Neurological and Psychiatric Symptoms of COVID-19: A Narrative Review

Amber N. Edinoff 1,*, Maithreyi Chappidi 2, E. Saunders Alpaugh 3, Bailey C. Turbeville 4, Evan P. Falgoust 4, Elyse M. Cornett 5, Kevin S. Murnane 1,6,7, Adam M. Kaye 8 and Alan D. Kaye 5

1 Department of Psychiatry and Behavioral Medicine, Louisiana State University Health Science Center Shreveport, Shreveport, LA 71103, USA; kevin.murnane@lsuhs.edu
2 Department of Neurology Shreveport, Louisiana State University Health Science Center Shreveport, Shreveport, LA 71103, USA; maithreyi.chappidi@lsuhs.edu
3 Department of Anesthesiology, Louisiana State University Health Science Center New Orleans, New Orleans, LA 70112, USA; edward.alpaugh@lsuhs.edu
4 School of Medicine, Louisiana State University Health Science Center Shreveport, Shreveport, LA 71103, USA; bct002@lsuhs.edu (B.C.T.); epf001@lsuhs.edu (E.P.F.)
5 Department of Anesthesiology, Louisiana State University Health Science Shreveport, Shreveport, LA 71103, USA; elyse.bradley@lsuhs.edu (E.M.C.); alan.kaye@lsuhs.edu (A.D.K.)
6 Louisiana Addiction Research Center, Shreveport, LA 71103, USA
7 Department of Pharmacology, Toxicology & Neuroscience, Louisiana State University Health Shreveport, Shreveport, LA 71103, USA
8 Department of Pharmacy Practice, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, CA 95211, USA; akaye@pacific.edu
* Correspondence: amber.edinoff@lsuhs.edu

Abstract: Recently dubbed Long COVID or Long-Haul COVID, those recovering from the initial COVID-19 infection may maintain clinical signs for longer than two or more weeks following the initial onset of the infection. The virus can gain entry into the CNS through axonal transport mediated through the olfactory nerve or hematogenous spread and can also cross the blood–brain barrier to access the temporal lobe and the brainstem. The neurologic and neuropsychiatric symptoms associated with COVID-19 patients are becoming a highly studied area due to the increased frequency of reported cases. Multiple hospital case series and observational studies have found a headache to be a common symptom among patients who are symptomatic with the SARS-CoV-2 virus. The headache described by many of these patients is similar to new daily persistent headache (NDPH). NDPH potentially develops in response to pro-inflammatory cytokines during a persistent systemic or CNS inflammation, mostly due to the initial infection. The treatments investigated were high-dose steroids, tetracycline derivatives, onabotulinum toxin type A, and long-term multidrug regimens. Among the identified symptoms of post-COVID-19 viral illness, fatigue appears to be the most ubiquitous. High-dose vitamin C is currently a suggested therapy proposed for its antioxidant, anti-inflammatory, and immunomodulatory properties. The mental health consequences of this diagnosis are being identified among large portions of COVID-19 survivors. Among these consequences, cases of major depressive disorder (MDD) and anxiety are being reported and closely examined. The aim of this narrative review is to highlight the neurological and psychiatric symptoms that have been associated with Long-Haul COVID and their possible treatments.

Keywords: COVID-19; long haul; anxiety; depression; fatigue; headaches

1. Introduction

Following the initial outbreaks of COVID-19, caused by the SARS-CoV-2 virus, multiple prolonged post-infectious symptoms have continued to appear. Patients who have initially recovered from the initial viral illness continue to present with a worsening quality of life and a delayed return to work, which causes a significant burden on the healthcare
community. Recently dubbed Long-Haul COVID, this occurs in those recovering from the initial COVID-19 infection who maintain clinical signs not seen before their COVID-19 infection for longer than two or more weeks following the initial onset of the infection [1]. Long-Haul COVID is further defined as Post-COVID-19 Syndrome and is when patients remain symptomatic with symptoms experienced during their COVID-19 infection without another possible etiology lasting for twelve weeks [2]. COVID-19 can enter the CNS through axonal transport mediated through the olfactory nerve or hematogenous spread. The virus can also cross the blood–brain barrier and access the temporal lobe and the brainstem, inflecting various reactions believed to contribute to neurologic and psychiatric manifestations. Further evidence of this entry has been demonstrated through a viral detection in the cerebral spinal fluid (CSF) of several patients [3,4]. Although respiratory complications are often associated, other presenting symptoms appear to involve various organ systems, including the CNS.

Even after recovery from a COVID-19 infection, patients can demonstrate a variety of neurologic and psychiatric conditions. These sequelae include headaches, depression, fatigue, cognitive impairment, delirium, and reported cases of psychosis [1,5]. More severe outcomes reported include cases of encephalitis, Guillain–Barre Syndrome, and strokes [1,4,5]. Further associated symptoms include anosmia, anhedonia, and dizziness. Elderly individuals are more vulnerable to developing these possible neuropsychiatric and cognitive impairments [6–8]. This is related to factors associated with increasing age and having more medical comorbidities [6]. As cases of prolonged symptoms continue to occur, a pattern of CNS and peripheral nervous system (PNS) involvement appears to be significant and may contribute to an overall worse quality of life and poorer outcomes [4]. At this time, there is no consensus on what exactly constitutes this Long-Haul COVID syndrome or its diagnostic criteria [2].

Following the initial infection, the secondary inflammatory reaction associated with COVID-19 produces a significant cytokine and chemokine response in one proposed mechanism [1]. The laboratory markers of inflammation such as IL-6, procalcitonin, ferritin, C-reactive protein (CRP), D-Dimer, and pro-BNP are typically elevated, especially in severe cases [1]. Additionally, microscopic pathological findings have been associated with many different organ systems, including congestion and edemas in the brain. They may contribute to prolonged neurological and psychiatric symptoms for months following the initial onset of the viral symptoms [9]. Although several therapies have targeted the anti-inflammatory response associated with COVID-19, the CNS remains vulnerable to the viral effects. Many CNS prolonged related symptoms may be directly related to COVID-19. Members of the coronavirus family such as the Middle Eastern Respiratory virus have shown long-term symptoms after the initial infection [10]. The virus that causes COVID-19 enters the brain via the viral S protein, which can bind to the ACE2 receptor [11]. This receptor is widely expressed in neurons, astrocytes, and oligodendrocytes throughout the brain [12]. Figure 1 shows the proposed mechanism of COVID-19 and neuroinflammation. Research suggests that the activation of the glial cells contributes to neuroinflammation, which leads to the effects of COVID-19 on the CNS [13]. The use of monoclonal antibodies in the acute phase of a COVID-19 infection seeks to neutralize this viral S protein [14]. Looking at these past viruses and the history of their infections, we may be able to predict what long-term effects COVID-19 may cause in patients. Early recognition and appropriate care may reduce the overall severity of neurologic and psychiatric conditions, especially for the elderly or patients with pre-existing medical comorbidities. The aim of this manuscript is the highlight the neurological and psychiatric symptoms that have been associated with Long-Haul COVID and their possible treatments, if available.
2. Neurological and Neuropsychiatric Symptoms of COVID-19

During the acute phase of a COVID-19 infection, it is estimated that about 36% of patients develop neurological symptoms and about 25% of these are thought to stem from the direct involvement of the CNS [15]. It is unclear who will develop any chronic symptoms as a result of a COVID-19 infection, but it is thought that the variation in viral load and a differential immune response play roles in the different clinical forms and possible formation of prolonged symptoms in COVID-19 infections [14]. These two factors seem to play a role in determining if a person will develop chronic symptoms after a COVID-19 infection.

Multiple hospital case series and observational studies are finding headaches to be a common symptom among patients who are symptomatic with the SARS-CoV-2 virus. A meta-analysis of many studies from China highlighted that a headache was reported in 6–15% of patients [16]. However, preliminary data from the United States, Australia, Korea, and China suggest that approximately 60% of patients infected with COVID-19 will present...
with symptoms of a headache at some point throughout the infection [17]. Most of the case series from the meta-analysis above reported no link between a headache and a fever in the patient population analyzed [16]. This relationship is important because distinguishing the associated symptoms with a COVID-19 headache could be relevant in future studies to narrow down the specific presentation of a newly emerging phenomenon.

The clinical characteristics of headaches associated with COVID-19 are being researched to differentiate a distinct presentation from other more common types of headaches. In a cross-sectional observational study, healthcare professionals with clinically diagnosed COVID-19 and reported headache symptoms participated. The study assessed the presence of headaches during the infection as well as the potential association of the patients with a personal history of headaches. The clinical symptoms used in the criteria to provide the COVID-19 diagnosis for the study included a collection of highly reported symptoms such as a fever, a cough, shortness of breath, chills, muscle pain, a sore throat, and a new loss of taste or smell. In the study, a laboratory confirmation was not performed in all cases, but RT-PCR or serologic tests were performed if the clinical diagnosis was unclear. Most of the participants were diagnosed based on the clinical symptoms alone, but PCR or serologic testing confirmation was used in 47.3% of the cases. The findings of the study showed that 25.9% of the group reported a history of headaches and 74.1% reported no prior history of a primary headache [16]. This finding suggests that most participants were experiencing a potentially previously unexperienced symptom (a headache) as a result of the infection.

Among the patients with COVID-19 who have reported experiencing a headache, characteristics such as duration, location, and quality can aid researchers in determining the etiology of headaches associated with the virus. Although a noticeable heterogeneity among headache symptoms has been reported, the overwhelming majority of reports include characteristics such as being holocranial, hemicranial, or located in the occipital region of the head and worsening with movement [16]. Headaches secondary to an infection exacerbated by a head movement or simultaneously displaying symptoms of photo-/phonophobia are of particular interest due to the potential etiology as a result of meningeal inflammation [18]. Although the hypothetical etiology of meningeal inflammation has not yet been elucidated, various mechanisms have supported the hypothesis. One proposed mechanism is the activation of the trigeminovascular system due to the neurotropic characteristics of SARS-CoV-2 with a peripheral activation after entry into the nasal cavity through the trigeminal branches. Another mechanism for entry is the binding of the virus to ACE2 receptors among the endothelial cells of the blood–brain barrier. A third potential mechanism supporting the meningeal inflammation hypothesis is a viral action onto the immune system to cause a cytokine storm through a hyperinflammatory state through IL-6 [19]. IL-6 has previously been demonstrated to have a role in neuroinflammation and elevated levels have also been noted in infected patients. A prospective study noted lower levels of IL-6 in patients with headaches than those without, possibly suggestive of a localized inflammation in those patients. Although neither mechanism has been confirmed, further studies are necessary to confirm these theories.

3. Daily Persistent Headache: Treatment and COVID-19 Relation

Having a headache with an initial infection is one thing, but many patients may have a persistent headache [20]. The headache described by many of these patients appears to be similar to new daily persistent headache (NDPH). NDPH was first described in 1986, but little is known of the condition, including the cause(s), pathophysiology, and treatment [21].

3.1. New Daily Persistent Headache

NDPH is a rare headache disorder described by a persistent headache with a specific and clearly remembered onset that continues daily without remitting. This type of headache often occurs after a viral illness. Due to the persistence and therapeutic refractoriness of NDPH, it is often described as disabling. The headache is described as mild to severe, constant, bilateral in most, and associated with migraine symptoms (pulsating quality,
photophobia, etc.), especially in patients with a viral illness at the onset of NDPH [22]. Of the patients with known precipitating events that occurred near to the onset of NDPH, most are attributed to a viral infection/febrile illness, especially in the pediatric population. The diagnosis of this headache type is based on a typical history with a continuous daily headache for ≥3 months and unremarkable neurologic exam/neuroimaging studies [23]. More pediatric patients are diagnosed than adult patients and women are diagnosed more often than men in adults. Most NDPH-described patients (80–98%) are Caucasian. Although the symptoms of several patients spontaneously resolve, the long-term prognosis is still unknown [21].

Studies regarding NDPH in post-COVID-19 infections are sparse at this time. However, a prospective study looked at headaches and the evolution of headaches in COVID-19 patients [24]. This study involved 130 patients, 97 of whom had a headache as a symptom when they were diagnosed with COVID-19 via positive PCR tests. Of those 97 patients with headaches, 28 of those had a headache for six weeks [24]. Of these 28 patients, 6 had a headache as a prodromal symptom of their impending COVID-19 infection. Although this study only followed these patients for six weeks and, therefore, they did not meet the criteria of NDPH, they would likely meet the needed criteria for three months. Longer studies are required and the link is still in its infancy.

3.2. Proposed Pathophysiology

Many predict that a viral infection causes an immune response that leads to the development of NDPH. A significant portion of patients experienced an infection/flu-like illness at the onset of the headaches. A few authors have associated NDPH with an Epstein–Barr virus (EBV) infection with 23–82% of patients correlating the onset of NDPH with an EBV infection in several small studies. Other studies have found evidence of recent Herpes simplex virus (HSV) and Cytomegalovirus as well as several other viral infections as the precipitating event, making a recent COVID-19 infection seem suitable as another possible cause of NDPH (21). In an acute COVID-19 infection, a theory of the development of a headache can stem from the release of several neuropeptides. The neuropeptides are thought to be glutamate, calcitonin gene-related peptide (CGRP), substance P, and pituitary adenylate cyclase-activating polypeptide (PACAP) from nociceptive sensory fibers that innervate blood vessels located in the meninges and other cranial structures. The neuropeptides lead to vasodilation, the degranulation of mast cells, and plasma extravasation into vascular structures [25].

NDPH also potentially develops in response to pro-inflammatory cytokines, which are released during a persistent systemic or CNS inflammation, mostly due to the initial infection. In a study looking at inflammatory marker tumor necrosis factor-alpha (TNF-α) levels in the CSF and serum of NDPH patients, 19 out of 20 patients from an inpatient headache unit had increased CSF TNF-α levels and normal serum TNF-α levels. This study suggested that the pain may be due to a chronic CNS inflammation, cytokine production, and persistent glial activation arising from precipitating factors [21]. This is likely the case in COVID-19 infections [26]. There are also thoughts that the pathophysiology of its features, which are similar to migraines, may reflect the activation of the trigeminovascular system by this inflammation or the direct involvement of the SARS-CoV-2 virus, which is supported by concomitant anosmia [24].

Several authors have noted that many NDPH patients had characteristics of connective tissue disorders with cervical spine joint hypermobility present. Others noted many patients with previous endotracheal intubation and NDPH. Thus, cervical spine hyperextension may also be involved in the pathogenesis of NDPH [21]. Several patients with severe COVID-19 infections required intubation, creating another avenue for recent COVID-19 infections to possibly cause NDPH [20,21].
3.3. Treatment

There is currently no specific treatment for NDPH. In clinical practice, most clinicians treat NDPH based upon the prominent headache type, whether migraine-like or tension-like symptoms. However, most treatments are either ineffective or are only partially effective [21] As a general observation, NDPH yields better prognoses if treated earlier. Even the case series of post-infectious NDPH of a shorter duration have shown favorable responses [22]. Many cases of NDPH spontaneously resolve [27]. However, there are a few treatment regimens that aim to decrease the immune response that potentially causes NDPH. These are detailed below.

Methylprednisolone: A study observed a treatment response to a 5-day high-dose IV methylprednisolone course in 9 NDPH patients who were post-infection. Of these, 6 who received intravenous methylprednisolone also received oral steroids for 2–3 weeks. All of the six patients reported an improvement. The time frame of the improvement varied, with a few experiencing an improvement after two weeks and others after 6–8 weeks. Of these 9 patients, 5 were treated within 2 weeks after the headache began instead of at least 3 months of headaches required for an NDPH diagnosis, which could be cited as a weakness of the study because the patients did not meet the full criteria for the diagnosis. Thus, a treatment with high-dose IV corticosteroids may not be as favorable in classic cases that fulfill the diagnostic criteria and further studies are required to assess its effectiveness [28].

Tetracycline derivatives: A study observed four patients with NDPH who also had high CSF TNF-α levels. They were given doxycycline twice daily for three months. Three of the four patients reported that an infection precipitated their headaches. All patients had an improvement within three months of the initiation of doxycycline with at least a 50% reduction in the frequency of headaches [21].

Onabotulinum toxin type A: In a retrospective review of NDPH patients treated with onabotulinum toxin A for 30 months, approximately half of the patients experienced a reduction in their headache frequency and approximately 75% demonstrated at least a partial improvement in headache severity after 12 months of treatment (3–4 injections) [29]. Several case reports have shown a significant improvement in individual patients with the complete to near-complete relief of symptoms when treated every three months [21].

Long-term multidrug regimens: A study that followed thirty patients diagnosed with NDPH who were treated for five years was investigated. Of the 30 patients, no patients identified the onset of a headache with an infection/febrile illness. Muscle relaxants were first administered. If no effect was observed, then tricyclic antidepressants, selective serotonin reuptake inhibitors, and anti-epileptic drugs were used as a treatment. After five years of treatment, 50% of the patients reported at least mild symptoms and 50% reported no improvement.

3.4. Fatigue

Among the identified symptoms of a post-COVID-19 viral illness, fatigue appears to be the most ubiquitous. Other infectious illnesses, including MERS-CoV, Q-Fever, Epstein–Barr virus, Ross River Virus (RRV), and rickettsiosis, have also seen a similar associated prolonged fatigue in the post-recovery period [30]. Additionally, bacterial and parasitic infections such as *Coxiella burnetii*, *Mycoplasma pneumonia*, and *Giardia lamblia* manifest multiple symptoms of persistent malaise [31]. Multiple clinical trials reported fatigue as the most prevalent among the post-recovery symptoms and cases have reported symptoms lasting up to 100 days following the initial symptoms of COVID-19 [1]. Similar studies have also demonstrated that physical and mental fatigue features persisted in the majority of studied patients following an initial infection of COVID-19 [32]. Although multiple clinical investigations of fatigue related to COVID-19 have been performed, a further prospective analysis of post-viral fatigue symptoms and an investigation into the pathophysiology is recommended.

A recent analysis identified pre-existing depression, anxiety, and the female gender as indications of a higher risk of developing chronic fatigue from COVID-19. Among the
studies examining the symptoms of fatigue, commonly associated indicators of the severity of the illness include the requirements of hospital admission, supplemental oxygen, and intensive care. However, these predispositions in the studied populations did not show any causal effects [33]. Additionally, the inflammatory markers (including LDH, CRP, lymphocyte count, IL-6, and sCD25) did not show this association. A few researchers have hypothesized that immune dysregulation plays a role in post-viral symptoms as SARS-CoV-2 involves a recently understood secondary cytokine storm that causes a variety of chemokine responses in the host immune system. Multiple studies have assessed alterations to the immune system, but have not shown any plausible biological explanation for its relation to Chronic Fatigue Syndrome (CFS) [30].

Similar analyses have examined a variety of predisposing comorbidities, the severity of the illness, and the characterization of the fatigue experienced post-recovery. Townsend et al. collected data from 128 subjects utilizing the Chalder Fatigue Scale (CFQ-11), which showed that 52.3% had continued fatigue symptoms at a median onset of 10 weeks. Additionally, this study concluded that there was no correlation between the length of illness, inpatient admission, the need for supplemental oxygen or critical care, or length of hospital stay either in the fatigue or CFQ score. The rate of fatigue in this cohort was higher than that found in the general population and similar to those with chronic disease states. Similarly, up to 40% of patients reported fatigue for up to a year post-SARS infections although the rate of post-COVID-19 fatigue was shown to be much higher in patients recovered from EBV, Q-Fever, or RRV [30].

Herck et al., who presented a similar patient-reported study, utilized the CIS-Fatigue score, which separates the severity based on the perception of the patient of feeling mentally or physically exhausted and in good or bad shape and the score classifies the severity of fatigue as mild, moderate, or severe. This study followed 239 subjects with a median age of 50 years and a confirmed COVID-19 infection. The scores were obtained at 10 and 23 weeks. From the follow-up analysis after treatment from at least one healthcare professional at 23 weeks, a significant number of patients reported severe fatigue at 10 and 23 weeks (85.4% and 78.7%, respectively). The patients reported a reduction in the mean fatigue scores (−2 points, \( p < 0.001 \)). However, at the end of the second period, 23 weeks, the physical fatigue reduction was more than the mental fatigue reduction (physical: −2 points \( p < 0.001 \); mental: 0 points, \( p < 0.52 \)). The authors concluded that online COVID-19 support group participants also showed a significant reduction in the mean score. However, the prevalence of severe fatigue was still high [33].

3.5. Proposed Treatment of Fatigue

High-dose vitamin C is currently a suggested therapy because of its antioxidant, anti-inflammatory, and immunomodulatory properties. Also known as ascorbic acid, vitamin C functions as a co-enzyme with a versatile involvement in many cellular processes. It promotes the synthesis of collagen and carnitine. It is further involved in the formation of neurotransmitters such as serotonin and dopamine as well as multiple biochemically active substances, including nitric oxide, noradrenaline, and amidated peptides. For this reason, vitamin C may help treat the signs of fatigue, cognitive disorders, pain, and symptoms of depression, which can manifest in the setting of oxidative stress and inflammation. A recent review of nine clinical trials demonstrated a positive impact of vitamin C therapy and a significant reduction in fatigue. Three out of the four controlled trials in this study showed a significant decrease in fatigue scores in the vitamin C group (31). Four of the five observations also noted a reduction in the pre and post levels of fatigue with the use of vitamin C [31]. Additionally, associated features, including sleep disturbances, pain, depression, and lack of concentration, also improved following high-dose vitamin C therapy [31].
4. Psychiatric Symptoms and COVID-19 Relation

Aside from COVID-19 delirium, the post-acute sequelae of the infection manifest as mood and cognitive impairments. Although the exact mechanism of these manifestations is yet to be understood, the perpetual presence of these symptoms is found in Long COVID syndrome. The cause of this effect of COVID-19 on cognition may result from four possible pathogenic mechanisms: direct encephalitis; systemic inflammation caused by the infection; peripheral organ dysfunction caused by hypoxia; or cerebrovascular changes [15]. There is a theory that the NLRP3 inflammasome may play a role in the neurological symptoms seen in infections caused by the COVID-19 virus [15]. There is evidence that this inflammasome plays a role in the pathogenesis as well as the detrimental outcomes of Acute Respiratory Distress Syndrome. Ventilation-induced hypercapnia has been shown in experiments to lead to a cognitive impairment with increased NLRP2 inflammasome activity. Inflammasome activation along with the increased acidity caused by other pro-inflammatory immune pathways likely exert a negative effect on cerebral functions [15]. Moreover, there is experimental evidence that systemic MLP3 inflammasome-mediated inflammation can adversely affect the brain and lead to the pathological accumulation of neurodegeneration-associated peptides such as amyloid-β [34]. There is also a theory that cerebral hypoprofusion can accelerate amyloid-β formation and may be linked to tau pathology. This ischemia may increase the risk of the development of Lewy body disease by inducing the phosphorylation of alpha-synuclein [35].

The mental health consequences of this diagnosis are being identified among large numbers of COVID-19 survivors. Among these consequences, cases of major depressive disorder (MDD) and anxiety are being reported and closely examined. A case-control study conducted on individuals from the United States and Canada compared depression, stress, anhedonia, and cognitive impairment measures in individuals with a previously confirmed diagnosis of COVID-19 with controls with no prior diagnosis of COVID-19. Individual sample t-tests were performed to assess the differences between the previously affected and the control groups. The study found that relative to the control group, the previously diagnosed group reported significantly higher depression, anhedonia, and perceived stress (36). Depression was measured using the Beck Depression Inventory-II (BD-II) and the data indicated a significantly higher BD-II score ($t (98) = -2.60, p < 0.01$) for individuals with a prior COVID-19 diagnosis compared with the control group (36). Anxiety was scored using a subscale of the Mood and Anxiety Symptom Questionnaire (MASQ) called the Anxious Arousal subscale. Individuals with a prior COVID-19 diagnosis reported significantly higher Anxious Arousal scores ($t (98) = 4.45, p < 0.001$) compared with the control group [36].

In the same case, case-control, anhedonia, and cognitive function were compared between the two groups. Anhedonia, a loss of interest or pleasure, was measured using the Snaith–Hamilton Pleasure Scale (SHAPS). The individuals from the previously diagnosed COVID-19 group displayed significantly higher SHAPS scores compared with the controls ($t (98) = -2.98, p = 0.004$) [36]. This finding suggests that the individuals who were previously diagnosed with COVID-19 reported a reduced capacity to experience pleasure. Lastly, participants from both groups were given the Attention Network Test (ANT), which measures attention and cognitive functioning. The ANT is a behavioral test used to assess three attentional networks, which are alerting, orienting, and executive control. The study results indicated a selective impairment in the attention/executive functioning aspect of the ANT for the previously diagnosed group. No statistically significant differences in alerting and orienting abilities were noted [36]. Although no pathophysiologic explanation for the executive function impairment was confirmed, it was hypothesized that the post-infection executive function disturbances could result from frontal lobe pathology [37]. The current COVID-19 studies are building a strong case of evidence of mood and cognitive disturbances as ramifications of the virus, necessitating the need for researchers to continue their focus on the specific mechanisms of these neuropsychiatric consequences.
Psychosis has been associated with many other viral infections. One study looked at data obtained during the H1N1, Ebola, SARS, Middle Eastern Respiratory Virus, and COVID-19 outbreaks. It was noted that 0.9 to 4% of people exposed during an epidemic or a pandemic were estimated to have developed psychosis or psychotic symptoms [38]. This incidence was significantly higher than the average incidence of psychosis in the general population of 0.015% [39]. One case in the literature details the account of a 52-year-old male who had no past psychiatric history with new-onset agitation, anxiety, paranoia, and mutism after having a confirmed infection with COVID-19 [38]. This paranoia, a symptom of psychosis, ultimately led to a suicide attempt. He received milieu therapy, psychopharmacology, and electroconvulsive therapy during his hospitalization. The authors hypothesized that those who develop psychotic symptoms may have higher IgG titers of the virus in question (such as COVID-19) in their CSF [38].

Another case study found an association between COVID-19 and brief psychotic disorder [40]. This case detailed the course of a 36-year-old previously healthy woman who also had no past personal psychiatric or even family psychiatric history. She presented with new-onset psychosis after being diagnosed with COVID-19. Her psychosis manifested as persecutory delusions and decreased sleep. Her associated COVID-19 symptoms included rhinorrhea and nasal congestion. However, she did not have documentation of anosmia. She was treated with antipsychotics and benzodiazepines, which helped her to show an initial improvement. However, her psychosis further improved with the resolution of her COVID-19 symptoms [40]. These cases highlight the need to monitor the development of new psychotic symptoms even in patients with no past psychiatric history. The treatment seems to be a short duration of antipsychotics.

5. Conclusions

Many survivors of long-standing COVID-19 experience lingering symptoms after the resolution of the infection and many currently do not have a definitive treatment. Other conditions such as NDPH and persistent symptoms from other viral infections serve as a framework for understanding and treating the similar symptoms of long-term COVID-19 infections. Several of the neurological and psychiatric system symptoms are presumed to be caused by the immune response to the virus in the meninges and/or the CSF. There are thoughts that the activation of glial cells or the hypoprofusion of the cerebral tissue can be a causal mechanism for the persistent symptoms seen after the initial infection of COVID-19. These persistent symptoms can range from NDPH to fatigue to depression to psychosis to neurocognitive disorders. What is surprising about this infection is its possible ability to wreak havoc on the CNS and cause either the accumulation of amyloid-β or the creation of tau proteins or Lewy bodies.

This discovery leads to the theory that those who suffer from COVID-19 may have an increased risk of neurocognitive disorders or the worsening of a current neurocognitive disorder. More research is required to delineate if there really is a connection to either an increased risk or the worsening of neurocognitive disorders. Prior infections seen in other viruses in the coronavirus family can help researchers to guess how persistent symptoms could play out and affect patients; however, the virus that causes COVID-19 seems to be in a league of its own. It is of the utmost importance that clinicians start to recognize that patients can continue to have symptoms that result from a COVID-19 infection that may be different from their initial presentation. As an early treatment tends to lend itself to better outcomes in these Long-Haul COVID symptoms, clinicians should be able to accurately identify these symptoms as possibly being linked to the original infection. It is certain to keep researchers, clinicians, and patients on their toes for the next few years to come.

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