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The putative glymphatic signature of chronic fatigue syndrome: A new view on the disease pathogenesis and therapy

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A B S T R A C T

The underlying pathophysiology of chronic fatigue syndrome remains incompletely understood and there are no curative treatments for this disorder at present. However, increasing neuroimaging evidence indicates that functional and structural abnormalities exist in the brains of chronic fatigue syndrome patients, suggesting that the central nervous system is involved in this disorder and that at least some chronic fatigue syndrome patients may have an underlying neurological basis for their illness. In the present paper, we speculate that glymphatic dysfunction, causing toxic build up within the central nervous system, may be responsible for at least some cases of chronic fatigue syndrome. We further postulate that cerebrospinal fluid diversion such as lumboperitoneal shunting may be beneficial to this subgroup of patients by restoring glymphatic transport and waste removal from the brain. Although recent evidence indicates that at least some chronic fatigue syndrome patients may benefit from cerebrospinal fluid drainage, further studies are needed to confirm this finding and to determine whether this can be attributed to enhancement of glymphatic fluid flow and interstitial fluid clearance. If confirmed, this could offer promising avenues for the future treatment of chronic fatigue syndrome. Clearly, given the relative invasive nature of cerebrospinal fluid diversion, such procedures should be reserved for chronic fatigue syndrome patients who are severely debilitated, or for those with severe headaches. Anyhow, it seems worthwhile to make every effort to identify new therapies for patients who suffer from this devastating disease, especially given that there are currently no effective treatments for this condition.

Introduction

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), is a highly debilitating disease of unknown origin that is characterized by severe fatigue for more than 6 months, which does not improve with rest and may be exacerbated by physical or mental activity [1]. In addition, CFS is associated to a wide spectrum of symptoms, including, but not limited to, post-exertional malaise, unrefreshing sleep, memory and concentration problems, lymph node sensitivity, headaches, and joint and muscle pain [1]. Its pathophysiology remains incompletely understood and a variety of abnormalities, including endocrine dysfunction, autonomic nervous system imbalance and altered immunity, among others, have been described in association with CFS [2]. The estimated prevalence of the disease is between 0.1% and 5% [1]. This wide range of prevalence estimates may be in part due to the lack of standardized diagnostic criteria [1]. Currently, in the absence of clinically established diagnostic tests or known biomarkers, CFS is a symptom-based clinical diagnosis, whereby other conditions with similar symptom profiles must be excluded [1,3]. There are no known curative treatments for patients with CFS at present [4]. The therapy options available for CFS are aimed at symptom relief and improved ambulatory function, and include cognitive behavioral therapy and graded exercise therapy [3]. However, there are serious concerns about the robustness of the claims made about the efficacy of cognitive behavioral therapy and graded exercise therapy [5].

Taken together, the unclear etiology and diagnostic uncertainty of CFS point to the complex and multifactorial nature of the disease. This raises the question of whether CFS is a single disease entity with one definitive cause or represents a variety of conditions each with their own cause but similar symptoms [1]. Moreover, the idiopathic nature of CFS has led to a long-standing debate about whether patients with CFS are suffering from an organic illness, or whether their condition is psychological in nature. Increasing neuroimaging evidence indicates that functional and structural abnormalities exist in the brains of CFS patients. Indeed, previous studies have demonstrated reduced cerebral blood flow and brain volume loss in patients with CFS [6–8]. This suggests that the central nervous system (CNS) may play a critical role in the pathogenesis of CFS, and that at least some patients may have

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their illness on a neurological basis. In the absence of a clear understanding of the underlying pathophysiology of CFS, there is a need to clarify the mechanisms responsible for CNS involvement. An increased understanding could lead to the development of promising novel diagnostic and therapeutic strategies for this devastating disorder. In the present paper, we speculate that glymphatic dysfunction may be responsible for at least some cases of CFS, and that cerebrospinal fluid (CSF) diversion may be beneficial to this subgroup of patients by favoring waste clearance and restoring glymphatic flow.

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 [9]. CSF enters the brain along periarterial channels to exchange with interstitial fluid (ISF), which is in turn cleared from the brain along perivenous pathways [9]. 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 [10]. From the subarachnoid space, CSF is driven into the perivascular (or Virchow-Robin) spaces by a combination of arterial pulsatility, respiration, slow vasomotion, and CSF pressure gradients [10,11]. 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 [10]. 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 [12]. Since the glymphatic system plays a key role in the clearance of potentially neurotoxic proteins, including Aβ [9], glymphatic pathway dysfunction may be involved in the development of Alzheimer's disease (AD) [13].

Glymphatic dysfunction as a possible contributing factor to chronic fatigue syndrome

An intriguing finding in a previous study of patients with CFS was that their magnetic resonance imaging (MRI) scans of the brain frequently showed tiny foci of increased signal intensity in the subcortical white matter on T2-weighted images, so-called 'unidentified bright objects' (UBOs) [14]. This study compared MRI findings in 47 normal healthy controls with that of 144 CFS patients [14]. Areas of increased signal intensity in the white matter were found in 78% of the CFS patients, whereas only 21% in the control group showed such areas [14]. While the origin of these MRI findings remains unclear, dilated Virchow-Robin spaces, possibly due to edema or congregation of lymphocytes in the spaces, have been postulated to be the reason for the UBOs seen on MRI scans of CFS patients [14]. As such, it has been suggested that CFS may involve the perivascular spaces of the brain [14]. Interestingly, recent evidence indicates that dilated perivascular spaces could be the site where chemical processes generate fatigue in multiple sclerosis patients [15]. Given that the perivascular spaces have an important role in the homeostasis of cerebral fluids in the CNS [16], we hypothesize that the common occurrence of UBOs in CFS patients may result from retention of ISF in distended perivascular spaces. As discussed below, in the case of CFS, there may be a steady accumulation of interstitial waste products as a result of glymphatic dysfunction, probably due to impaired perivenous outflow.

An initial disorder of the lymphatic drainage might be responsible for impaired perivenous outflow, which in turn may result in enlargement of perivascular spaces. Indeed, if CSF outflow is reduced as a consequence of lymphatic disorders, local perivascular CSF recirculation may be impaired and, consequently, the perivascular spaces may dilate due to fluid retention [16]. This would lead to an impaired ISF drainage and stagnation of flow in the perivascular spaces and interstitium with subsequent accumulation of toxic substances. Additionally, the diffuse stagnation of flow in the interstitium and perivascular spaces might also favor inflammation. It has been suggested that the symptoms of CFS reflect a low-grade inflammation in the CNS [17]. A recent study using positron emission tomography found that neuroinflammation was present in widespread brain areas in CFS patients and that the severity of neuropsychologic symptoms correlated with the degree of inflammation [18].

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 [19]. CSF also drains along spinal nerve roots to lumbar lymph nodes [19]. Intriguingly, in 2015, two independent studies reported the presence of dura-associated lymphatic vessels in the brain [20,21]. These studies further suggested a connection between the newly identified meningeal lymphatic vessels and the recently discovered glymphatic system. It was found that dural lymphatic vessels absorb CSF from the adjacent subarachnoid space and brain ISF via the glymphatic system [20]. 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 [22].

Considering all of the above, it is conceivable that disturbances of the lymphatic and glymphatic drainage pathways may work together in the pathogenesis of CFS. Interestingly, Perrin [23] suggested the involvement of CSF and lymphatic drainage in patients with CFS/ME with dysfunction within the immune system, causing toxic build up within the CNS. This lymphatic hypothesis [23,24] and the glymphatic hypothesis proposed in the present paper might be considered complementary and might reflect the link between the lymphatic and glymphatic pathways, which have been regarded as serial elements of a wider functional system [22].

Cerebrospinal fluid diversion for the treatment of chronic fatigue syndrome

Given that UBOs may be more common in CFS patients than in controls, and in case impaired perivenous outflow might be responsible for enlargement of perivascular spaces and impaired ISF drainage, we speculate that CSF diversion may be beneficial to at least some CFS patients by favoring the clearance of metabolic and inflammatory waste products, and restoring glymphatic flow. It is interesting to note that a recent study reported that CSF diversion, while promoting CSF clearance and/or reducing parenchymal compression, was beneficial in a series of patients with enlarged Virchow-Robin spaces without ventriculomegaly [25].

Temporary external lumbar CSF drainage could be initially carried out to determine whether a permanent lumboperitoneal shunt would be beneficial to the patient suffering from CFS. If external lumbar CSF drainage results in marked symptomatic improvement, then definitive CSF diversion such as lumboperitoneal shunting could be performed. If UBOs are indeed dilated ISF spaces, they would be expected to undergo some decrease in diameter after CSF drainage. In addition, the levels of one or more toxins in the CSF might function as a biomarker for the effectiveness of CSF drainage to reduce the levels of these toxins in the brain. Toxins must be cleared from the brain interstitium to the CSF compartment. Glymphatic dysfunction may impede this drainage of toxins from the ISF into CSF. This would result in higher concentrations of toxins lingering in the ISF rather than being transported into the CSF. As CSF withdrawal may unblock stagnation of glymphatic transport, the level of toxins in the CSF would be expected to increase due to the improvement of ISF flow. Therefore, a significant increase of toxins in