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COVID-19 and chronic fatigue syndrome: Is the worst yet to come?

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ABSTRACT

There has been concern about possible long-term sequelae resembling myalgic encephalomyelitis/chronic fatigue syndrome in COVID-19 patients. Clarifying the mechanisms underlying such a "post-COVID-19 fatigue syndrome" is essential for the development of preventive and early treatment methods for this syndrome. In the present paper, by integrating insights pertaining to the glymphatic system and the nasal cerebrospinal fluid outflow pathway with findings in patients with chronic fatigue syndrome, idiopathic intracranial hypertension, and COVID-19, I provide a coherent conceptual framework for understanding the pathophysiology of post-COVID-19 fatigue syndrome. According to this hypothesis, this syndrome may result from damage to olfactory sensory neurons, causing reduced outflow of cerebrospinal fluid through the cribriform plate, and further leading to congestion of the glymphatic system with subsequent toxic build-up within the central nervous system. I further postulate that patients with post-COVID-19 fatigue syndrome may benefit from cerebrospinal fluid drainage by restoring glymphatic transport and waste removal from the brain. Obviously, further research is required to provide further evidence for the presence of this post-viral syndrome, and to provide additional insight regarding the relative contribution of the glymphatic-lymphatic system to it. Other mechanisms may also be involved. If confirmed, the glymphatic-lymphatic system could represent a target in combating post-COVID-19 fatigue syndrome. Moreover, further research in this area could also provide new insights into the understanding of chronic fatigue syndrome.

Introduction

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a public health emergency of international concern [1]. The most common symptoms of patients with COVID-19 are fever, cough, shortness of breath, and myalgia/fatigue [1]. Anosmia (loss of smell) and dysgeusia (altered sensation of taste) have been reported in 33–80% of patients with COVID-19 [2]. SARS-CoV-2 is mainly transmitted human-to-human through close contact, respiratory droplets, fomites, and contaminated surfaces [1]. Importantly, a chronic post-viral syndrome characterized by chronic fatigue, variable nonspecific myalgia, depression and sleep disturbances has previously been reported following SARS coronavirus infection, which emerged from South East Asia in early 2003 [3]. These long-term adverse effects of SARS are similar to those experienced by patients with chronic fatigue syndrome (CFS) and fibromyalgia syndrome [3]. Emerging reports also indicate a significant ongoing symptom burden in patients with COVID-19 [4]. A recent study found that while symptom burden in subjects recovering from hospital admission with COVID-19 had generally improved at early follow-up, 53% reported persistent breathlessness, 34% persistent cough and 69% persistent fatigue [4]. Perrin et al. [5] recently proposed that, as happened after the SARS outbreak, a proportion of COVID-19 affected patients may go on to develop a severe "Post-COVID-19 Syndrome" characterized by long-term adverse effects resembling myalgic encephalomyelitis (ME)/CFS symptomatology such as persistent fatigue, diffuse myalgia, depressive symptoms, and non-restorative sleep. In their letter, the authors present a case report describing a patient with possible post-COVID-19 syndrome [5]. Given that these likely post-COVID-19 syndrome cases, in addition to existing ME/CFS cases, will place additional burden on our already hard pressed healthcare system [5], and in order to prevent long-term ME/CFS-like sequelae, clarifying the mechanisms underlying post-COVID-19 syndrome is crucially important. In the present article, I propose that post-COVID-19 fatigue syndrome may result from damage to olfactory sensory neurons, causing an increased resistance to cerebrospinal fluid (CSF) outflow, and further leading to congestion of the glymphatic system with subsequent toxic build-up within the central nervous system (CNS).

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Discussion

The glymphatic system

Recent research has led to the discovery of the "glymphatic system", a brain-wide network of perivascular channels along which a large proportion of subarachnoid CSF recirculates through the brain parenchyma, facilitating the clearance of interstitial solutes, including amyloid-β (Aβ), from the brain, and which is connected to the peripheral lymphatic system [6]. CSF enters the brain along periarterial channels to exchange with interstitial fluid (ISF), which is in turn cleared from the brain along perivenous pathways [6]. As ISF exits the brain through the perivenous route, it travels to the lymphatic vessels of the head and neck, the CSF proteins and metabolites then being further transported to the general circulation [7]. From the subarachnoid space, CSF is driven into the Virchow-Robin spaces by a combination of arterial pulsatility, respiration, slow vasomotion, and CSF pressure gradients [7,8]. The subsequent transport of CSF into the dense and complex brain parenchyma is facilitated by aquaporin-4 (AQP4) water channels which are expressed in a highly polarized manner in astrocytic endfeet ensheathing the cerebral vasculature [7]. This brain-wide pathway has been called the "glymphatic system", based upon its similarity in function to the peripheral lymphatic system, and its dependence upon astroglial water transport through the water channel AQP4 [9]. Since the glymphatic system plays a key role in the clearance of potentially neurotoxic proteins, including Aβ [6], glymphatic pathway dysfunction may be involved in the development of Alzheimer's disease [10].

Post-glymphatic clearance pathways

Historically, the outflow of subarachnoid CSF, and the ISF that drains into this compartment, have been thought to take place through arachnoid granulations that project into the dural venous sinuses [11,12]. However, CSF also drains along lymphatic vessels [11–13]. It has been shown that in some species such as rabbit and sheep, lymphatic vessels are responsible for around 30–50% of total outflow of CSF [12]. Lymphatic drainage of CSF to cervical lymph nodes occurs via the cribriform plate and nasal lymphatics, as well as via dural lymphatics and along cranial nerves [11,12]. In 2015, two independent studies reported the presence of dura-associated lymphatic vessels in the mouse brain [14,15]. These studies further suggested a connection between the newly identified meningeal lymphatic vessels and the previously discovered glymphatic system. It was found that dural lymphatic vessels absorb CSF from the adjacent subarachnoid space and brain ISF via the glymphatic system [14]. It appears that the perivenous drainage of interstitial solutes provides these solutes access to the sinus-associated lymphatics, either directly since these large veins merge to form the dural sinuses, or indirectly via the cisternal CSF compartments associated with these structures [16]. Interestingly, Absinta et al. [17] found that human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by magnetic resonance imaging (MRI). Their data clearly and consistently demonstrated the existence of lymphatic vessels within the dura mater [17]. While there are lymphatic vessels in the meninges [14,15], there is evidence in both humans and other mammals pointing to drainage of the CSF through the cribriform plate [11,13,18]. The cribriform plate is a fenestrated bony plate of the ethmoid bone that separates the cranial and nasal cavities [13]. Extensions of the subarachnoid space that follow the olfactory tracts, cross the cribriform plate, and project into the nasal submucosa alongside olfactory nerves [11]. There is a dense lymphatic network within the nasal submucosa that then drains this CSF and solute to the deep cervical lymph nodes [11,13].

SARS-CoV-2 may increase the resistance to CSF outflow through the cribriform plate

Anosmia is one of the most prevalent symptoms and the most common neurological manifestation of SARS-CoV-2 infection [19,20]. Olfactory dysfunction was reported in 85.6% of patients with mild-to-moderate COVID-19 [21]. It appeared before the other symptoms in 11.8% of cases [21]. The exact pathophysiology of anosmia in COVID-19 infection remains to be established. The initial step of odour detection takes place in the pseudostratified olfactory epithelium mainly composed of olfactory sensory neurons surrounded by supporting cells known as sustentacular cells [20]. Olfactory sensory neurons have cilia in direct contact with the environment in order to detect odorants [20]. Recent findings suggest that damage of support cells in the olfactory epithelium could be a plausible mechanism of anosmia in COVID-19 [22]. Bryche et al. [20] explored the impact of SARS-CoV-2 infection on the olfactory system in golden Syrian hamsters. The authors observed massive damage of the olfactory epithelium as early as 2 days post nasal instillation of SARS-CoV-2, resulting in a major loss of cilia necessary for odour detection. These damages were associated with infection of a large proportion of sustentacular cells but not of olfactory neurons [20]. Death of sustentacular cells does not seem to necessarily cause death of olfactory receptor neurons [22]. Death and regeneration of sustentacular cells occurs much faster than death and regeneration of olfactory neurons [22]. Therefore, rapid replenishment of sustentacular cells is consistent with the rapid recovery of the sense of smell that is clinically observed in most COVID-19 patients [22]. However, while the large majority regain their sense of smell within 1 to 3 weeks, there are reports of some COVID-19 patients remaining anosmic or hyposmic for months or more [22]. The most likely explanation is that in those cases, a larger area of the sensory epithelium was affected, possibly with a more profound destruction of the epithelium that included death of a larger number of olfactory receptor neurons [22].

As noted above, CSF drains through the cribriform plate into lymphatic vessels and this space is in immediate vicinity of, and between, the olfactory nerve fibers [22]. It has been suggested that SARS-CoV-2 infection can cause blockage of lymph vessels since the virus can infect lymph endothelial cells branching to the nasal cavity [23,24]. I further hypothesize that a decrease in the number of olfactory sensory neurons, which can be caused by SARS-CoV-2 infection, may increase the resistance to CSF outflow through the cribriform plate. Indeed, Norwood et al. [13] explored the chronic effects of chemical olfactory sensory neuron ablation on CSF drainage through the cribriform plate in mice. The authors found that ablation of olfactory sensory neurons, which removes the low-resistance pathway for fluid through the cribriform plate, disrupted CSF drainage through the cribriform plate [13]. Mollanji et al. [25] previously demonstrated that acute blockage of CSF outflow by surgically obstructing the cribriform plate results in an increase in resting intracranial pressure (ICP) in sheep, supporting the concept that the olfactory pathway represents a major site for CSF drainage. In the study by Norwood et al. [13], normal ICP was maintained. Interestingly, a growing body of evidence indicates that a substantial proportion of patients with CFS may represent a variant of idiopathic intracranial hypertension (IIH) without pathologically elevated ICP [26–28]. IIH is a condition of raised ICP of unknown cause characterized by headache and visual disturbance, with papilledema the hallmark of raised ICP [28]. I hypothesize that post-COVID-19 fatigue syndrome, like CFS, may be a form of IIH, resulting from an excess of CSF in the glymphatic system. This view will be elaborated in the following sections.

Supportive evidence that a significant proportion of patients with CFS may represent a variant of IIH

Based on CSF pressure readings in CFS patients, in whom headache was a prominent symptom, and their clinical response to CSF drainage,

Higgins et al. [26–28] hypothesized that CFS and IIH may be related. Indeed, their study suggests that if headache is a prominent symptom in patients diagnosed with CFS, then a substantial proportion of patients with CFS may represent a variant of IIH without intracranial hypertension or papilledema, which responds to CSF withdrawal in the same way as IIH patients do. Higgins et al. [27] measured CSF pressure by lumbar puncture in 20 patients diagnosed with CFS, in whom headache was a prominent symptom. CSF pressure was found to be>20 cmH_2O in five patients, four of whom fulfilled the criteria for IIH. These latter four patients were relabelled as IIH and treated accordingly. Mean CSF pressure was 19 cmH_2O, which is towards the high end of normal [27]. Even more importantly, the authors also found that CSF withdrawal produced a symptomatic improvement in 17 patients (85%), that is in all five patients whose CSF pressures were>20 cmH_2O and in 12 patients whose CSF pressures were between 12 and 20 cmH_2O [27]. This improvement usually developed during, or soon after the procedure and lasted from a few minutes to several weeks. It generally took the form of reduced headache, a heightened alertness and a reduced sense of fatigue [27]. The authors suggested that incomplete forms of IIH, with average CSF pressures much lower than in the syndrome in full, may manifest as CFS [26–28].

The improvements noted following CSF drainage in these CFS patients at least suggest a neurological basis of some of their symptoms. However, a curious question remains as to why CFS patients with CSF pressures within the normal range should benefit from lowering of the CSF pressure. CSF withdrawal not only lowers CSF pressure, but also promotes the turnover of CSF, and I believe that CSF drainage may favorably affect the fluid dynamics of the glymphatic system, and that this could be an alternative explanation as to why CSF withdrawal may be beneficial in a subgroup of CFS patients [29]. As discussed below, this latter view [29] is now supported by very recent observations confirming that a significant proportion of CFS patients represent a variant of IIH [30] and that IIH may be considered as a manifestation of "glymphedema" of the brain [31].

Very recent evidence in the literature provides strong support for the view that a large portion of patients with CFS have indeed a degree of IIH, which may explain many of their CFS symptoms. Indeed, Bragée et al. [30] published a retrospective, cross-sectional study, performed at a specialist clinic for referred patients with severe ME/CFS as defined by the Canada Consensus Criteria. The first 272 patients with ME/CFS were invited to participate, and 229 who provided prompt informed consent were included. MRI of the brain was performed on 205 participants. IH was assessed indirectly by the quotient of the optic nerve sheath diameter (ONSD)/eyeball transverse diameter (ETD) on both sides as measured on MRI of the brain. Imaging evidence of the excess CSF along the optic nerve sheaths is one of the cardinal signs of IIH. The ONSD/ETD ratios are considered a more adequate predictor of IH than ONSD as they eliminate body size-related variability [30]. The ONSD/ETD ratio has a normal value of 0.19 ± 0.02, and values > 0.25 are related to IH with severe symptoms [30]. In their ME/CFS study population, Bragée et al. [30] found that 171 participants (83%) had ONSD/ETD ratios $>$ 0.22. ONSD/ETD ratios > 0.22 has been found in 5% of the normal population [30]. 65 participants (32%) had an ONSD/ETD ratio > 0.25. The authors concluded that 83% of the patients with ME/CFS had signs of possible IH, including 32% who had values indicating more severe states of IH [30].

Supportive evidence that IIH (and possibly a majority of CFS) is associated with a congestion of the glymphatic system

In a very recent state-of-the art review, Nicholson et al. [31] detailed the new discoveries of both the glymphatic system and lymphatic vessels lining the dura mater in human brains, and connected them with our current understanding of the pathophysiology of IIH. The authors concluded that IIH can be summarized in the following pathological triad: restriction of the venous CSF outflow pathway, overflow of the compensating lymphatic CSF outflow pathway, and congestion of the glymphatic system. As further noted by the authors, the ICP may be highly variable amongst different patients, depending on the efficiency of the lymphatic system to resorb the CSF and on the severity of transverse sinus stenoses. It is likely that there is a subclinical form of IIH in patients with a degree of CSF outflow impairment but in whom the signs and symptoms do not yet meet the criteria for IIH [31]. It is therefore likely that IIH without papilledema (i.e., with normal or near-normal ICP) is probably underdiagnosed among patients with chronic migraines or isolated tinnitus [31]. Papilledema and raised ICP could probably therefore be considered as the most severe stage of the disease, whereas headache and pulsatile tinnitus with normal ICP (and without papilledema) could be considered as benign stages of IIH [31]. This may explain why the radiological signs of IIH are frequently found in patients with chronic headache or isolated pulsatile tinnitus without papilledema or raised ICP [31]. As noted above, imaging evidence of the excess CSF along the sheaths of cranial nerves is one of the cardinal signs of IIH [31]. Most typically, this is found along the optic nerve sheaths. This excess of CSF seems to be related to the engorgement of the lymphatic CSF outflow pathway [31].

The presence of tinnitus and headache in patients with COVID-19

With regard to the presence of tinnitus and headache in patients with COVID-19, recent studies are of particular interest. Viola et al. [32] investigated the prevalence of tinnitus in a sample of 185 COVID-19 patients through an online questionnaire. 43 patients (23.2%) reported tinnitus. 3/43 (7.0%) described their tinnitus as pulsatile. Caronna et al. [33] found that 74.6% (97/130) of patients with COVID-19 had headache. In all patients with headache, 24.7% (24/97) of patients had severe pain with migraine-like features. After 6 weeks, of 74 followed-up patients with headache, 37.8% had ongoing headache. Headache was the prodromal symptom of COVID-19 in 21.4% of patients with persistent headache ($p = 0.010$). Interestingly, patients with headache had more anosmia/ageusia (54.6% vs. 18.2%; $p < 0.0001$). The authors hypothesized that pathophysiologically, the migraine-like features may reflect an activation of the trigeminovascular system by inflammation or direct involvement of SARS-CoV-2 , a hypothesis supported by concomitant anosmia [33]. Here, I present an alternative explanation for the link between headache and anosmia. I propose that headache in a subset of COVID-19 patients may result from reduced outflow of CSF through the cribriform plate due to an increased rate of olfactory sensory neuron death, and that these cases of COVID-19 may represent a variant of IIH. This view could be supported by the presence of anosmia in COVID-19 patients with headache as described by Caronna et al. [33].

Hypothesis for a possible pathophysiological mechanism underlying post-COVID-19 fatigue syndrome

Inside the nasal cavity, concomitant and remaining anosmia in COVID-19 may indicate a more profound destruction of the olfactory epithelium, resulting in death of a larger number of olfactory receptor neurons [22]. Such major loss of olfactory receptor neurons may lead to reduced CSF drainage to nasal mucosa via the cribriform plate, provided that nasal lymphatic drainage has a significant role in CSF outflow in humans. The latter is still a matter of debate. In a recent study, Melin et al. [34] examined the efflux of intrathecal gadobutrol to nasal mucosa utilizing multi-phase, long-term MRI in humans. Despite a strong enrichment of CSF tracer in CSF spaces nearby the cribriform plate, there was no significant enrichment of CSF tracer in nasal mucosa, as measured in superior, medial and inferior turbinates, or in the nasal septum. Therefore, the authors questioned the importance of CSF drainage to the human nasal mucosa [34]. These study findings contradict the findings of other studies [18,35]. de Leon et al. [18] utilized dynamic positron emission tomography to measure CSF

clearance in humans and found significant levels of CSF tracer in the superior nasal turbinates. The authors concluded that the human nasal turbinate is part of the CSF clearance system. Their results were anatomically consistent with observations from a human postmortem study by Johnston et al. [35], demonstrating a CSF egress pathway through the cribriform plate. Johnston et al. [35] concluded that CSF absorption into nasal lymphatics is a characteristic feature of all mammals including humans, and speculated that some disorders of the CSF system, such as IIH, may relate either directly or indirectly to a lymphatic CSF absorption deficit. In the present article, I propose that post-COVID-19 fatigue syndrome may result from damage to olfactory sensory neurons, causing a reduction in CSF outflow through the cribriform plate, and further leading to congestion of the glymphatic system with subsequent toxic build-up within the CNS. From this point of view, post-COVID-19 fatigue syndrome, like CFS, might be a form of IIH, resulting from an excess of CSF in the glymphatic system. The view that at least a subgroup of COVID-19 patients may represent a variant of IIH is supported by a very recent study [36]. Silva et al. [36]. described the characteristics of headache and the CSF profile during SARS-CoV-2 infection in a consecutive series of COVID-19 patients. The authors excluded those who presented any clinical or laboratory evidence for meningitis or meningoencephalitis. In this cross-sectional study, 13 out of 56 COVID-19 patients submitted to CSF analysis had severe, persistent headache. In 11 patients (84.6%), the CSF opening pressure was above 20 cmH_2O and in 6 of these (46.1%), above 25 cmH_2O [36]. CSF opening pressures higher than 25 cmH_2O were considered elevated, and from 20 cmH_2O to 25 cmH_2O equivocal [36]. The authors concluded that in a significant proportion of COVID-19 patients, headache was associated to intracranial hypertension in the absence of meningitic or encephalitic features [36].

Implications for therapy of CFS

The above research findings support the view that IIH and a large portion of CFS cases are manifestations of the same disorder across a spectrum of disease severity, in which the subset of CFS patients have a condition identical to IIH in terms of its glymphatic pathogenesis but whose CSF pressures lie within the normal range. This suggests that the CNS may play a critical role in the pathogenesis of this subset of CFS patients, and that most CFS patients may have their illness on an organic and neurological basis. This further suggests that treatments available for IIH might be appropriate for CFS. In this regard, Higgins et al. [37] previously described a 49-year-old woman with a long and debilitating history of CFS who was targeted for investigation of ICP because of headache. Lumbar puncture revealed an opening pressure of 20 cmH_2O. There was no papilledema. Further investigation showed narrowings at the anterior ends of the transverse sinuses, typical of those seen in IIH and associated with pressure gradients. Stenting of both transverse sinuses brought about a life-changing remission of symptoms, including pressure headache, fatigue, concentration, and pain, with no regression in 2 years of follow-up [37]. We previously postulated that CSF diversion such as lumboperitoneal shunting may also be beneficial to this subgroup of CFS patients by restoring glymphatic transport and waste removal from the brain [29]. In order to identify CFS patients who are good candidates for this specific treatment, only CFS patients who report headache or pulsatile tinnitus, and who have an ONSD/ETD ratio $>$ 0.22, should be included. This subset of CFS patients may represent a benign stage of IIH with normal ICP and without papilledema, which responds to CSF withdrawal in the same way as IIH patients do. This may open the door to promising, future treatments of CFS by using CSF shunt devices.

Implications for therapy of post-COVID-19 fatigue syndrome

If indeed a subgroup of remitted COVID-19 patients are likely to experience long-term sequelae resembling ME/CFS, then early intervention and supportive treatments at the end of the acute phase of COVID-19 may be particularly important in preventing these long-term consequences [5]. In the present article, I propose that post-COVID-19 fatigue syndrome may result from damage to olfactory sensory neurons, causing a reduced outflow of CSF through the cribriform plate, and further leading to congestion of the glymphatic system with subsequent toxic build-up within the CNS. If confirmed, this hypothesis could have remarkable implications in clinical practice. Then glymphatic-lymphatic drainage therapies should be recommended as early treatment steps for post-COVID-19 fatigue syndrome. For instance, osteopathic manipulative medicine could be a practical option for promoting lymphatic drainage, as several studies have provided important proof of principle [38]. It has been argued that ME/CFS can be treated using the Perrin technique, based on traditional osteopathic concepts, to restore a healthier neuro-lymphatic flow. The Perrin technique is a system of manual diagnosis and treatment that is based on the hypothesis that ME/CFS is a disorder of the lymphatic drainage of the CNS, which leads to five physical signs [39]. I further postulate that patients with post-COVID-19 fatigue syndrome may also benefit from CSF drainage in the same way as CFS patients do [26–28].

Conclusions

There has been concern about possible long-term sequelae resembling ME/CFS in COVID-19 patients. Clarifying the mechanisms underlying such a “post-COVID-19 fatigue syndrome” is essential for the development of preventive and early treatment methods for this syndrome. In the present paper, by integrating insights pertaining to the glymphatic system and the cribriform plate CSF outflow pathway with findings in patients with CFS, IIH, and COVID-19, I provide a coherent conceptual framework for understanding the pathophysiology of post-COVID-19 fatigue syndrome. According to this hypothesis, this syndrome may result from damage to olfactory sensory neurons, causing reduced outflow of CSF through the cribriform plate, and further leading to congestion of the glymphatic system with subsequent toxic build-up within the CNS. I further postulate that patients with post-COVID-19 fatigue syndrome may benefit from CSF drainage by restoring glymphatic transport and waste removal from the brain. Obviously, further research is required to provide further evidence for the presence of this post-viral syndrome, and to provide additional insight regarding the relative contribution of the glymphatic-lymphatic system to it. Other mechanisms may also be involved. If confirmed, the glymphatic-lymphatic system could represent a target in combating post-COVID-19 fatigue syndrome. Moreover, further research in this area could also provide new insights into the understanding of CFS.

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Conflict of interest statement

Dr. Peter Wostyn is the inventor of pending patent applications pertaining to chronic fatigue syndrome treatment using cerebrospinal fluid diversion procedures.

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