International Journal of
Molecular Sciences

MDPI

Perspective

Glymphatic System Dysregulation as a Key Contributor to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Mohsen Nemat-Gorgani *, Michael Anthony Jensen and Ronald Wayne Davis

Stanford Genome Technology Center, Department of Biochemistry, Stanford University, Palo Alto, CA 94304, USA; m.a.jensen@stanford.edu (M.A.J.); ron.davis@stanford.edu (R.W.D.)
* Correspondence: mohsenn@stanford.edu

Abstract

Defined by the World Health Organization as a neurological disorder, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a disabling illness, affecting millions of people worldwide. First reported in the early nineteenth century, ME/CFS is uniquely characterized by a wide array of symptoms, including fatigue, brain fog, post-exertional malaise (PEM), sleep dysfunction, and orthostatic intolerance (OI). Despite decades of extensive research, there are no effective medical treatments or simple diagnostics for ME/CFS, with an estimated 90% of patients remaining undiagnosed. The recently discovered glymphatic system, a lymphatic analog of the brain, is believed to be responsible for the removal of toxic metabolic wastes accumulated in the course of daily activities, primarily during sleep. A link between glymphatic dysfunction and some neurological disorders such as Alzheimer's disease has already been established, raising the possibility of its involvement in ME/CFS. Accordingly, we believe the ME/CFS medical/scientific community will be interested in seriously considering GD an important contributor to its pathophysiology. If so, therapeutics that modulate glymphatic function may also benefit patients with ME/CFS.

Keywords: ME/CFS; neuroimmune; neurological disorders; sleep disturbance; AQP4 water channels; glymphatic system; glymphatic dysfunction

check for updates

Academic Editor: Fabrizio Michetti

Received: 14 October 2025
Revised: 21 November 2025
Accepted: 25 November 2025
Published: 27 November 2025

Citation: Nemat-Gorgani, M.; Jensen, M.A.; Davis, R.W. Glymphatic System Dysregulation as a Key Contributor to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Int. J. Mol. Sci.* **2025**, *26*, 11524. https://doi.org/10.3390/ijms262311524

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

A condition resembling Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) was recognized as an unknown post-viral illness following a series of outbreaks worldwide in the 1930s [1]. Since 1969, ME/CFS has been classified as a neurological disease in the International Classification of Diseases by the World Health Organization (WHO, ICD G93.3) [2], which is described as a "dysfunction of integrative brain regions" by the National Institutes of Health [3]. Our own interest in the neurological aspect of ME/CFS pathophysiology was initiated upon encountering the presence of autoantibodies in the plasma samples of some patients where demyelination may be occurring [4].

Major symptoms of ME/CFS include fatigue, sleep disturbance, post-exertional malaise (PEM), orthostatic intolerance (OI) and brain fog [5,6]. Among these, PEM and sleep disturbance are generally considered hallmark symptoms, while there are other symptoms that overlap with fibromyalgia and Long COVID, to name a few chronic conditions [7,8], with 49% of Long COVID patients meeting the ME/CFS criteria [9]. Degree of illness also ranges from mild to severe, and in many cases the patients are bedridden [10], suggesting major molecular changes leading to a complex array of symptoms [11].

A prominent feature of ME/CFS is PEM, often called a "crash" [10], which results from overexertion after performing even normal physical or mental activities, and which may be related to heightened innate immune response and neuroinflammation believed to be occurring in the patients [12]. Feeling unrefreshed after sleep is a common and defining symptom, and persistence of the "crash" phase is often long and painful [13,14]. Therefore, by understanding the root pathophysiology of ME/CFS, not only may chances of recovery be increased, but also it may be possible to avoid the "crash" altogether. While physicians can identify patients with ME/CFS using special symptom metrics (e.g., Canadian Consensus Criteria), there are currently no simple diagnostic tests [15–17]; furthermore, there is no cure for ME/CFS, and treatment is difficult, requiring a cocktail of medications and changes in diet and lifestyle, which cannot address all symptoms. Therefore, the biggest challenge facing the scientific community is finding a common denominator that may explain the myriad of symptoms experienced in ME/CFS. This would provide the necessary roadmap to its etiology where the puzzle pieces of ME/CFS may finally be assembled. Ultimately, this would translate into a better understanding of the disease that may lead to more effective treatment, a prospect for recovery from the "crash," and the possibility of getting closer to a cure.

As a complex, heterogeneous, and multisystem disease, ME/CFS has been examined from a wide array of perspectives, exploring various potential contributing factors and biological abnormalities. With the recent discovery of the glymphatic system (the brain lymphatics for waste removal) [18], its dysfunction has been described to be the root cause of many neurological pathologies, including Alzheimer's disease [19]. With the understanding that ME/CFS is a complex neurological disorder (WHO, ICD G93.3) [2], we investigated the possibility of its association with glymphatic system function. Accordingly, here we propose that a dysfunctional glymphatic system (GD) also plays an important role in most, if not all, symptoms in ME/CFS. While some connections between ME/CFS and recovered COVID-19 patients have already been described in association with GD [20,21], we attempt to provide a more comprehensive display.

2. The Glymphatic System

The glymphatic system (glial–lymphatic) is the lymphatic analog of the brain necessary for the removal of metabolic wastes (e.g., lactate, glutamate, reactive oxygen species, ammonia, and protein aggregates such as tau and β-amyloid) [18,19]. This unique system plays a critical role in brain homeostasis by facilitating cerebrospinal fluid (CSF) and interstitial fluid (ISF) exchange through directional fluid movement via the periarterial and perivenous pathways (Figure 1); here, efflux fluids drain into the meningeal lymphatic vessels and eventually exit from the central nervous system (CNS) to the bloodstream [22].

Also, unique to the glymphatic system are perivascular spaces containing astrocytes (glia), which are essentially housekeeping cells that maintain neuronal homeostasis. The astrocyte end-feet processes that wrap around blood vessels in the brain comprise aquaporin-4 (AQP4) water channels (Figure 1B). These channels regulate fluid balance across the blood–brain barrier (BBB) and facilitate the flow of CSF through the perivascular spaces of the brain, thereby contributing to the waste removal process (Figure 2A).

While the glymphatic and meningeal lymphatic systems work together to remove waste products from the brain, other factors are involved to assist with the cleanup process. For example, damaged or misfolded proteins can form amyloid structures (protein aggregates) that may build up and block the AQP4 channels and hinder CSF–ISF exchange. These amyloid structures are normally broken down by lysosomal proteases as part of autophagy, a cellular waste removal mechanism that works together with the glymphatic

system [24]; this is believed to be impaired in ME/CFS [25]. Furthermore, degradation of the amyloid structures may also take place by catalytic antibodies, or "catabodies" [26].

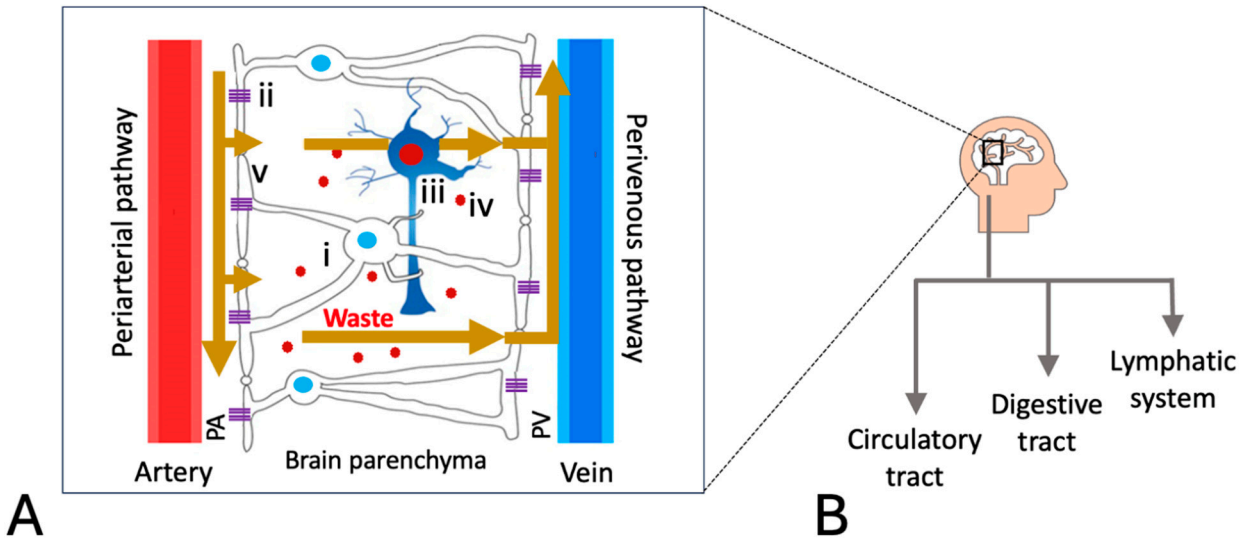

Figure 1. (**A**) Schematic presentation of a functional glymphatic system with clearance of protein aggregates and metabolic wastes mediated through fluid movement from CSF into the brain and from ISF out of the brain (i, astrocyte; ii, AQP4 channel; iii, neuron; iv, metabolic waste; v, astrocyte end-feet; PA, periarterial space; PV, perivenous space) and (**B**) downstream pathways interconnected with the glymphatic system [23].

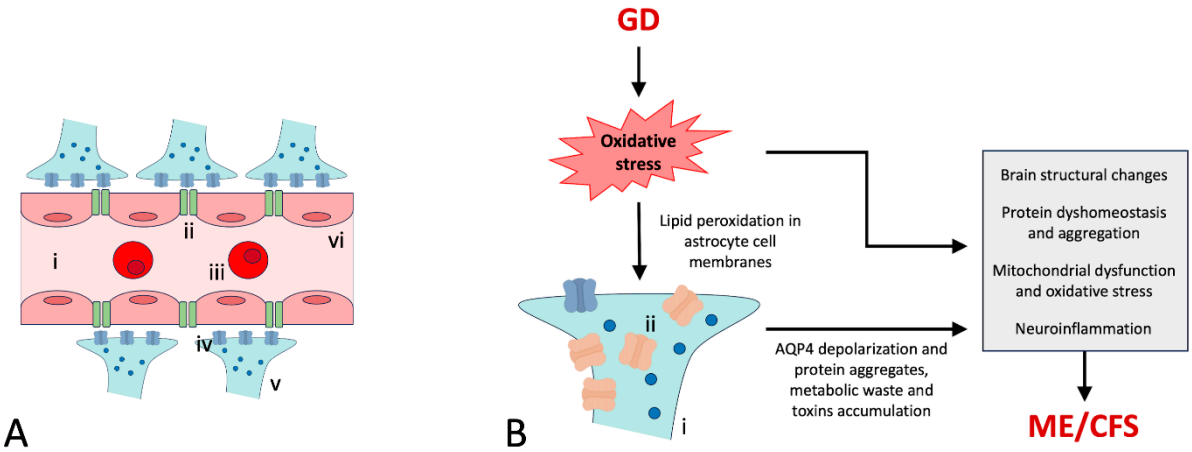

Figure 2. (**A**) Schematic presentation of the blood–brain barrier and AQP4 channel localization, which enable astrocytes to mediate brain fluid homeostasis under normal conditions (i, artery; ii, tight junction; iii, RBC; iv, AQP4 water channel protein ("polarized distribution"); v, astrocyte end-feet (with water molecules); vi, endothelial cells of the blood–brain barrier), and (**B**) dysfunctional astrocyte showing AQP4 depolarization due to oxidative stress (i, depolarized AQP4; ii, end-feet of astrocytes).

3. Blood–Brain Barrier Dysfunction

The BBB is vital to the CNS, protecting it from pathogens and toxins that are circulating in the blood. It is a restricted structure between the brain parenchyma and circulating blood. The breakdown of the BBB has been reported to occur in many pathologies, such as neurodegenerative- [27], autoimmune- [28], and infection-related diseases [29–31].

Composed of astrocytes, pericytes, and brain endothelial cells, the structural anatomy of the BBB and the glymphatic system partially overlap [32] and are complementary

mechanisms [33], with GD being a possible risk factor for BBB dysfunction [34]. Moreover, BBB dysfunction and neuroinflammation have been described in ME/CFS [35–37].

The endothelial cells are the major structural and functional components of the BBB and are sealed together with tight and adhesion junctions (Figure 2A). A number of studies have indicated that elevated levels of reactive oxygen species (ROS) can affect BBB integrity by a number of mechanisms, the main ones of which are altering expression, altering distribution, and causing modification of tight-junction proteins [38–40]. BBB dysfunction can cause an accumulation of toxic substances in the interstitial fluid surrounding neurons and glial cells. This in turn may lead to GD, which can then result in pathological changes (see below).

4. Glymphatic System Dysfunction (GD)

A number of reports have indicated that immune system dysregulation and neuroinflammation can impair the glymphatic waste removal process. Immune cells and inflammatory factors can accumulate in perivascular spaces, disrupting glymphatic function and leading to a cycle of inflammation that further damages the system and the brain. Conversely, GD can result in the reduced clearance of inflammatory mediators, exacerbating neuroinflammation [41–43].

There are several other factors that may contribute to a dysfunctional glymphatic system, including obesity, depression, and stroke [44–46], in addition to neurological disorders [19]. Alzheimer's disease, for example, can be the result of amyloid buildup due to GD [18,19,23]. Disrupted sleep and blood flow can also significantly impede the brain's waste clearance process; when there is waste overaccumulation, this promotes a cascade of events, from protein fragment aggregation to dysautonomia, neuroinflammation, and cognitive impairment [44,47,48].

5. Role of AQP4 in the Glymphatic System

AQP4 water channels are the primary pathway for water movement into the brain's interstitial space, and when dysfunctional, this process is significantly reduced. AQP4 proteins are expressed at the plasma membrane of astrocytes throughout the central nervous system and are essential to the functioning of the glymphatic system. They facilitate the exchange of fluids between CSF and ISF (Figure 1) [49], thereby playing a crucial role in preserving fluid homeostasis of the brain. Reduced function of AQP4 [50] under pathological conditions substantially inhibits proper waste clearance from the brain, leading to a buildup of amyloid-β, tau, and toxic metabolites such as lactate, causing GD and neurodegenerative diseases such as Alzheimer's and Parkinson's, as well as brain swelling from injuries [51]. Anti-AQP4 autoantibodies may also target AQP4 components, as observed in the CNS autoimmune disease neuromyelitis optica (NMO) [52]. This attack may lead to inflammation of and damage to the optic nerves and spinal cord. Furthermore, the autoantibody is used as a key diagnostic marker for the disease. We also hypothesize that anti-AQP4 autoantibodies may be involved in the pathophysiology of ME/CFS as a neuroimmune disorder.

One of the most consequential effects of ROS accumulation, under impaired glymphatic function [53], is astrocyte membrane damage by lipid peroxidation, due to its high polyunsaturated fatty acid content [54]. This can affect AQP4 polarization, with AQP4 being highly concentrated in the end-feet of astrocytes (Figure 2). The arrangement occurring in a normal, healthy situation is crucial for the glymphatic system since it enables the rapid and efficient flow of CSF and ISF to clear waste from the brain. Accordingly, astrocyte depolarization may initiate a vicious cycle, resulting in more severe GD and leading to the accumulation of toxic byproducts and a higher risk of neurodegenerative diseases.

A current hypothesis in ME/CFS research suggests that because of adrenergic dysfunction, chronic high levels of norepinephrine may interfere with AQP4 regulation, leading to potential impairment of glymphatic function [55]. Because of its central role in waste clearance, AQP4 is a target of interest for developing therapies to treat a range of neurological and psychiatric disorders [56–58].

6. GD in the Pathophysiology of ME/CFS

ME/CFS is a poorly understood disease, affecting ~1% of the world population, according to a recent report [59], and more than 9 in 10 people may not be diagnosed by a doctor [60]. It is a debilitating, multisystem chronic illness characterized by disturbances in the CNS, cell energy metabolism, and the immune and cardiovascular systems [61]. It is also associated with chronic inflammation, gastrointestinal dysfunction, and cognitive impairment [62]. In addition to these conditions, reduced cerebral blood flow [63,64] and a dysfunctional glymphatic system [65–69], could potentially explain many symptoms of ME/CFS.

Next, we attempt to explore some of the key symptoms and show how they may be traced back to specific dysfunctions of the glymphatic system.

7. Infection

Our current understanding is that in the majority of ME/CFS cases, the onset is triggered by an infection [70,71], which can also cause GD [21,72]. Impairment of the immune system, the production of autoantibodies, inflammation, mitochondrial dysfunction, and damage to the nervous system are some of the key elements of an infection that may contribute to ME/CFS pathogenesis [62,73]. BBB dysfunction and neuroinflammation, which are connected to GD, could occur concomitantly as a result [31,74,75]; moreover, infection can cause astrocyte instability at the BBB and promote displacement of the AQP4 channels [76].

Herpesviruses have been frequently associated with ME/CFS, and of these, infections with Epstein–Barr virus (EBV), human herpesvirus-6 (HHV-6), and cytomegalovirus (CMV) are considered some of the triggering factors for ME/CFS [77]. After an acute infection, these viruses may persist for life in the body and may later be reactivated.

Epigenetic silencing is also key to preventing viral reactivation [78], with both lytic and non-lytic cycles being controlled by the host's enzymatic, metabolic, and other regulatory factors. Of the many different types of viruses involved in ME/CFS, reactivation mechanisms of EBV have been of particular interest. Accordingly, a large number of factors, including metabolites [79], stressors [80], and several biological agents, such as bacteria, viruses, and fungi, have been reported to cause reactivation [81]; each may be connected to GD, especially in the context of neurological symptoms [43].

Neuroinflammation of the brain caused by GD releases proinflammatory cytokines (e.g., TNF-α, IL-1β, and IL-6) that can enter circulation, reach other parts of the body, and trigger systemic inflammation/immune dysregulation [43]. As part of a vicious cycle, tissue damage at these remote locations then releases more proinflammatory cytokines that circulate back to the brain and perpetuate GD. Furthermore, polyautoimmune disorders (e.g., Sjögren's syndrome and systemic lupus erythematosus) exacerbate the process. Comorbidities are also a major factor, especially with multi-symptom diseases like ME/CFS, and though considered primarily a neurological disease, ME/CFS does have an autoimmune component that feeds into the cycle and may contribute to systemic immune dysregulation [62].

8. Platelet Hyperactivation

Platelets play a crucial role in forming blood clots to stop bleeding after vascular injury. Various studies in ME/CFS have indicated platelet hyperactivation and defects in clotting by fibrous amyloids [82]; accordingly, fibrin amyloid microclots are resistant to breakdown and could limit oxygen delivery to tissues by obstructing blood flow. Also, cerebral blood flow issues have been reported in ME/CFS [83], which can cause GD [84], thereby linking the two pathophysiologies.

9. Neuroinflammation

Neuroinflammation has been described in both ME/CFS [85] and GD [86]. Here, oxidative stress, a major symptom in ME/CFS (described above), can cause GD in a number of ways, including astrocyte dysfunction [87] and NLRP3 inflammasome activation [86]. Moreover, accumulation of protein aggregates, such as amyloid-β, an important outcome of GD, may cause the release of pro-inflammatory cytokines [88] and result in neuroinflammation [89]. Of these cytokines, IFN-α-induced persistent fatigue is believed to be associated with ME/CFS [90].

10. Heavy Metal Toxicity

Heavy metal toxicity can affect multiple organs and has been described as being related to both GD [91] and ME/CFS [92]. Toxicity by heavy metals, such as cadmium, lead, and mercury, can cause overproduction of ROS, oxidative stress, lipid peroxidation, inflammation, antioxidant depletion (e.g., of glutathione), disruption of astrocyte function, and protein inactivation and aggregation [93]. There are a number of reports, too, indicating that heavy metal toxicity may contribute to more common symptoms of ME/CFS, most notably sleep disturbance [92].

11. Oxidative Stress, Hypoxia, and Endothelial Dysfunction

Oxidative stress is believed to be a significant contributor to the pathophysiology of ME/CFS [94,95]. Because the brain consumes ~20% of the body's total oxygen, it is extremely sensitive to oxidative damage due to its high cell membrane polyunsaturated fatty acid content [54] and weak antioxidant defense [96]. A dysfunctional glymphatic system therefore may result in an accumulation of ROS in the brain exceeding the capacity of the antioxidant system to neutralize harmful free radicals, the consequences of which include lactic acidosis and increased production of proinflammatory cytokines that lead to both BBB dysfunction [97] and neuroinflammation/GD (Figure 3) [42,98].

For proper CSF–ISF exchange, AQP4 must be localized to the end-feet processes in direct contact with the blood vessels. This "polarized distribution" of AQP4 (Figure 2A iv) [99] facilitates CSF circulation and efficient metabolic waste removal. Any disruption of AQP4 expression or its displacement can interrupt the CSF–ISF exchange [76], causing an accumulation of waste products. Accordingly, a loss of AQP4 polarization has been shown to trigger a wide range of brain pathologies, including stroke [100] and Alzheimer's disease [57]. Hypoxia can be a direct cause of oxidative stress due to increasing the production of ROS, which is primarily due to mitochondrial dysfunction [101,102].

There is a bidirectional relationship between hypoxia and endothelial dysfunction, where endothelial dysfunction can be driven by hypoxia [103] and vice versa [104] (Figure 4). Cerebral blood flow abnormalities have been reported in ME/CFS [83], resulting in hypoxia due to an inadequate supply of oxygen; this impairs the glymphatic system [105] and leads to neurological symptoms in ME/CFS such as cognitive difficulties and brain fog [61]. Furthermore, neuroinflammation [106] and sleep disturbance [107] can be the result of hypoxia.

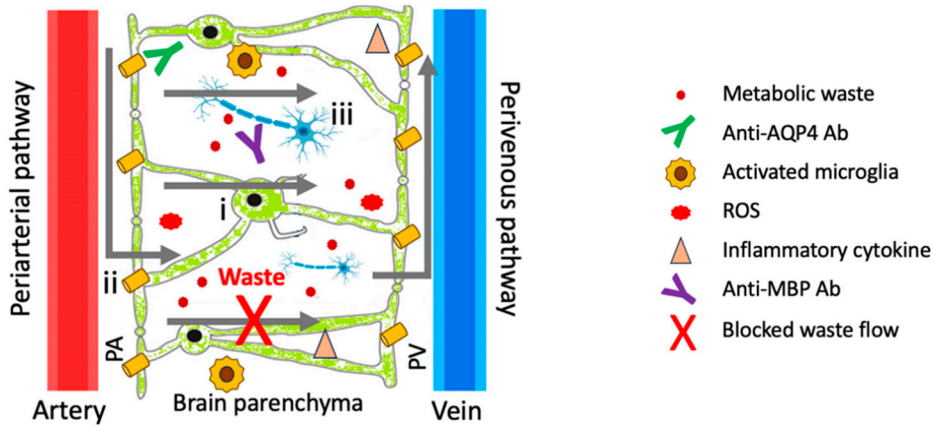

Figure 3. Schematic representation of GD/chronic neuroinflammation. Here, metabolic waste accumulation upon GD can promote the generation of ROS and proinflammatory cytokines, thereby activating NLRP3 inflammasome in microglia, which leads to neuroinflammation and neurodegeneration. i, Astrocyte; ii, AQP4 channel; iii, neuron.

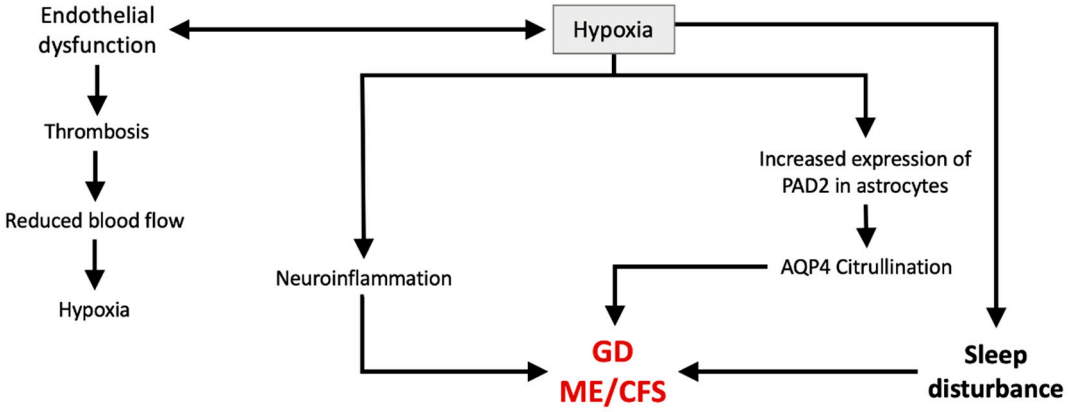

Figure 4. The bidirectional relationship between hypoxia and endothelial dysfunction, which may play an important role in the pathophysiology of ME/CFS and GD.

Hypoxia may also have a significant role in the autoimmune process. In response to low oxygen levels, hypoxia-inducible factor 1a (HIF-1a) regulates gene expression of the transcription factor NF-kB and peptidyl arginine deiminase (PAD) [108].

PAD is involved in citrullination of protein structures by converting arginine residues to citrulline, an unusual amino acid. The resulting post-translational modification (PTM) can change the structure and conformation of the tissue substrate and thus trigger an immune response. As an example, autoantibodies raised against citrullinated myelin basic protein could cause demyelination [4]. As related to AQP4, PAD2 expression has been observed in astrocytes [109] and was found to be increased under different environmental conditions, including hypoxia [110]. This would suggest that autoantibodies (anti-AQP4) may be produced against some of the AQP4-modified components, affecting its function and causing possible impairment of the glymphatic waste clearance mechanism.

12. Mitochondrial Dysfunction and Fragmentation

Mitochondrial dysfunction is believed to play an important role in the pathophysiology of ME/CFS [111]. When the glymphatic system is impaired, it may result in protein (e.g., amyloid-β) aggregate accumulation, which further facilitates mitochondrial membrane permeabilization and the loss of mitochondrial function (Figure 5) [112–116].

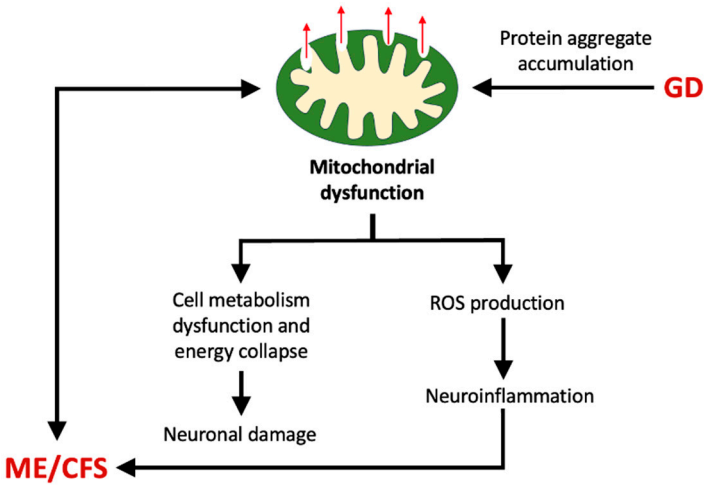

Figure 5. Proposed relationship of mitochondrial dysfunction between GD and ME/CFS. An accumulation of protein aggregates induced by GD may cause mitochondrial membrane permeabilization and energy collapse, which could promote oxidative stress and neurodegeneration.

Mitochondrial dysfunction can also increase the level of ROS and thereby cause neuroinflammation [117]; this has been reported in both ME/CFS [118] and GD [86] (Figure 5). A common feature of mitochondrial dysfunction is fragmentation, which often results from an imbalance between the processes of fission and fusion [119]. Both oxidative stress and viral infection (e.g., HHV-6) are believed to be responsible for mitochondrial fragmentation in ME/CFS [120,121]. Although mitochondrial fragmentation has not been specifically described as being related to the glymphatic system, it may occur as part of the general mechanism of mitochondrial dysfunction reported for GD [47].

13. Post-Exertional Malaise (PEM)

As a hallmark symptom that is most significant to ME/CFS, PEM is characterized by a disproportionate worsening of fatigue, pain, and cognitive dysfunction, and is a manifestation of a "crash." A "crash" may last for days, weeks, or longer, even after minor exertion. Endothelial dysfunction [122], impaired oxygen delivery issues [83,123], disruption in metabolic pathways with the accumulation of waste products [124], and problems with red blood cell (RBC) biomechanics may be involved [125–127], which may also affect glymphatic function. Of these, abnormal cerebral blood flow [83] and an accumulation of metabolic wastes such as lactate can hamper the glymphatic clearance system. Also, endothelial dysfunction can impact the glymphatic system by impairing the BBB [41].

Recent studies of patients with Long COVID, particularly those experiencing PEM, have found amyloid-containing deposits in skeletal muscle tissue [14]. These can have major consequences related to the glymphatic system since amyloid structures from peripheral circulation can pass through a dysfunctional BBB, a process that is believed to be bidirectional [128], in addition to having the capacity to cause its disruption [129]. Interestingly, fibrin amyloid microclots have been observed in ME/CFS patients [82], similarly to Long COVID, as described above. Based on these observations, we propose that GD and the pathophysiology of PEM in ME/CFS are connected.

14. Lactic Acidosis

Lactate is normally cleared from the brain via the glymphatic pathway as part of its metabolic waste removal mechanism (Figure 1) [66,98]. Accordingly, lactate accumulation in the brain may occur under GD, contributing to acidosis. Lactate is also believed to

be elevated in ME/CFS, even in resting conditions, and is correlated with the severity of PEM [124]. Increased brain lactate levels may also occur as the result of low blood flow to the brain [130] or by impaired pyruvate dehydrogenase activity in ME/CFS [131]. Moreover, lactic acidosis is a marker of mitochondrial dysfunction [132,133], occurring when mitochondria are unable to perform oxidative phosphorylation effectively. Impaired mitochondrial energy metabolism has been reported for ME/CFS [134], which was further confirmed by earlier studies of elevated brain lactate [135].

15. Brain Fog

Brain fog is a primary symptom of ME/CFS, which many patients find profoundly debilitating. Described as a feeling of "mental fogginess" and as difficulty thinking, focusing, and remembering [5], it is a subjective feeling of cognitive impairment and is generally believed to be a symptom of neurological dysfunction [136]. A connection to BBB dysfunction has recently been found in Long COVID [137–139]. Brain fog has also been described in relation to GD and COVID-19 [140,141]. A number of factors believed to cause brain fog in ME/CFS, including oxidative stress [142], neuroinflammation [35], BBB dysfunction [139], reduced cerebral blood flow [136], and lactic acidosis [143], have also been described to induce glymphatic dysfunction, as discussed above.

16. Dysautonomia and Vagus Nerve Stimulation

The autonomic nervous system (ANS) regulates functions of the internal organs (e.g., cardiac output/heartrate, blood pressure, temperature, and digestion) by maintaining a balance between the sympathetic and parasympathetic nervous systems. Dysautonomia is a core feature of ME/CFS [144,145], potentially contributing to a number of key symptoms, including Postural Orthostatic Tachycardia Syndrome (POTS) and orthostatic hypotension, as part of orthostatic intolerance (OI) [146,147] (Figure 6). Symptoms of dysautonomia, which include dizziness, lightheadedness, fatigue, and headache, limit daily activities for many people with ME/CFS; these symptoms are known to worsen upon standing and are relieved by lying down. Reduced heart rate variability (HRV) [148], which has significance in relation to fatigue severity in ME/CFS [149], are included in this category of symptoms. The ANS also plays a crucial role in regulating the glymphatic system where dysautonomia may promote glymphatic failure [150–152].

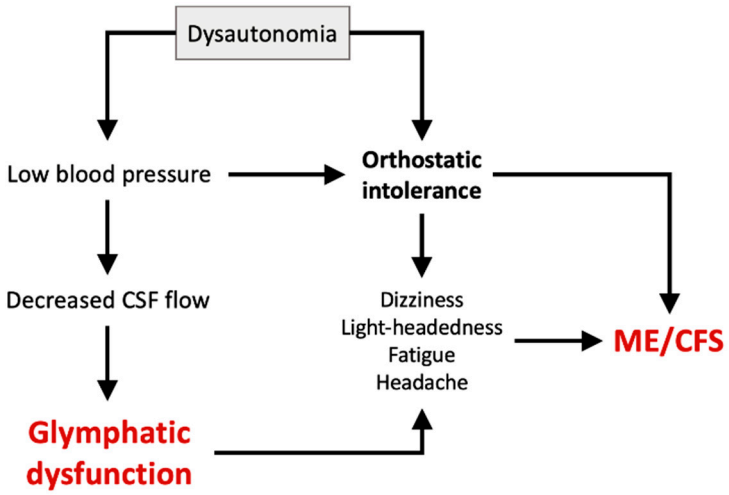

Figure 6. Proposed relationship between dysautonomia, GD, and ME/CFS. Dysautonomia may cause orthostatic intolerance, leading to ME/CFS. A lowering of blood pressure can cause a decrease in cerebral blood flow and thereby impact the glymphatic system.

As a major part of the ANS, the vagus nerve influences functions such as heartrate, breathing, and digestion (Figure 7). Reports indicate that vagus nerve dysfunction may be part of the pathophysiology of ME/CFS; here, some patients may benefit from vagus nerve stimulation by alleviating symptoms such as fatigue and PEM [153].

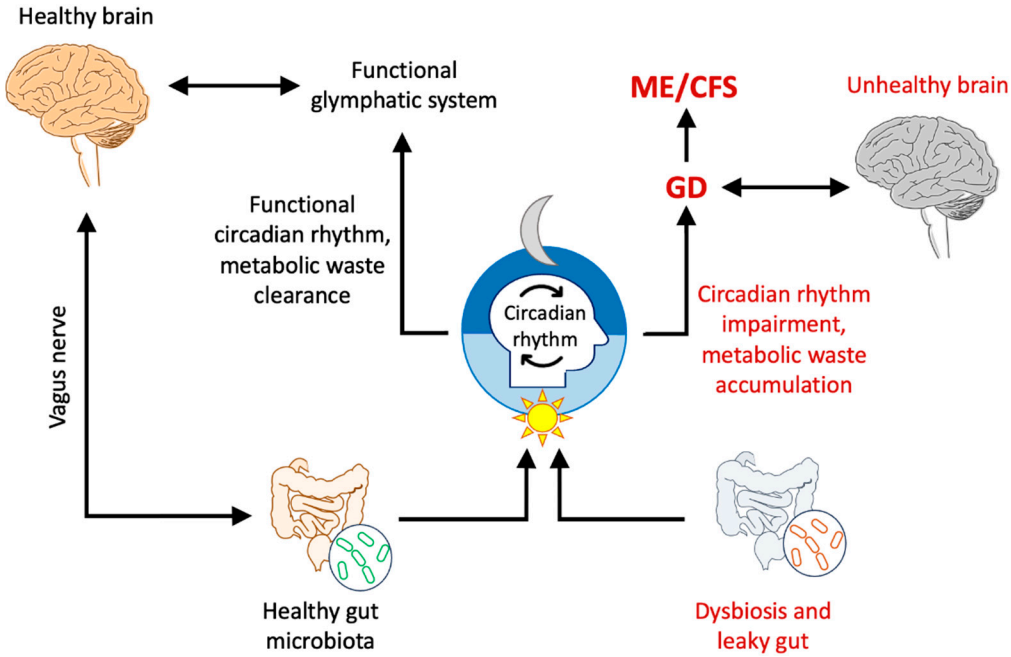

Figure 7. A potential role of the gut microbiota in the glymphatic system, mediated by circadian rhythm regulation. An impairment in the circadian rhythm, mediated by dysbiosis, can significantly affect glymphatic clearance function and lead to neurological disorders, including ME/CFS.

The glymphatic system is also strongly associated with the vagus nerve, and its stimulation is believed to accelerate the CSF flow into the brain parenchyma and enhance the CSF–ISF exchange [150]. The vagus nerve also plays a crucial role in the brain–gut axis, a bidirectional communication between the brain and the digestive system [154] (Figure 7); its stimulation may help restore balance to the gut microbiome [153], which is important to the pathophysiology of ME/CFS and the glymphatic system.

17. Circadian Rhythm and Sleep Dysfunction

Unrefreshing sleep is a key hallmark of ME/CFS, affecting up to 95% of patients [155]. During sleep, the glymphatic system clears CNS metabolite wastes and other harmful substances that accumulate throughout daily brain activity [156], with astrocytes playing a major role [157]. The glymphatic system is primarily active during non-rapid eye movement (NREM) sleep [158] at a point when ME/CFS patients have greater sleep instability [159]. Moreover, the glymphatic system is influenced by the circadian rhythm, and a malfunctioning of its activity may hinder efficient removal of toxic proteins; this promotes aggregation, with toxicity to neurons, resulting in neurological disorder (Figure 7) [160]. Accordingly, the glymphatic system and sleep dysfunction appear to be closely linked, where the CSF–ISF exchange is compromised by sleep cycle abnormalities [161]. Oxidative stress and neuroinflammation, two of the consequences of GD [42,53], occur in ME/CFS [94,95] and can also impact quality of sleep [162,163].

18. Dehydration, Hypovolemia, and Cardiac Output

Dehydration can be a serious problem in some patients with very severe ME/CFS as a consequence of impaired swallowing [164]. These patients are in a debilitated state

and unable to eat or drink, leading to malnutrition and dehydration. Dehydration can be a significant problem since it may lead to hypovolemia, affecting cardiac output as a result [165]. As a consequence, individuals with ME/CFS may exhibit lowered cardiac output due to hypovolemia [166]. Also, since the glymphatic system requires adequate fluid volume for efficient waste clearance, hypovolemia can potentially disrupt proper CSF–ISF exchange, leading to GD in these patients [167].

19. Gut–Brain Axis Dysregulation and Dysbiosis

The gut–brain axis is a bidirectional communication system between the gastrointestinal tract and the CNS. A healthy gut microbiome (balanced community of microorganisms, including bacteria, viruses, and fungi) is believed to be essential for normal physiological activities, including the circadian rhythm and sleep (Figure 7) [168].

A disruption in gut–brain communication, which has been reported for ME/CFS [169], has also shown to affect the glymphatic clearance system [168]. Moreover, dysbiosis, an imbalance in the composition of the gut microbiota, has been reported for both ME/CFS [170] and glymphatic dysfunction [171], causing neurological problems [172].

20. Idiopathic Intracranial Hypertension (IIH)

IIH, a condition where there is elevated pressure within the skull that causes fatigue and headaches, has been reported in ME/CFS [173]. This corresponds to increased intracranial pressure (ICP), which is affected by high CSF buildup in these patients [174], some of whom may benefit from IIH treatments, including surgery [175]. Craniocervical instability, which involves a weakening of the ligaments supporting the head and upper neck, and Ehlers–Danlos syndrome, both frequently reported in ME/CFS [174,176], are believed to be contributing factors to IIH [177]. IIH is also associated with impaired glymphatic function [178,179].

21. Brain Temperature

Since the brain is naturally hotter than the rest of the body, blood circulation acts to "cool" it by removing "hot blood" [180,181]. Abnormal cerebral blood flow and neuroinflammation are believed to be two of the main contributing factors in causing elevated brain temperature in ME/CFS [182]. Hyperthermia may also hamper glymphatic function by obstructing the flow of CSF through perivascular spaces (Figure 3), thereby reducing the efficiency of waste removal in the brain [183].

22. Brain pH

Brain pH regulation is crucial for neuronal function. To maintain acid–base balance, the brain has developed various mechanisms, including a buffering system in astrocytes [184]. Some studies suggest a potential decrease in the brain pH of ME/CFS patients, possibly due to a buildup of lactic acid [130]; this is also related to GD, since the glymphatic system plays a key role in cleaning waste products (e.g., lactate) from the brain [66,98] (see "Lactic Acidosis," above).

23. GD Modulation for ME/CFS

Due to potential GD in ME/CFS, patients may benefit from treatments that improve the CSF influx/CSF–ISF efflux process in the brain to remove waste. For example, modulation of the glymphatic system can be accomplished by targeting perivascular CSF flow and AQP4 water channels, and by monitoring tracer flow in the brain parenchyma [32,185]. While certain lifestyle and behavioral modifications (e.g., improved sleep, exercise, meditation [156,186,187]) have been suggested, there are noninvasive techniques that have been

tested with success in both GD and ME/CFS, including electroacupuncture [188,189] and repetitive transcranial magnetic stimulation (rTMS), which is used to facilitate cortical neural activity in the glymphatic system [190–192]. Moreover, therapeutics (noradrenaline and specific serotonergic antidepressants) for GD and ME/CFS have been associated with increased astrocytes and upregulated AQP4 expression; these include ketamine [187,193] and mirtazapine (improves glial cell line-derived neurotrophic factor production) [65,186]. Noninvasive techniques for glymphatic system modulation that hold promise for the treatment of ME/CFS include visual circuit activation (low-intensity 40 hertz blue light) [194], focused ultrasound combined with microbubbles [195], and multisensory gamma stimulation [196]; lymphatic–venous anastomosis is another consideration but is a much more invasive procedure [197]. Additional glymphatic modulation drugs that may also improve astrocyte and AQP4 function in ME/CFS include atipamezole, escitalopram [65], and systemic dexmedetomidine (promotes slow-wave activity, with a ∼32% increase in tracer influx and a ∼6-fold increase in hippocampal clearance) [198].

24. Concluding Remarks

In this article, we attempted to provide our perspective on the potential relationship between glymphatic dysfunction and the key symptoms of ME/CFS. The ideas presented here suggest commonalities in some of their essential features that may be useful to the ME/CFS scientific/medical community for deeper insight into the disease and better patient treatment.

ME/CFS has had a complex history, having been dismissed as a true pathology before being recognized as a biological disease. More recently, the ME/CFS scientific community has been interested in establishing the molecular basis of this disease, while being focused on several key areas, including the function of the immune system, metabolomics, muscle fatigue, and the nervous system. Even now, after all the efforts made during the past decades, an estimated 90% of people with ME/CFS are believed to be undiagnosed due to an absence of simple diagnostic tests [60]. Symptom overlap and comorbidities highlight the complexity of the disease, which suggest that a better understanding of its pathophysiology is urgently needed.

ME/CFS is now generally considered a neuroimmune disorder, involving interaction of neurological and immunological processes [199], and an overactive innate immune response [12]. Moreover, there is evidence of immune exhaustion [200], which may underlie many of the symptoms. ME/CFS is frequently characterized by PEM, where physical or mental exertion may lead to a worsening of symptoms, referred to as a "crash." Other characteristic symptoms include unrefreshing sleep, fatigue, muscle pain, headache, orthostatic intolerance, and hypersensitivity to sensory stimuli. Of these, PEM and sleep disturbances are the hallmark symptoms of ME/CFS. With the recent discovery of the glymphatic system providing a mechanism for the removal of metabolic waste products from the brain, primarily during sleep, we were interested in exploring the relationship between GD and symptoms of ME/CFS. The details presented above suggest that glymphatic dysfunction may indeed be connected to the main characteristics of ME/CFS and may play a pivotal role in contributing to its pathophysiology. Therefore, we hope our approach will provide a clearer picture of the neurological component of ME/CFS. Attempts towards developing therapeutics for GD have already been initiated, the results of which may be of value for the effective treatment of ME/CFS, with an increased chance of recovery from the "crash" and ultimately a cure for this debilitating, chronic, and complex illness.

Author Contributions: Conceptualization: M.N.-G. and M.A.J.; writing—original draft preparation: M.N.-G. and M.A.J.; writing—review and editing: M.N.-G. and M.A.J.; supervision: R.W.D.;

project administration: R.W.D.; funding acquisition: R.W.D. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the generous contribution of the Khosla Family Gift Fund.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Clayton, E.W. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: An IOM report on redefining an illness. *JAMA* **2015**, *313*, 1101–1102. [CrossRef]
2. Carruthers, B.M.; van de Sande, M.I.; De Meirleir, K.L.; Klimas, N.G.; Broderick, G.; Mitchell, T.; Staines, D.; Powles, A.C.; Speight, N.; Vallings, R.; et al. Myalgic encephalomyelitis: International Consensus Criteria. *J. Intern. Med.* **2011**, *270*, 327–338, Correction in *J. Intern. Med.* **2017**, *284*, 353. [CrossRef]
3. Walitt, B.; Singh, K.; LaMunion, S.R.; Hallett, M.; Jacobson, S.; Chen, K.; Enose-Akahata, Y.; Apps, R.; Barb, J.J.; Bedard, P.; et al. Deep phenotyping of post-infectious myalgic encephalomyelitis/chronic fatigue syndrome. *Nat. Commun.* **2024**, *15*, 907. [CrossRef]
4. Jensen, M.A.; Dafoe, M.L.; Wilhelmy, J.; Cervantes, L.; Okumu, A.N.; Kipp, L.; Nemat-Gorgani, M.; Davis, R.W. Catalytic Antibodies May Contribute to Demyelination in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Biochemistry* **2024**, *63*, 9–18. [CrossRef] [PubMed]
5. Ocon, A.J. Caught in the thickness of brain fog: Exploring the cognitive symptoms of Chronic Fatigue Syndrome. *Front. Physiol.* **2013**, *4*, 63. [CrossRef]
6. Azcue, N.; Gómez-Esteban, J.C.; Acera, M.; Tijero, B.; Fernandez, T.; Ayo-Mentxakatorre, N.; Pérez-Concha, T.; Murueta-Goyena, A.; Lafuente, J.V.; Prada, Á.; et al. Brain fog of post-COVID-19 condition and Chronic Fatigue Syndrome, same medical disorder? *J. Transl. Med.* **2022**, *20*, 569. [CrossRef] [PubMed]
7. Schutzer, S.E.; Liu, T.; Tsai, C.F.; Petyuk, V.A.; Schepmoes, A.A.; Wang, Y.T.; Weitz, K.K.; Bergquist, J.; Smith, R.D.; Natelson, B.H. Myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia are indistinguishable by their cerebrospinal fluid proteomes. *Ann. Med.* **2023**, *55*, 2208372. [CrossRef]
8. Komaroff, A.L.; Lipkin, W.I. ME/CFS and Long COVID share similar symptoms and biological abnormalities: Road map to the literature. *Front. Med.* **2023**, *10*, 1187163. [CrossRef] [PubMed]
9. Jason, L.A.; Dorri, J.A. ME/CFS and Post-Exertional Malaise among Patients with Long COVID. *Neurol. Int.* **2022**, *15*, 1. [CrossRef]
10. Dafoe, W. Extremely Severe ME/CFS-A Personal Account. *Healthcare* **2021**, *9*, 504. [CrossRef]
11. Cortes Rivera, M.; Mastronardi, C.; Silva-Aldana, C.T.; Arcos-Burgos, M.; Lidbury, B.A. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Comprehensive Review. *Diagnostics* **2019**, *9*, 91. [CrossRef]
12. Che, X.; Ranjan, A.; Guo, C.; Zhang, K.; Goldsmith, R.; Levine, S.; Moneghetti, K.J.; Zhai, Y.; Ge, L.; Mishra, N.; et al. Heightened innate immunity may trigger chronic inflammation, fatigue and post-exertional malaise in ME/CFS. *npj Metab. Health Dis.* **2025**, *3*, 34. [CrossRef]
13. Vøllestad, N.K.; Mengshoel, A.M. Post-exertional malaise in daily life and experimental exercise models in patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Front. Physiol.* **2023**, *14*, 1257557. [CrossRef]
14. Appelman, B.; Charlton, B.T.; Goulding, R.P.; Kerkhoff, T.J.; Breedveld, E.A.; Noort, W.; Offringa, C.; Bloemers, F.W.; van Weeghel, M.; Schomakers, B.V.; et al. Muscle abnormalities worsen after post-exertional malaise in long COVID. *Nat. Commun.* **2024**, *15*, 17. [CrossRef]
15. Maksoud, R.; Magawa, C.; Eaton-Fitch, N.; Thapaliya, K.; Marshall-Gradisnik, S. Biomarkers for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): A systematic review. *BMC Med.* **2023**, *21*, 189. [CrossRef]
16. Hunter, E.; Alshaker, H.; Bundock, O.; Weston, C.; Bautista, S.; Gebregzabhar, A.; Virdi, A.; Croxford, J.; Dring, A.; Powell, R.; et al. Development and validation of blood-based diagnostic biomarkers for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) using EpiSwitch. *J. Transl. Med.* **2025**, *23*, 1048. [CrossRef] [PubMed]
17. Xiong, R.; Aiken, E.; Caldwell, R.; Vernon, S.D.; Kozhaya, L.; Gunter, C.; Bateman, L.; Unutmaz, D.; Oh, J. AI-driven multi-omics modeling of myalgic encephalomyelitis/chronic fatigue syndrome. *Nat. Med.* **2025**, *31*, 2991–3001. [CrossRef] [PubMed]
18. Plog, B.A.; Nedergaard, M. The Glymphatic System in Central Nervous System Health and Disease: Past, Present, and Future. *Annu. Rev. Pathol.* **2018**, *13*, 379–394. [CrossRef]
19. Rasmussen, M.K.; Mestre, H.; Nedergaard, M. The glymphatic pathway in neurological disorders. *Lancet Neurol.* **2018**, *17*, 1016–1024. [CrossRef] [PubMed]
20. Wostyn, P.; De Deyn, P.P. The putative glymphatic signature of chronic fatigue syndrome: A new view on the disease pathogenesis and therapy. *Med. Hypotheses* **2018**, *118*, 142–145. [CrossRef]

21. Wu, L.; Zhang, Z.; Liang, X.; Wang, Y.; Cao, Y.; Li, M.; Zhou, F. Glymphatic system dysfunction in recovered patients with mild COVID-19: A DTI-ALPS study. *iScience* **2024**, *27*, 108647. [CrossRef]
22. Licastro, E.; Pignataro, G.; Iliff, J.J.; Xiang, Y.; Lo, E.H.; Hayakawa, K.; Esposito, E. Glymphatic and lymphatic communication with systemic responses during physiological and pathological conditions in the central nervous system. *Commun. Biol.* **2024**, *7*, 229. [CrossRef] [PubMed]
23. Hablitz, L.M.; Nedergaard, M. The Glymphatic System: A Novel Component of Fundamental Neurobiology. *J. Neurosci.* **2021**, *41*, 7698–7711. [CrossRef]
24. Potokar, M.; Jorgačevski, J. Targeting autophagy in astrocytes: A potential for neurodegenerative disease intervention. *Front. Cell Neurosci.* **2025**, *19*, 1584767. [CrossRef]
25. Gottschalk, G.; Peterson, D.; Knox, K.; Maynard, M.; Whelan, R.J.; Roy, A. Elevated ATG13 in serum of patients with ME/CFS stimulates oxidative stress response in microglial cells via activation of receptor for advanced glycation end products (RAGE). *Mol. Cell. Neurosci.* **2022**, *120*, 103731. [CrossRef]
26. Meretoja, V.V.; Paul, S.; Planque, S.A. Hydrolysis and Dissolution of Amyloids by Catabodies. *Methods Mol. Biol.* **2017**, *1643*, 111–134, Erratum in *Methods Mol. Biol.* **2017**, *1643*, E1. [CrossRef] [PubMed]
27. Chen, T.; Dai, Y.; Hu, C.; Lin, Z.; Wang, S.; Yang, J.; Zeng, L.; Li, S.; Li, W. Cellular and molecular mechanisms of the blood-brain barrier dysfunction in neurodegenerative diseases. *Fluids Barriers CNS* **2024**, *21*, 60. [CrossRef] [PubMed]
28. Williams, J.L.; Klein, R.S. Blood-Brain Barrier Dysfunction during Central Nervous System Autoimmune Diseases. In *The Blood Brain Barrier and Inflammation*; Lyck, R., Enzmann, G., Eds.; Springer International Publishing: Cham, Switzerland, 2017; pp. 175–186.
29. Patabendige, A.; Janigro, D. The role of the blood-brain barrier during neurological disease and infection. *Biochem. Soc. Trans.* **2023**, *51*, 613–626. [CrossRef]
30. Chen, Z.; Li, G. Immune response and blood-brain barrier dysfunction during viral neuroinvasion. *Innate Immun.* **2021**, *27*, 109–117. [CrossRef]
31. Galea, I. The blood-brain barrier in systemic infection and inflammation. *Cell. Mol. Immunol.* **2021**, *18*, 2489–2501. [CrossRef]
32. Gao, Y.; Liu, K.; Zhu, J. Glymphatic system: An emerging therapeutic approach for neurological disorders. *Front. Mol. Neurosci.* **2023**, *16*, 1138769. [CrossRef]
33. Verheggen, I.C.M.; Van Boxtel, M.P.J.; Verhey, F.R.J.; Jansen, J.F.A.; Backes, W.H. Interaction between blood-brain barrier and glymphatic system in solute clearance. *Neurosci. Biobehav. Rev.* **2018**, *90*, 26–33. [CrossRef] [PubMed]
34. Li, Y.; Li, M.; Yang, L.; Qin, W.; Yang, S.; Yuan, J.; Jiang, T.; Hu, W. The relationship between blood-brain barrier permeability and enlarged perivascular spaces: A cross-sectional study. *Clin. Interv. Aging* **2019**, *14*, 871–878. [CrossRef] [PubMed]
35. Tate, W.; Walker, M.; Sweetman, E.; Helliwell, A.; Peppercorn, K.; Edgar, C.; Blair, A.; Chatterjee, A. Molecular Mechanisms of Neuroinflammation in ME/CFS and Long COVID to Sustain Disease and Promote Relapses. *Front. Neurol.* **2022**, *13*, 877772. [CrossRef]
36. Tate, W.P.; Walker, M.O.M.; Peppercorn, K.; Blair, A.L.H.; Edgar, C.D. Towards a Better Understanding of the Complexities of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Long COVID. *Int. J. Mol. Sci.* **2023**, *24*, 5124. [CrossRef]
37. Komaroff, A.L.; Dantzer, R. Causes of symptoms and symptom persistence in long COVID and myalgic encephalomyelitis/chronic fatigue syndrome. *Cell Rep. Med.* **2025**, *6*, 102259. [CrossRef]
38. Elahy, M.; Jackaman, C.; Mamo, J.C.; Lam, V.; Dhaliwal, S.S.; Giles, C.; Nelson, D.; Takechi, R. Blood-brain barrier dysfunction developed during normal aging is associated with inflammation and loss of tight junctions but not with leukocyte recruitment. *Immun. Ageing* **2015**, *12*, 2. [CrossRef]
39. Lochhead, J.J.; McCaffrey, G.; Quigley, C.E.; Finch, J.; DeMarco, K.M.; Nametz, N.; Davis, T.P. Oxidative stress increases blood-brain barrier permeability and induces alterations in occludin during hypoxia-reoxygenation. *J. Cereb. Blood Flow Metab.* **2010**, *30*, 1625–1636. [CrossRef] [PubMed]
40. Schreibelt, G.; Kooij, G.; Reijerkerk, A.; van Doorn, R.; Gringhuis, S.I.; van der Pol, S.; Weksler, B.B.; Romero, I.A.; Couraud, P.O.; Piontek, J.; et al. Reactive oxygen species alter brain endothelial tight junction dynamics via RhoA, PI3 kinase, and PKB signaling. *FASEB J.* **2007**, *21*, 3666–3676. [CrossRef]
41. Chen, S.; Wang, H.; Zhang, L.; Xi, Y.; Lu, Y.; Yu, K.; Zhu, Y.; Regina, I.; Bi, Y.; Tong, F. Glymphatic system: A self-purification circulation in brain. *Front. Cell Neurosci.* **2025**, *19*, 1528995. [CrossRef]
42. Zou, K.; Deng, Q.; Zhang, H.; Huang, C. Glymphatic system: A gateway for neuroinflammation. *Neural Regen. Res.* **2024**, *19*, 2661–2672. [CrossRef]
43. Cai, Y.; Zhang, Y.; Leng, S.; Ma, Y.; Jiang, Q.; Wen, Q.; Ju, S.; Hu, J. The relationship between inflammation, impaired glymphatic system, and neurodegenerative disorders: A vicious cycle. *Neurobiol. Dis.* **2024**, *192*, 106426. [CrossRef]
44. Wafford, K.A. Aberrant waste disposal in neurodegeneration: Why improved sleep could be the solution. *Cereb. Circ. Cogn. Behav.* **2021**, *2*, 100025; Erratum in *Cereb. Circ. Cogn. Behav.* **2022**, *3*, 100038. [CrossRef]

45. Zhan, M.; Liu, X.; Xia, X.; Yang, Y.; Xie, Y.; Zhang, L.; Lin, C.; Zhu, J.; Ding, W.; Xu, S. Promotion of neuroinflammation by the glymphatic system: A new insight into ethanol extracts from Alisma orientale in alleviating obesity-associated cognitive impairment. *Phytomedicine* **2024**, *122*, 155147. [CrossRef]
46. Barlattani, T.; Grandinetti, P.; Cintio, A.D.; Montemagno, A.; Testa, R.; D'Amelio, C.; Olivieri, L.; Tomasetti, C.; Rossi, A.; Pacitti, F.; et al. Glymphatic System and Psychiatric Disorders: A Rapid Comprehensive Scoping Review. *Curr. Neuropharmacol.* **2024**, *22*, 2016–2033. [CrossRef]
47. Kopeć, K.; Szleszkowski, S.; Koziorowski, D.; Szlufik, S. Glymphatic System and Mitochondrial Dysfunction as Two Crucial Players in Pathophysiology of Neurodegenerative Disorders. *Int. J. Mol. Sci.* **2023**, *24*, 10366. [CrossRef] [PubMed]
48. Buongiorno, M.; Marzal, C.; Fernandez, M.; Cullell, N.; de Mena, L.; Sánchez-Benavides, G.; de la Sierra, A.; Krupinski, J.; Compta, Y. Altered sleep and neurovascular dysfunction in alpha-synucleinopathies: The perfect storm for glymphatic failure. *Front. Aging Neurosci.* **2023**, *15*, 1251755. [CrossRef] [PubMed]
49. Kato, D.; Kameda, H.; Kinota, N.; Fujii, T.; Xiawei, B.; Simi, Z.; Takai, Y.; Chau, S.; Miyasaka, Y.; Mashimo, T.; et al. Loss of aquaporin-4 impairs cerebrospinal fluid solute clearance through cerebrospinal fluid drainage pathways. *Sci. Rep.* **2024**, *14*, 27982. [CrossRef]
50. Dai, J.; Lin, W.; Zheng, M.; Liu, Q.; He, B.; Luo, C.; Lu, X.; Pei, Z.; Su, H.; Yao, X. Alterations in AQP4 expression and polarization in the course of motor neuron degeneration in SOD1G93A mice. *Mol. Med. Rep.* **2017**, *16*, 1739–1746. [CrossRef] [PubMed]
51. Wang, Y.; Huang, C.; Guo, Q.; Chu, H. Aquaporin-4 and Cognitive Disorders. *Aging Dis.* **2022**, *13*, 61–72. [CrossRef]
52. Jarius, S.; Paul, F.; Weinshenker, B.G.; Levy, M.; Kim, H.J.; Wildemann, B. Neuromyelitis optica. *Nat. Rev. Dis. Primers* **2020**, *6*, 85. [CrossRef]
53. Gu, S.; Li, Y.; Jiang, Y.; Huang, J.H.; Wang, F. Glymphatic Dysfunction Induced Oxidative Stress and Neuro-Inflammation in Major Depression Disorders. *Antioxidants* **2022**, *11*, 2296. [CrossRef]
54. Bazinet, R.P.; Layé, S. Polyunsaturated fatty acids and their metabolites in brain function and disease. *Nat. Rev. Neurosci.* **2014**, *15*, 771–785. [CrossRef] [PubMed]
55. Carnac, T. A Systems-Based Hypothesis for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Phosphatidylcholine Deficiency, Insulin Signaling and Noradrenergic Neuron Dysregulation. *Preprints* **2025**. [CrossRef]
56. Verkman, A.S.; Smith, A.J.; Phuan, P.W.; Tradtrantip, L.; Anderson, M.O. The aquaporin-4 water channel as a potential drug target in neurological disorders. *Expert Opin. Ther. Targets* **2017**, *21*, 1161–1170. [CrossRef]
57. Peng, S.; Liu, J.; Liang, C.; Yang, L.; Wang, G. Aquaporin-4 in glymphatic system, and its implication for central nervous system disorders. *Neurobiol. Dis.* **2023**, *179*, 106035. [CrossRef] [PubMed]
58. Silverglate, B.; Gao, X.; Lee, H.P.; Maliha, P.; Grossberg, G.T. The aquaporin-4 water channel and updates on its potential as a drug target for Alzheimer's disease. *Expert Opin. Ther. Targets* **2023**, *27*, 523–530. [CrossRef] [PubMed]
59. Park, J.W.; Park, B.J.; Lee, J.S.; Lee, E.J.; Ahn, Y.C.; Son, C.G. Systematic review of fatigue severity in ME/CFS patients: Insights from randomized controlled trials. *J. Transl. Med.* **2024**, *22*, 529, Erratum in *J. Transl. Med.* **2024**, *22*, 603. [CrossRef]
60. Grach, S.L.; Seltzer, J.; Chon, T.Y.; Ganesh, R. Diagnosis and Management of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Mayo Clin. Proc.* **2023**, *98*, 1544–1551. [CrossRef]
61. Wirth, K.J.; Scheibenbogen, C.; Paul, F. An attempt to explain the neurological symptoms of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *J. Transl. Med.* **2021**, *19*, 471, Erratum in *J. Transl. Med.* **2022**, *20*, 25. [CrossRef]
62. Rasa, S.; Nora-Krukle, Z.; Henning, N.; Eliassen, E.; Shikova, E.; Harrer, T.; Scheibenbogen, C.; Murovska, M.; Prusty, B.K.; EUROMENE. Chronic viral infections in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *J. Transl. Med.* **2018**, *16*, 268. [CrossRef]
63. Biswal, B.; Kunwar, P.; Natelson, B.H. Cerebral blood flow is reduced in chronic fatigue syndrome as assessed by arterial spin labeling. *J. Neurol. Sci.* **2011**, *301*, 9–11. [CrossRef]
64. Yoshiuchi, K.; Farkas, J.; Natelson, B.H. Patients with chronic fatigue syndrome have reduced absolute cortical blood flow. *Clin. Physiol. Funct. Imaging* **2006**, *26*, 83–86. [CrossRef]
65. Yan, T.; Qiu, Y.; Yu, X.; Yang, L. Glymphatic Dysfunction: A Bridge Between Sleep Disturbance and Mood Disorders. *Front. Psychiatry* **2021**, *12*, 658340. [CrossRef] [PubMed]
66. Vittorini, M.G.; Sahin, A.; Trojan, A.; Yusifli, S.; Alashvili, T.; Bonifácio, G.V.; Paposhvili, K.; Tischler, V.; Lampl, C.; Sacco, S.; et al. The glymphatic system in migraine and other headaches. *J. Headache Pain.* **2024**, *25*, 34. [CrossRef]
67. Yi, T.; Gao, P.; Zhu, T.; Yin, H.; Jin, S. Glymphatic System Dysfunction: A Novel Mediator of Sleep Disorders and Headaches. *Front. Neurol.* **2022**, *13*, 885020. [CrossRef] [PubMed]
68. Xie, L.; Kang, H.; Xu, Q.; Chen, M.J.; Liao, Y.; Thiyagarajan, M.; O'Donnell, J.; Christensen, D.J.; Nicholson, C.; Iliff, J.J.; et al. Sleep drives metabolite clearance from the adult brain. *Science* **2013**, *342*, 373–377. [CrossRef]
69. Bateman, G.A.; Bateman, A.R. A perspective on the evidence for glymphatic obstruction in spaceflight associated neuro-ocular syndrome and fatigue. *npj Microgravity* **2024**, *10*, 23. [CrossRef] [PubMed]
70. Dehlia, A.; Guthridge, M.A. The persistence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) after SARS-CoV-2 infection: A systematic review and meta-analysis. *J. Infect.* **2024**, *89*, 106297. [CrossRef] [PubMed]

71. Hanson, M.R. The viral origin of myalgic encephalomyelitis/chronic fatigue syndrome. *PLoS Pathog.* **2023**, *19*, e1011523. [CrossRef]
72. Chaganti, J.R.; Talekar, T.K.; Brew, B.J. Asymmetrical glymphatic dysfunction in patients with long Covid associated neurocognitive impairment- correlation with BBB disruption. *BMC Neurol.* **2025**, *25*, 112. [CrossRef]
73. Poenaru, S.; Abdallah, S.J.; Corrales-Medina, V.; Cowan, J. COVID-19 and post-infectious myalgic encephalomyelitis/chronic fatigue syndrome: A narrative review. *Ther. Adv. Infect. Dis.* **2021**, *8*, 20499361211009385. [CrossRef]
74. Tice, C.; McDevitt, J.; Langford, D. Astrocytes, HIV and the Glymphatic System: A Disease of Disrupted Waste Management? *Front. Cell. Infect. Microbiol.* **2020**, *10*, 523379. [CrossRef]
75. Sepehrinezhad, A.; Stolze Larsen, F.; Ashayeri Ahmadabad, R.; Shahbazi, A.; Sahab Negah, S. The Glymphatic System May Play a Vital Role in the Pathogenesis of Hepatic Encephalopathy: A Narrative Review. *Cells* **2023**, *12*, 979. [CrossRef]
76. Generoso, J.S.; Thorsdottir, S.; Collodel, A.; Dominguini, D.; Santo, R.R.E.; Petronilho, F.; Barichello, T.; Iovino, F. Dysfunctional Glymphatic System with Disrupted Aquaporin 4 Expression Pattern on Astrocytes Causes Bacterial Product Accumulation in the CSF during Pneumococcal Meningitis. *mBio* **2022**, *13*, e0188622. [CrossRef] [PubMed]
77. Shikova, E.; Reshkova, V.; Kumanova, A.; Raleva, S.; Alexandrova, D.; Capo, N.; Murovska, M.; On Behalf of The European Network on Me/Cfs Euromene. Cytomegalovirus, Epstein-Barr virus, and human herpesvirus-6 infections in patients with myalgic encephalomyelitis/chronic fatigue syndrome. *J. Med. Virol.* **2020**, *92*, 3682–3688. [CrossRef]
78. Tsai, K.; Cullen, B.R. Epigenetic and epitranscriptomic regulation of viral replication. *Nat. Rev. Microbiol.* **2020**, *18*, 559–570. [CrossRef] [PubMed]
79. Shi, F.; Shang, L.; Zhou, M.; Lv, C.; Li, Y.; Luo, C.; Liu, N.; Lu, J.; Tang, M.; Luo, X.; et al. Epstein-Barr virus-driven metabolic alterations contribute to the viral lytic reactivation and tumor progression in nasopharyngeal carcinoma. *J. Med. Virol.* **2024**, *96*, e29634. [CrossRef] [PubMed]
80. Sausen, D.G.; Bhutta, M.S.; Gallo, E.S.; Dahari, H.; Borenstein, R. Stress-Induced Epstein-Barr Virus Reactivation. *Biomolecules* **2021**, *11*, 1380. [CrossRef]
81. Indari, O.; Ghosh, S.; Bal, A.S.; James, A.; Garg, M.; Mishra, A.; Karmodiya, K.; Jha, H.C. Awakening the sleeping giant: Epstein-Barr virus reactivation by biological agents. *Pathog. Dis.* **2024**, *82*, ftae002. [CrossRef]
82. Nunes, J.M.; Kruger, A.; Proal, A.; Kell, D.B.; Pretorius, E. The Occurrence of Hyperactivated Platelets and Fibrinaloid Microclots in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). *Pharmaceuticals* **2022**, *15*, 931. [CrossRef]
83. van Campen, C.L.M.C.; Rowe, P.C.; Visser, F.C. Worsening Symptoms Is Associated with Larger Cerebral Blood Flow Abnormalities during Tilt-Testing in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). *Medicina* **2023**, *59*, 2153. [CrossRef] [PubMed]
84. Ang, P.S.; Zhang, D.M.; Azizi, S.A.; Norton de Matos, S.A.; Brorson, J.R. The glymphatic system and cerebral small vessel disease. *J. Stroke Cerebrovasc. Dis.* **2024**, *33*, 107557. [CrossRef]
85. VanElzakker, M.B.; Brumfield, S.A.; Lara Mejia, P.S. Corrigendum: Neuroinflammation and Cytokines in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): A Critical Review of Research Methods. *Front. Neurol.* **2019**, *10*, 316. [CrossRef] [PubMed]
86. Szlufik, S.; Kopeć, K.; Szleszkowski, S.; Koziorowski, D. Glymphatic System Pathology and Neuroinflammation as Two Risk Factors of Neurodegeneration. *Cells* **2024**, *13*, 286. [CrossRef]
87. Gouix, E.; Buisson, A.; Nieoullon, A.; Kerkerian-Le Goff, L.; Tauskela, J.S.; Blondeau, N.; Had-Aissouni, L. Oxygen glucose deprivation-induced astrocyte dysfunction provokes neuronal death through oxidative stress. *Pharmacol. Res.* **2014**, *87*, 8–17. [CrossRef]
88. LaRocca, T.J.; Cavalier, A.N.; Roberts, C.M.; Lemieux, M.R.; Ramesh, P.; Garcia, M.A.; Link, C.D. Amyloid beta acts synergistically as a pro-inflammatory cytokine. *Neurobiol. Dis.* **2021**, *159*, 105493. [CrossRef]
89. Kim, Y.K.; Na, K.S.; Myint, A.M.; Leonard, B.E. The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2016**, *64*, 277–284. [CrossRef] [PubMed]
90. Russell, A.; Hepgul, N.; Nikkheslat, N.; Borsini, A.; Zajkowska, Z.; Moll, N.; Forton, D.; Agarwal, K.; Chalder, T.; Mondelli, V.; et al. Persistent fatigue induced by interferon-alpha: A novel, inflammation-based, proxy model of chronic fatigue syndrome. *Psychoneuroendocrinology* **2019**, *100*, 276–285. [CrossRef]
91. Li, B.; Xia, M.; Zorec, R.; Parpura, V.; Verkhratsky, A. Astrocytes in heavy metal neurotoxicity and neurodegeneration. *Brain Res.* **2021**, *1752*, 147234. [CrossRef]
92. Arron, H.E.; Marsh, B.D.; Kell, D.B.; Khan, M.A.; Jaeger, B.R.; Pretorius, E. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: The biology of a neglected disease. *Front. Immunol.* **2024**, *15*, 1386607. [CrossRef]
93. Ijomone, O.K.; Ukwubile, I.I.; Aneke, V.O.; Olajide, T.S.; Inyang, H.O.; Omotosho, O.I.; Oyerinde, T.O.; Anadu, V.E.; Gbayisomore, T.J.; Okeowo, O.M.; et al. Glial Perturbation in Metal Neurotoxicity: Implications for Brain Disorders. *Neuroglia* **2025**, *6*, 4. [CrossRef]
94. Lee, J.S.; Kim, H.G.; Lee, D.S.; Son, C.G. Oxidative Stress is a Convincing Contributor to Idiopathic Chronic Fatigue. *Sci. Rep.* **2018**, *8*, 12890. [CrossRef]

95. Shankar, V.; Wilhelmy, J.; Curtis, E.J.; Michael, B.; Cervantes, L.; Mallajosyula, V.; Davis, R.W.; Snyder, M.; Younis, S.; Robinson, W.H.; et al. Oxidative stress is a shared characteristic of ME/CFS and Long COVID. *Proc. Natl. Acad. Sci. USA* **2025**, *122*, e2426564122. [CrossRef]
96. Lee, K.H.; Cha, M.; Lee, B.H. Neuroprotective Effect of Antioxidants in the Brain. *Int. J. Mol. Sci.* **2020**, *21*, 7152. [CrossRef]
97. Lochhead, J.J.; Ronaldson, P.T.; Davis, T.P. The role of oxidative stress in blood-brain barrier disruption during ischemic stroke: Antioxidants in clinical trials. *Biochem. Pharmacol.* **2024**, *228*, 116186. [CrossRef]
98. Lundgaard, I.; Lu, M.L.; Yang, E.; Peng, W.; Mestre, H.; Hitomi, E.; Deane, R.; Nedergaard, M. Glymphatic clearance controls state-dependent changes in brain lactate concentration. *J. Cereb. Blood Flow Metab.* **2017**, *37*, 2112–2124. [CrossRef]
99. Bojarskaite, L.; Nafari, S.; Ravnanger, A.K.; Frey, M.M.; Skauli, N.; Åbjørsbråten, K.S.; Roth, L.C.; Amiry-Moghaddam, M.; Nagelhus, E.A.; Ottersen, O.P.; et al. Role of aquaporin-4 polarization in extracellular solute clearance. *Fluids Barriers CNS* **2024**, *21*, 28. [CrossRef] [PubMed]
100. Frydenlund, D.S.; Bhardwaj, A.; Otsuka, T.; Mylonakou, M.N.; Yasumura, T.; Davidson, K.G.; Zeynalov, E.; Skare, O.; Laake, P.; Haug, F.M.; et al. Temporary loss of perivascular aquaporin-4 in neocortex after transient middle cerebral artery occlusion in mice. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 13532–13536. [CrossRef] [PubMed]
101. Debevec, T.; Millet, G.P.; Pialoux, V. Hypoxia-Induced Oxidative Stress Modulation with Physical Activity. *Front. Physiol.* **2017**, *8*, 84. [CrossRef] [PubMed]
102. Liu, Y.; Xue, C.; Lu, H.; Zhou, Y.; Guan, R.; Wang, J.; Zhang, Q.; Ke, T.; Aschner, M.; Zhang, W.; et al. Hypoxia causes mitochondrial dysfunction and brain memory disorder in a manner mediated by the reduction of Cirbp. *Sci. Total Environ.* **2022**, *806*, 151228. [CrossRef]
103. Janaszak-Jasiecka, A.; Siekierzycka, A.; Płoska, A.; Dobrucki, I.T.; Kalinowski, L. Endothelial Dysfunction Driven by Hypoxia-The Influence of Oxygen Deficiency on NO Bioavailability. *Biomolecules* **2021**, *11*, 982. [CrossRef]
104. Rossetti, G.M.K.; Oliver, S.J.; Sandoo, A.; Macdonald, J.H. Hypoxia-induced endothelial dysfunction: Could targeting oxidative stress provide protection? *Exp. Physiol.* **2023**, *108*, 1026–1028. [CrossRef] [PubMed]
105. Wang, J.; Tian, Y.; Qin, C.; Meng, L.; Feng, R.; Xu, S.; Zhai, Y.; Liang, D.; Zhang, R.; Tian, H.; et al. Impaired glymphatic drainage underlying obstructive sleep apnea is associated with cognitive dysfunction. *J. Neurol.* **2023**, *270*, 2204–2216. [CrossRef]
106. Hambali, A.; Kumar, J.; Hashim, N.F.M.; Maniam, S.; Mehat, M.Z.; Cheema, M.S.; Mustapha, M.; Adenan, M.I.; Stanslas, J.; Hamid, H.A. Hypoxia-Induced Neuroinflammation in Alzheimer's Disease: Potential Neuroprotective Effects of. *Front. Physiol.* **2021**, *12*, 712317. [CrossRef] [PubMed]
107. Guo, C.; Lan, L.; Yan, Y.; Kang, M. Effects of acute exposure to hypoxia on sleep structure in healthy adults: A systematic review. *Sleep. Med. Rev.* **2024**, *75*, 101928. [CrossRef]
108. Yfantis, A.; Mylonis, I.; Chachami, G.; Nikolaidis, M.; Amoutzias, G.D.; Paraskeva, E.; Simos, G. Transcriptional Response to Hypoxia: The Role of HIF-1-Associated Co-Regulators. *Cells* **2023**, *12*, 798. [CrossRef]
109. Algeciras, M.E.; Takahara, H.; Bhattacharya, S.K. Mechanical stretching elevates peptidyl arginine deiminase 2 expression in astrocytes. *Curr. Eye Res.* **2008**, *33*, 994–1001. [CrossRef] [PubMed]
110. Sambandam, T.; Belousova, M.; Accaviti-Loper, M.A.; Blanquicett, C.; Guercello, V.; Raijmakers, R.; Nicholas, A.P. Increased peptidylarginine deiminase type II in hypoxic astrocytes. *Biochem. Biophys. Res. Commun.* **2004**, *325*, 1324–1329. [CrossRef]
111. Syed, A.M.; Karius, A.K.; Ma, J.; Wang, P.Y.; Hwang, P.M. Mitochondrial Dysfunction in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Physiology* **2025**, *40*, 319–328. [CrossRef]
112. Meratan, A.A.; Ghasemi, A.; Nemat-Gorgani, M. Membrane integrity and amyloid cytotoxicity: A model study involving mitochondria and lysozyme fibrillation products. *J. Mol. Biol.* **2011**, *409*, 826–838. [CrossRef]
113. Ghobeh, M.; Ahmadian, S.; Meratan, A.A.; Ebrahim-Habibi, A.; Ghasemi, A.; Shafizadeh, M.; Nemat-Gorgani, M. Interaction of Aβ(25-35) fibrillation products with mitochondria: Effect of small-molecule natural products. *Biopolymers* **2014**, *102*, 473–486. [CrossRef]
114. Oladzad Abbasabadi, A.; Javanian, A.; Nikkhah, M.; Meratan, A.A.; Ghiasi, P.; Nemat-Gorgani, M. Disruption of mitochondrial membrane integrity induced by amyloid aggregates arising from variants of SOD1. *Int. J. Biol. Macromol.* **2013**, *61*, 212–217. [CrossRef]
115. Dehghani, Z.; Meratan, A.A.; Saboury, A.A.; Nemat-Gorgani, M. α-Synuclein fibrillation products trigger the release of hexokinase I from mitochondria: Protection by curcumin, and possible role in pathogenesis of Parkinson's disease. *Biochim. Biophys. Acta Biomembr.* **2020**, *1862*, 183251. [CrossRef]
116. Meratan, A.A.; Nemat-Gorgani, M. Mitochondrial membrane permeabilization upon interaction with lysozyme fibrillation products: Role of mitochondrial heterogeneity. *Biochim. Biophys. Acta* **2012**, *1818*, 2149–2157. [CrossRef]
117. Solleiro-Villavicencio, H.; Rivas-Arancibia, S. Effect of Chronic Oxidative Stress on Neuroinflammatory Response Mediated by CD4. *Front. Cell Neurosci.* **2018**, *12*, 114. [CrossRef]
118. Lee, J.S.; Sato, W.; Son, C.G. Brain-regional characteristics and neuroinflammation in ME/CFS patients from neuroimaging: A systematic review and meta-analysis. *Autoimmun. Rev.* **2024**, *23*, 103484. [CrossRef] [PubMed]

119. Knott, A.B.; Bossy-Wetzel, E. Impairing the mitochondrial fission and fusion balance: A new mechanism of neurodegeneration. *Ann. N. Y. Acad. Sci.* **2008**, *1147*, 283–292. [CrossRef] [PubMed]
120. Wu, S.; Zhou, F.; Zhang, Z.; Xing, D. Mitochondrial oxidative stress causes mitochondrial fragmentation via differential modulation of mitochondrial fission-fusion proteins. *FEBS J.* **2011**, *278*, 941–954. [CrossRef]
121. Schreiner, P.; Harrer, T.; Scheibenbogen, C.; Lamer, S.; Schlosser, A.; Naviaux, R.K.; Prusty, B.K. Human Herpesvirus-6 Reactivation, Mitochondrial Fragmentation, and the Coordination of Antiviral and Metabolic Phenotypes in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Immunohorizons* **2020**, *4*, 201–215. [CrossRef] [PubMed]
122. Lubell, J. Letter: Could endothelial dysfunction and vascular damage contribute to pain, inflammation and post-exertional malaise in individuals with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)? *J. Transl. Med.* **2022**, *20*, 40. [CrossRef]
123. McCully, K.K.; Natelson, B.H. Impaired oxygen delivery to muscle in chronic fatigue syndrome. *Clin. Sci.* **1999**, *97*, 603–608, discussion 611–603. [CrossRef]
124. Ghali, A.; Lacout, C.; Ghali, M.; Gury, A.; Beucher, A.B.; Lozac'h, P.; Lavigne, C.; Urbanski, G. Elevated blood lactate in resting conditions correlate with post-exertional malaise severity in patients with Myalgic encephalomyelitis/Chronic fatigue syndrome. *Sci. Rep.* **2019**, *9*, 18817. [CrossRef] [PubMed]
125. Saha, A.K.; Schmidt, B.R.; Wilhelmy, J.; Nguyen, V.; Do, J.; Suja, V.C.; Nemat-Gorgani, M.; Ramasubramanian, A.K.; Davis, R.W. Erythrocyte Deformability as a Potential Biomarker for Chronic Fatigue Syndrome. *Blood* **2018**, *132*, 4874. [CrossRef]
126. Saha, A.K.; Schmidt, B.R.; Wilhelmy, J.; Nguyen, V.; Abugherir, A.; Do, J.K.; Nemat-Gorgani, M.; Davis, R.W.; Ramasubramanian, A.K. Red blood cell deformability is diminished in patients with Chronic Fatigue Syndrome. *Clin. Hemorheol. Microcirc.* **2019**, *71*, 113–116. [CrossRef] [PubMed]
127. Saha, A.K.; Schmidt, B.R.; Wilhelmy, J.; Nguyen, V.; Do, J.K.; Suja, V.C.; Nemat-Gorgani, M.; Ramasubramanian, A.K.; Davis, R.W. Altered Erythrocyte Biophysical Properties in Chronic Fatigue Syndrome. *Biophys. J.* **2019**, *116*, 122a. [CrossRef]
128. Preis, L.; Villringer, K.; Brosseron, F.; Düzel, E.; Jessen, F.; Petzold, G.C.; Ramirez, A.; Spottke, A.; Fiebach, J.B.; Peters, O. Assessing blood-brain barrier dysfunction and its association with Alzheimer's pathology, cognitive impairment and neuroinflammation. *Alzheimers Res. Ther.* **2024**, *16*, 172. [CrossRef]
129. Wang, D.; Chen, F.; Han, Z.; Yin, Z.; Ge, X.; Lei, P. Relationship Between Amyloid-β Deposition and Blood-Brain Barrier Dysfunction in Alzheimer's Disease. *Front. Cell Neurosci.* **2021**, *15*, 695479. [CrossRef]
130. Murrough, J.W.; Mao, X.; Collins, K.A.; Kelly, C.; Andrade, G.; Nestadt, P.; Levine, S.M.; Mathew, S.J.; Shungu, D.C. Increased ventricular lactate in chronic fatigue syndrome measured by 1H MRS imaging at 3.0 T. II: Comparison with major depressive disorder. *NMR Biomed.* **2010**, *23*, 643–650. [CrossRef]
131. Fluge, Ø.; Mella, O.; Bruland, O.; Risa, K.; Dyrstad, S.E.; Alme, K.; Rekeland, I.G.; Sapkota, D.; Røsland, G.V.; Fosså, A.; et al. Metabolic profiling indicates impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrome. *JCI Insight* **2016**, *1*, e89376. [CrossRef]
132. Boenzi, S.; Diodato, D. Biomarkers for mitochondrial energy metabolism diseases. *Essays Biochem.* **2018**, *62*, 443–454. [CrossRef]
133. Glancy, B.; Kane, D.A.; Kavazis, A.N.; Goodwin, M.L.; Willis, W.T.; Gladden, L.B. Mitochondrial lactate metabolism: History and implications for exercise and disease. *J. Physiol.* **2021**, *599*, 863–888. [CrossRef]
134. Armstrong, C.W.; McGregor, N.R.; Lewis, D.P.; Butt, H.L.; Gooley, P.R. Metabolic profiling reveals anomalous energy metabolism and oxidative stress pathways in chronic fatigue syndrome patients. *Metabolomics* **2015**, *11*, 1626–1639. [CrossRef]
135. Godlewska, B.R.; Sylvester, A.L.; Emir, U.E.; Sharpley, A.L.; Clarke, W.T.; Williams, S.R.; Gonçalves, A.J.; Raman, B.; Valkovič, L.; Cowen, P.J. Brain and muscle chemistry in myalgic encephalitis/chronic fatigue syndrome (ME/CFS) and long COVID: A 7T magnetic resonance spectroscopy study. *Mol. Psychiatry* **2025**, *30*, 5215–5226. [CrossRef] [PubMed]
136. Denno, P.; Zhao, S.; Husain, M.; Hampshire, A. Defining brain fog across medical conditions. *Trends Neurosci.* **2025**, *48*, 330–348. [CrossRef]
137. Fujimoto, Y.; Abe, H.; Eiro, T.; Tsugawa, S.; Tanaka, M.; Hatano, M.; Nakajima, W.; Ichijo, S.; Arisawa, T.; Takada, Y.; et al. Systemic increase of AMPA receptors associated with cognitive impairment of long COVID. *Brain Commun.* **2025**, *7*, fcaf337. [CrossRef]
138. Rubin, L.H.; Shi, W.; Azola, A.; Bhattacharyya, A.; Dastgheyb, R.M.; Wu, J.; Penna, C.D.; Parker, H.; Santiuste, I.; Ehrenspeck, A.; et al. Blood-Brain barrier disruption in long COVID and cognitive correlates: A cross-sectional MRI study. *Brain Behav. Immun.* **2025**, *129*, 989–999. [CrossRef] [PubMed]
139. Greene, C.; Connolly, R.; Brennan, D.; Laffan, A.; O'Keeffe, E.; Zaporojan, L.; O'Callaghan, J.; Thomson, B.; Connolly, E.; Argue, R.; et al. Blood-brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment. *Nat. Neurosci.* **2024**, *27*, 421–432. [CrossRef]
140. Kim, M.; Lee, K.H.; Ko, J.S.; Kim, M.S.; Choi, K.S.; Seo, J.; Kim, M. Neurologic symptoms as a hallmark of glymphatic alteration in recovered patients with COVID-19. *BMC Neurol.* **2025**, *25*, 187. [CrossRef]
141. Genç, B.; Buruk, M.S.; Özçağlayan, A.; Kerim, A. Alterations in the Glymphatic System and Presence of Small Vessel Disease in Hospitalized and Non-hospitalized COVID Patients: A Study of PSMD Index and DTI-ALPS. *Acad. Radiol.* **2025**, *32*, 4146–4153. [CrossRef]

142. Walker, M.O.M.; Hall, K.H.; Peppercorn, K.; Tate, W.P. The significance of oxidative stress in the pathophysiology of Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). *Med. Res. Arch.* **2022**, *10*, 1. [CrossRef]
143. Rao, S.S.C.; Rehman, A.; Yu, S.; Andino, N.M. Brain fogginess, gas and bloating: A link between SIBO, probiotics and metabolic acidosis. *Clin. Transl. Gastroenterol.* **2018**, *9*, 162. [CrossRef]
144. Kemp, J.; Sunnquist, M.; Jason, L.A.; Newton, J.L. Autonomic dysfunction in myalgic encephalomyelitis and chronic fatigue syndrome: Comparing self-report and objective measures. *Clin. Auton. Res.* **2019**, *29*, 475–477. [CrossRef]
145. Azcue, N.; Del Pino, R.; Acera, M.; Fernández-Valle, T.; Ayo-Mentxakatorre, N.; Pérez-Concha, T.; Murueta-Goyena, A.; Lafuente, J.V.; Prada, A.; López de Munain, A.; et al. Dysautonomia and small fiber neuropathy in post-COVID condition and Chronic Fatigue Syndrome. *J. Transl. Med.* **2023**, *21*, 814. [CrossRef] [PubMed]
146. Robertson, D. The epidemic of orthostatic tachycardia and orthostatic intolerance. *Am. J. Med. Sci.* **1999**, *317*, 75–77. [CrossRef] [PubMed]
147. van Campen, C.L.M.C.; Rowe, P.C.; Visser, F.C. Deconditioning does not explain orthostatic intolerance in ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome). *J. Transl. Med.* **2021**, *19*, 193. [CrossRef]
148. Srinivasan, A.G.; Smith, S.S.; Pattinson, C.L.; Mann, D.; Sullivan, K.; Salmon, P.; Soleimanloo, S.S. Heart rate variability as an indicator of fatigue: A structural equation model approach. *Transp. Res. Part F Traffic Psychol. Behav.* **2024**, *103*, 420–429. [CrossRef]
149. Escorihuela, R.M.; Capdevila, L.; Castro, J.R.; Zaragozà, M.C.; Maurel, S.; Alegre, J.; Castro-Marrero, J. Reduced heart rate variability predicts fatigue severity in individuals with chronic fatigue syndrome/myalgic encephalomyelitis. *J. Transl. Med.* **2020**, *18*, 4. [CrossRef]
150. Nycz, B.; Mandera, M. The features of the glymphatic system. *Auton. Neurosci.* **2021**, *232*, 102774. [CrossRef]
151. Ryman, S.G.; Vakhtin, A.A.; Mayer, A.R.; van der Horn, H.J.; Shaff, N.A.; Nitschke, S.R.; Julio, K.R.; Tarawneh, R.M.; Rosenberg, G.A.; Diaz, S.V.; et al. Abnormal Cerebrovascular Activity, Perfusion, and Glymphatic Clearance in Lewy Body Diseases. *Mov. Disord.* **2024**, *39*, 1258–1268. [CrossRef]
152. Roura, I.; Pardo, J.; Martín-Barceló, C.; Falcon, C.; Oltra, J.; Campabadal, A.; Bargalló, N.; Serradell, M.; Mayà, G.; Montini, A.; et al. Clinical and brain volumetric correlates of decreased DTI-ALPS, suggestive of local glymphatic dysfunction, in iRBD. *npj Parkinsons Dis.* **2025**, *11*, 87. [CrossRef] [PubMed]
153. Faraji, N.; Payami, B.; Ebadpour, N.; Gorji, A. Vagus nerve stimulation and gut microbiota interactions: A novel therapeutic avenue for neuropsychiatric disorders. *Neurosci. Biobehav. Rev.* **2025**, *169*, 105990. [CrossRef] [PubMed]
154. Bonaz, B.; Bazin, T.; Pellissier, S. The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. *Front. Neurosci.* **2018**, *12*, 49. [CrossRef]
155. Mohamed, A.Z.; Andersen, T.; Radovic, S.; Del Fante, P.; Kwiatek, R.; Calhoun, V.; Bhuta, S.; Hermens, D.F.; Lagopoulos, J.; Shan, Z.Y. Objective sleep measures in chronic fatigue syndrome patients: A systematic review and meta-analysis. *Sleep Med. Rev.* **2023**, *69*, 101771. [CrossRef]
156. Reddy, O.C.; van der Werf, Y.D. The Sleeping Brain: Harnessing the Power of the Glymphatic System through Lifestyle Choices. *Brain Sci.* **2020**, *10*, 868. [CrossRef]
157. Haydon, P.G. Astrocytes and the modulation of sleep. *Curr. Opin. Neurobiol.* **2017**, *44*, 28–33. [CrossRef]
158. Corbali, O.; Levey, A.I. Glymphatic system in neurological disorders and implications for brain health. *Front. Neurol.* **2025**, *16*, 1543725. [CrossRef]
159. Jackson, M.L.; Bruck, D. Sleep abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis: A review. *J. Clin. Sleep Med.* **2012**, *8*, 719–728. [CrossRef]
160. Khandayataray, P.; Murthy, M.K. Exploring the nexus: Sleep disorders, circadian dysregulation, and Alzheimer's disease. *Neuroscience* **2025**, *574*, 21–41. [CrossRef]
161. Chong, P.L.H.; Garic, D.; Shen, M.D.; Lundgaard, I.; Schwichtenberg, A.J. Sleep, cerebrospinal fluid, and the glymphatic system: A systematic review. *Sleep Med. Rev.* **2022**, *61*, 101572. [CrossRef] [PubMed]
162. Davinelli, S.; Medoro, A.; Savino, R.; Scapagnini, G. Sleep and Oxidative Stress: Current Perspectives on the Role of NRF2. *Cell. Mol. Neurobiol.* **2024**, *44*, 52. [CrossRef]
163. Lei, X.; Xu, Z.; Chen, W. Association of oxidative balance score with sleep quality: NHANES 2007-2014. *J. Affect. Disord.* **2023**, *339*, 435–442. [CrossRef] [PubMed]
164. Baxter, H.; Speight, N.; Weir, W. Life-Threatening Malnutrition in Very Severe ME/CFS. *Healthcare* **2021**, *9*, 459. [CrossRef] [PubMed]
165. Pacagnella, R.C.; Borovac-Pinheiro, A. Assessing and managing hypovolemic shock in puerperal women. *Best Pract. Res. Clin. Obstet. Gynaecol.* **2019**, *61*, 89–105. [CrossRef] [PubMed]
166. Nunes, J.M.; Kell, D.B.; Pretorius, E. Cardiovascular and haematological pathology in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): A role for viruses. *Blood Rev.* **2023**, *60*, 101075. [CrossRef]
167. Reeves, B.C.; Karimy, J.K.; Kundishora, A.J.; Mestre, H.; Cerci, H.M.; Matouk, C.; Alper, S.L.; Lundgaard, I.; Nedergaard, M.; Kahle, K.T. Glymphatic System Impairment in Alzheimer's Disease and Idiopathic Normal Pressure Hydrocephalus. *Trends Mol. Med.* **2020**, *26*, 285–295. [CrossRef]

168. Che Mohd Nassir, C.M.N.; Che Ramli, M.D.; Mohamad Ghazali, M.; Jaffer, U.; Abdul Hamid, H.; Mehat, M.Z.; Hein, Z.M. The Microbiota-Gut-Brain Axis: Key Mechanisms Driving Glymphopathy and Cerebral Small Vessel Disease. *Life* **2024**, *15*, 3. [CrossRef]
169. König, R.S.; Albrich, W.C.; Kahlert, C.R.; Bahr, L.S.; Löber, U.; Vernazza, P.; Scheibenbogen, C.; Forslund, S.K. The Gut Microbiome in Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS). *Front. Immunol.* **2021**, *12*, 628741, Erratum in *Front. Immunol.* **2022**, *13*, 878196. [CrossRef]
170. Stallmach, A.; Quickert, S.; Puta, C.; Reuken, P.A. The gastrointestinal microbiota in the development of ME/CFS: A critical view and potential perspectives. *Front. Immunol.* **2024**, *15*, 1352744. [CrossRef]
171. Camberos-Barraza, J.; Guadrón-Llanos, A.M.; De la Herrán-Arita, A.K. The Gut Microbiome-Neuroglia Axis: Implications for Brain Health, Inflammation, and Disease. *Neuroglia* **2024**, *5*, 254–273. [CrossRef]
172. Suganya, K.; Koo, B.S. Gut-Brain Axis: Role of Gut Microbiota on Neurological Disorders and How Probiotics/Prebiotics Beneficially Modulate Microbial and Immune Pathways to Improve Brain Functions. *Int. J. Mol. Sci.* **2020**, *21*, 7551. [CrossRef]
173. Bragée, B.; Michos, A.; Drum, B.; Fahlgren, M.; Szulkin, R.; Bertilson, B.C. Signs of Intracranial Hypertension, Hypermobility, and Craniocervical Obstructions in Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Front. Neurol.* **2020**, *11*, 828. [CrossRef] [PubMed]
174. Hulens, M.; Dankaerts, W.; Rasschaert, R.; Bruyninckx, F.; De Mulder, P.; Bervoets, C. The Link Between Empty Sella Syndrome, Fibromyalgia, and Chronic Fatigue Syndrome: The Role of Increased Cerebrospinal Fluid Pressure. *J. Pain Res.* **2023**, *16*, 205–219. [CrossRef]
175. Higgins, J.N.P.; Axon, P.R.; Lever, A.M.L. Life changing response to successive surgical interventions on cranial venous outflow: A case report on chronic fatigue syndrome. *Front. Neurol.* **2023**, *14*, 1127702. [CrossRef]
176. Mudie, K.; Ramiller, A.; Whittaker, S.; Phillips, L.E. Do people with ME/CFS and joint hypermobility represent a disease subgroup? An analysis using registry data. *Front. Neurol.* **2024**, *15*, 1324879. [CrossRef]
177. Midtlien, J.P.; Curry, B.P.; Chang, E.; Kiritsis, N.R.; Aldridge, J.B.; Fargen, K.M. Characterizing a new clinical phenotype: The co-existence of cerebral venous outflow and connective tissue disorders. *Front. Neurol.* **2023**, *14*, 1305972. [CrossRef] [PubMed]
178. Eide, P.K.; Pripp, A.H.; Ringstad, G.; Valnes, L.M. Impaired glymphatic function in idiopathic intracranial hypertension. *Brain Commun.* **2021**, *3*, fcab043. [CrossRef]
179. Jones, O.; Cutsforth-Gregory, J.; Chen, J.; Bhatti, M.T.; Huston, J.; Brinjikji, W. Idiopathic Intracranial Hypertension is Associated with a Higher Burden of Visible Cerebral Perivascular Spaces: The Glymphatic Connection. *AJNR Am. J. Neuroradiol.* **2021**, *42*, 2160–2164. [CrossRef]
180. Kiyatkin, E.A. Brain temperature and its role in physiology and pathophysiology: Lessons from 20 years of thermorecording. *Temperature* **2019**, *6*, 271–333. [CrossRef]
181. Zhu, M.; Ackerman, J.J.; Sukstanskii, A.L.; Yablonskiy, D.A. How the body controls brain temperature: The temperature shielding effect of cerebral blood flow. *J. Appl. Physiol.* **2006**, *101*, 1481–1488. [CrossRef] [PubMed]
182. Mueller, C.; Lin, J.C.; Sheriff, S.; Maudsley, A.A.; Younger, J.W. Evidence of widespread metabolite abnormalities in Myalgic encephalomyelitis/chronic fatigue syndrome: Assessment with whole-brain magnetic resonance spectroscopy. *Brain Imaging Behav.* **2020**, *14*, 562–572. [CrossRef]
183. Bai, Y.; Yuan, M.; Mi, H.; Zhang, F.; Liu, X.; Lu, C.; Bao, Y.; Li, Y.; Lu, Q. Hypothermia reduces glymphatic transportation in traumatic edematous brain assessed by intrathecal dynamic contrast-enhanced MRI. *Front. Neurol.* **2022**, *13*, 957055. [CrossRef] [PubMed]
184. Theparambil, S.M.; Hosford, P.S.; Ruminot, I.; Kopach, O.; Reynolds, J.R.; Sandoval, P.Y.; Rusakov, D.A.; Barros, L.F.; Gourine, A.V. Astrocytes regulate brain extracellular pH via a neuronal activity-dependent bicarbonate shuttle. *Nat. Commun.* **2020**, *11*, 5073. [CrossRef]
185. Lohela, T.J.; Lilius, T.O.; Nedergaard, M. The glymphatic system: Implications for drugs for central nervous system diseases. *Nat. Rev. Drug Discov.* **2022**, *21*, 763–779. [CrossRef]
186. Castro-Marrero, J.; Sáez-Francàs, N.; Santillo, D.; Alegre, J. Treatment and management of chronic fatigue syndrome/myalgic encephalomyelitis: All roads lead to Rome. *Br. J. Pharmacol.* **2017**, *174*, 345–369. [CrossRef] [PubMed]
187. Wostyn, P.a.G.P. Can meditation-based approaches improve the cleansing power of the glymphatic system? *Explor. Neuroprotective Ther.* **2022**, *2*, 110–117. [CrossRef]
188. Liang, P.Z.; Li, L.; Zhang, Y.N.; Shen, Y.; Zhang, L.L.; Zhou, J.; Wang, Z.J.; Wang, S.; Yang, S. Electroacupuncture Improves Clearance of Amyloid-β through the Glymphatic System in the SAMP8 Mouse Model of Alzheimer's Disease. *Neural Plast.* **2021**, *2021*, 9960304. [CrossRef]
189. Zhu, Y.; Wang, J.; Yao, L.; Huang, Y.; Yang, H.; Yu, X.; Chen, X.; Chen, Y. Electroacupuncture at BL15 attenuates chronic fatigue syndrome by downregulating iNOS/NO signaling in C57BL/6 mice. *Anat. Rec.* **2023**, *306*, 3073–3084. [CrossRef]
190. Liu, Y.; Liu, X.; Sun, P.; Li, J.; Nie, M.; Gong, J.; He, A.; Zhao, M.; Yang, C.; Wang, Z. rTMS treatment for abrogating intracerebral hemorrhage-induced brain parenchymal metabolite clearance dysfunction in male mice by regulating intracranial lymphatic drainage. *Brain Behav.* **2023**, *13*, e3062. [CrossRef]

191. Sundman, M.H.; Liu, Y.; Chen, N.K.; Chou, Y.H. The glymphatic system as a therapeutic target: TMS-induced modulation in older adults. *Front. Aging Neurosci.* **2025**, *17*, 1597311. [CrossRef]
192. Miwa, K.; Inoue, Y. Repetitive transcranial magnetic stimulation ameliorates symptoms in patients with myalgic encephalomyelitis (chronic fatigue syndrome). *IBRO Neurosci. Rep.* **2023**, *15*, 335–341. [CrossRef]
193. Saligan, L.N.; Luckenbaugh, D.A.; Slonena, E.E.; Machado-Vieira, R.; Zarate, C.A. An assessment of the anti-fatigue effects of ketamine from a double-blind, placebo-controlled, crossover study in bipolar disorder. *J. Affect. Disord.* **2016**, *194*, 115–119. [CrossRef] [PubMed]
194. Wu, W.; Zhao, Y.; Cheng, X.; Xie, X.; Zeng, Y.; Tao, Q.; Yang, Y.; Xiao, C.; Zhang, Z.; Pang, J.; et al. Modulation of glymphatic system by visual circuit activation alleviates memory impairment and apathy in a mouse model of Alzheimer's disease. *Nat. Commun.* **2025**, *16*, 63. [CrossRef]
195. Liu, J.; He, J.; Chen, X.; Wu, D. Manipulation of glymphatic system by focused ultrasound: A promising treatment of neurological diseases. *J. Cereb. Blood Flow Metab.* **2025**, 271678X251383857. [CrossRef] [PubMed]
196. Murdock, M.H.; Yang, C.Y.; Sun, N.; Pao, P.C.; Blanco-Duque, C.; Kahn, M.C.; Kim, T.; Lavoie, N.S.; Victor, M.B.; Islam, M.R.; et al. Multisensory gamma stimulation promotes glymphatic clearance of amyloid. *Nature* **2024**, *627*, 149–156. [CrossRef]
197. Lahmar, T.; Thuau, F.; Pinard, G.; Boutoleau-Bretonniere, C.; Perrot, P.; Lancien, U. Brain lymphatic drainage pathways, deep cervical lymphatic surgery, and current insights: A systematic review. *J. Prev. Alzheimers Dis.* **2025**, 100335. [CrossRef]
198. Benveniste, H.; Lee, H.; Ding, F.; Sun, Q.; Al-Bizri, E.; Makaryus, R.; Probst, S.; Nedergaard, M.; Stein, E.A.; Lu, H. Anesthesia with Dexmedetomidine and Low-dose Isoflurane Increases Solute Transport via the Glymphatic Pathway in Rat Brain When Compared with High-dose Isoflurane. *Anesthesiology* **2017**, *127*, 976–988. [CrossRef] [PubMed]
199. Morris, G.; Maes, M. Myalgic encephalomyelitis/chronic fatigue syndrome and encephalomyelitis disseminata/multiple sclerosis show remarkable levels of similarity in phenomenology and neuroimmune characteristics. *BMC Med.* **2013**, *11*, 205. [CrossRef]
200. Eaton-Fitch, N.; Rudd, P.; Er, T.; Hool, L.; Herrero, L.; Marshall-Gradisnik, S. Immune exhaustion in ME/CFS and long COVID. *JCI Insight* **2024**, *9*, e183810. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.