Daily Persistent Headache and COVID-19

Subjects: Infectious Diseases

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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.

Headache COVID-19 fatigue

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][7][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].

2. 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 [9]. 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 [10]. 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 [11].

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 [12]. This 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 [12]. Of these 28 patients, 6 had a headache as a prodromal symptom of their impending COVID-19 infection. Although this 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. 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 researchers 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 [13].

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 suggested that the pain may be due to a chronic CNS inflammation, cytokine production, and persistent glial activation arising from precipitating factors [11]. This is likely the case in COVID-19 infections [14]. 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 [12].

Several researchers 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 [11]. Several patients with severe COVID-19 infections required intubation, creating another avenue for recent COVID-19 infections to possibly cause NDPH [11][15].

4. 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 [11] 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 [9]. Many cases of NDPH spontaneously resolve [16]. 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 [17].

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 [11].

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) [18]. 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 [11].

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.

5. 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 [19]. Additionally, bacterial and parasitic infections such as *Coxiella burnetii*, *Mycoplasma pneumonia*, and *Giardia lamblia* manifest multiple symptoms of persistent malaise [20]. 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 [21]. 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 [22]. 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) [19].

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 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 [19].

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 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 researchers 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 [22].

6. 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 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 [20]. Additionally, associated features, including sleep disturbances, pain, depression, and lack of concentration, also improved following high-dose vitamin C therapy [20].

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