnosis, symptoms also persisted 4 to 7 months post-infection [14]. These PACS symptoms were more frequent in COVID-19-infected female patients and were associated with lower serum SARS-CoV-2 IgG titers leading to humoral immune response, anosmia and diarrhea at disease onset [14].

Neuroimaging

MRI scans of those who were hospitalized from past COVID-19 infection showed a wide range of cerebral abnormalities ranging from intracerebral hemorrhagic lesions [11] to localization of the hypometabolic regions in the anterior and posterior cingulate cortex; involved in emotions, memory, depression, and actions [15]. MRI findings include abnormalities in the gray/white matter volumes in the medial temporal lobe in 43% of patients, hemorrhagic lesions in 30% of patients, and extensive isolated white matter microhemorrhages in 24% of patients [11]. The majority of patients (54%) in this retrospective observational study had intracerebral hemorrhagic lesions [11]. The cingulate cortex is involved in internally-directed cognition, and therefore, researchers have linked "brain fog" and other cognitive impairments resulting from COVID-19 infection to abnormalities in this brain region [10]. PET scans have also revealed hypometabolic activities in the cingulate cortex [10].

In rare cases, SARS-CoV-2 RNA was found in the cerebrospinal fluid of infected patients [11]. In addition, Yoon et al. examined patients that were admitted to a hospital in the United States with a positive PCR test, and who received MRI and computed tomography (CT) scans for neurological symptoms [10]. CT and/or MRI tests assessed Leukoencephalopathy, hemorrhage, and infarction. Clinical parameters such as body mass index, length of hospital stay, need for intubation, and development of acute renal injury were examined to determine whether these parameters correlated with MRI findings [10]. They found abnormal MRI results were significantly correlated with critical care unit admission of COVID-19 patients, as people with critical COVID cases also exhibited abnormal MRIs; hemorrhage, infarction, and leukoencephalopathy [10].

Cognitive and Neurological Effects

In the papers that met our inclusion criteria, the most common neurological symptoms of COVID-19 were fatigue and subjective reports of brain fog. For example, in a study by Graham et al., 81% of their study participants reported "brain fog" as a neurological manifestation, and 85% experienced fatigue [6]. The specific factors of brain fog were significantly more common in women, patients with respiratory problems at the onset of infection, and patients who were admitted to the ICU [4]. Patients complained that their brain fog affects their ability to think or concentrate [6]. Compared to the demographically matched US population, COVID-19 patients underperformed in cognitive tasks that involved attention and working memory [6]. The study by Asadi-Pooya et al. relied greatly on the subjective report of individuals with confirmed COVID-19 that have recovered from the illness, to study the prevalence of brain fog and its possible risk factors [4]. Data collection was acquired specifically using questionnaires, and patients were specifically phoned 3 months after being discharged from the hospital. 2696 patients fit the inclusion criteria; they were adult patients with a positive COVID-19 test, and they were admitted to healthcare facilities in Fars province, Iran from February 19, 2020, to November 20, 2020 [4]. 62.3% of the people were found to be affected by PACS; 7.2% of the patients reported PACS associated with brain fog [4]. In this large population-based study, the correlation between brain fog and the female sex, respiratory symptoms and severity of illness was identified portraying the importance of subjective reports and personal testimonies to further understand COVID-19 [4].

Psychiatric Symptoms

PACS shows associations with psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD), depression, and insomnia [4,16,17]. For example, in a study by Varatharaj et al., peripheral neuropathy, altered mental status, and cerebrovascular events were categorized as broad clinical symptoms linked to COVID-19 [16]. Data were compared to the geographic, demographic, and chronological presentation of all COVID-19 cases as reported by public health organizations under the UK government. Here, patients fulfilled the criteria for clinical case definitions for psychiatric diagnoses, which were classified by notifying a psychiatrist [16]. One study found that children affected by PACS were more likely to have ADHD [17]. Here, pre-COVID-19 ADHD diagnosis was substantially correlated with PACS diagnosis. In addition, PACS-associated psychiatric impairment was found to be more frequent in COVID-19-infected females than in males [4]. Of the sample

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(n=194) who were examined for brain fog, a female-to-male ratio of 102:92 was observed. As for the sample with no brain fog (n=2502), the female-to-male ratio was 1120:1382 [4]. A 1.417 odds ratio in females for reporting factors associated with brain fog was also observed [4].

Discussion

The present paper examined PACS in the context of four different domains: physical symptoms, neuroimaging findings, cognitive/neurological effects, and psychiatric symptoms. This research has shown that the COVID-19 viral invasion of vagal sensory neurons can lead to the progression of cough symptoms [12], in addition to causing inflammation and neural dysfunction that contribute to the development of PACS [1]. Neuroinflammation can also lead to the development of cough pathways, in addition to PACS neurological pathologies [12]. Cough, fatigue, and dyspnea were found to be among the common and persevering physical symptoms of COVID-19 [13]. Brain fog and fatigue are highly prevalent in study samples [6]. Hemorrhagic lesions [15], and localization of hypermetabolic regions in the anterior and posterior cingulate cortex were the common cerebral abnormalities observed in the MRI scans of previously hospitalized COVID-19 patients [11]. As stated above, the anterior and posterior cingulate cortices are involved in emotional processing, memory, depression, and decision-making [15]. Two cases of PACS are presented with abnormal FDG (fluorodeoxyglucose) PET imaging, indicated by hypometabolic regions of the cingulate cortex [15]. ADHD, depression, and insomnia are among the psychiatric symptoms associated with PACS [16]. In addition, PACS-associated psychiatric disorders were found to be more frequent in COVID-19-infected females than in males [4].

The neuroinflammation, psychiatric symptoms, and cognitive and neurological findings allowed a further understanding of the wide neurobiological effects of COVID-19 infection. Using neuroimaging techniques such as MRI, a wide range of cerebral abnormalities associated with the virus including its invasion of the cerebrospinal fluid in rare cases were identified [11]. According to neuroimaging studies, patients with prior COVID-19 infection also have thrombotic microangiopathy of cerebral blood vessels, increased bleeding propensity, and loss of self-regulation [18]. Although COVID-19 has been linked to an increased risk of thrombosis, it is unclear what associated mechanism is driving the continuous elevation in d-dimer- a sign of blood clotting disorder [13]. In addition, lung fibrosis may also develop if a chest radiograph shows signs of deterioration [13]. These findings are consistent with studies describing long-term problems in COVID-19-infected patients, as well as preliminary findings from small sample sizes [13]. Brain fog was also found to impair perceived mental clarity and the quality of life of infected patients [6]. Prolonged post-COVID "brain fog" was found to significantly correlate with female sex, early respiratory symptoms, and illness severity [4]. The association between chronic post-COVID brain fog and the female sex was particularly strong, suggesting that females may be more vulnerable to PACS than males; however, more work should be done to investigate the biological underpinnings of this correlation [4]. Children with PACS were also more likely to have ADHD, chronic urticaria (rash hives), and allergic rhinitis, indicating that clinicians caring for COVID-19-infected ADHD children should be on the lookout for PACS [15].

The prevalence of PACS continues to rely on the subjective reporting of cognitive complaints from previously-infected COVID-19 patients [4]. Subjective reporting can be considered a limitation to the accuracy of the studies conducted. One of the main drivers of subjective reporting is illness anxiety. This results in individuals over-reporting symptoms, skewing the studies that rely on data from questionnaires and telephone interviews post-COVID-19 infection. For example, in a study that relied on participants' reports of “brain fog” and fatigue as a neurological manifestation, the reports could be due to the participants self-reporting feelings of anxiety and confusion due to their uncertainty concerning their COVID-19 symptoms and diagnosis. post-COVID-19 [6]. Most of the studies reviewed were done in 2020 and 2021, so estimates of PACS might actually be artificially deflated and are expected to increase over time. The incidence of PACS is especially concerning given the relatively low COVID-19 vaccination rates worldwide. As of December 2022, it has been estimated that 68.7% of the world population has received at least one dose of the COVID-19 vaccine [19]. PACS should be a concern especially for low-income countries because only 25.1% of people in low-income countries have received at least one dose of the vaccine [19]. The lack of preparedness was a major contributor to the struggles healthcare facilities faced worldwide when the COVID-19 pandemic hit [20]. Items such as PPE, hospital equipment, sanitizing supplies, toilet paper, and water were in short supply. This burden eventually influenced patient care, surgeries, and surgical outcomes [20]. The estimated recovery rate for COVID-19 is a function of death rates, cases requiring hospitalization, quality of care, and discharge policies [21]. However, recovery from COVID-19 infection often does not account for PACS, brain fog, and other neurological symptoms of COVID-19; it simply accounts for acquiring a negative PCR test. Recovery rates worldwide might keep increasing due to the different methods used to combat and contain the spread of the virus. However, based on the present literature review, PACS is expected to persist and increase with time as more people may eventually be infected with the COVID-19 virus. Some of the studies included have smaller sample sizes and are only restricted to a specific population in one area of the world rather than including samples from multiple countries. This literature review will be beneficial in increasing the understanding of the cognitive implications of the COVID-19 pandemic on individuals and, ultimately, the healthcare system. A widespread understanding of PACS can allow clinicians to make informed decisions concerning post-COVID symptoms which will improve patient outcomes. Having an understanding of the impact on cognitive health due to COVID-19 can inform prevention efforts which could alleviate the burdens of the healthcare system for more efficient use of resources.

Conclusion

PACS is a neurocognitive entity that can be explored through many facets of clinical neuroscience. Therefore, the present paper is a view into the neurocognitive symptoms of COVID-19 which does not extensively capture the complexity of PACS in its entirety.

In conclusion, it is clear that COVID-19 infection is correlated with the onset of neurocognitive ailments such as fatigue, "brain fog", and psychiatric disorders that are linked with PACS. The pathway for SARS-CoV-2 to infect the CNS is not fully understood; however, neuroimaging techniques have revealed that areas such as the anterior and posterior cingulate cortex as well as markers in cerebrospinal fluid have been affected by COVID-19 infection. Having a clearer understanding of PACS will help to improve diagnosis and patient prognosis, as well as alleviate burdens on the healthcare system. This paper can support other works that describe associations between viral infection and neurocognitive impairments. In the future, more research should be done on understanding the etiology of neurocognitive complaints associated with viral infection.

List of Abbreviations Used

PACS: post-acute COVID-19 syndrome
CPAP: continuous positive airway pressure
MRI: magnetic resonance imaging
IV: intravenous therapy
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
PTSD: post-traumatic stress disorder
ADHD: attention deficit disorder
PET: positron emission tomography
ICU: intensive care unit
CFS: chronic fatigue syndrome
RNA: ribonucleic acid
PCR: polymerase chain reaction
CT: computed tomography
FDG: fluorodeoxyglucose
CNS: central nervous system

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

Our study did not require ethics approval and/or participant consent because no human participants or potentially unethical research methods were utilized.

Authors' Contributions

ANO: made contributions to the design of the study, acquisition and analysis of data, drafted the manuscript, and gave final approval of the version to be published
ZYH: made contributions to the design of the study, acquisition and analysis of data, drafted the manuscript, and gave final approval of the version to be published

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