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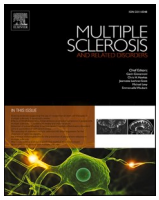

Review article

The glymphatic system and multiple sclerosis: An evolving connection

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ABSTRACT

Multiple sclerosis (MS) is a complex autoimmune disorder that affects the central nervous system, resulting in demyelination and an array of neurological manifestations. Recently, there has been significant scientific interest in the glymphatic system, which operates as a waste-clearance system for the brain. This article reviews the existing literature, and explores potential links between the glymphatic system and MS, shedding light on its evolving significance in the context of MS pathogenesis. The authors consider the pathophysiological implications of glymphatic dysfunction in MS, the impact of disrupted sleep on glymphatic function, and the bidirectional relationship between MS and sleep disturbances. By offering an understanding of the intricate interplay between the glymphatic system and MS, this review provides valuable insights which may lead to improved diagnostic techniques and more effective therapeutic interventions.

1. Introduction

In recent years, the neuroscientific community has shown increasing interest in the glymphatic system. Operating predominantly during sleep, this intricate waste clearance system facilitates the exchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF) in order to remove harmful proteins and waste products from brain tissue (Iliff et al., 2012). The glymphatic system's pivotal role in waste clearance and cerebral health positions it as a key player in various neurological conditions. Multiple sclerosis (MS) is a multi-faceted autoimmune disease characterised by the demyelination of nerve fibres in the central nervous system (CNS), which gives rise to a range of neurological symptoms (Howard et al., 2016). Sleep disorders have also become increasingly recognised within the context of neurological disorders, including MS. The current paper seeks to explore and to elucidate the intricate connections between these elements, and to provide insights into their contributions to the development and progression of MS.

2. Multiple sclerosis

MS is a CNS disorder of multi-factorial aetiology, which primarily affects young adults. It is characterised by chronic inflammation and neurodegeneration. Manifestations of MS can vary widely, with symptoms including cerebellar dysfunction, sensorimotor issues, visual disturbances, gastrointestinal problems and genitourinary impairment (Faguy, 2016). Lymphocyte-induced inflammation and activation of microglia are key factors in the development of MS. MS-associated inflammatory plaques exhibit a diverse range of immunological and pathological characteristics (Saade et al., 2018).

Patients with MS typically experience an initial phase of symptomatic disease, followed by a period of remission and thereafter, a repeating pattern of symptom recurrence (relapse) followed by the waning of symptoms (remission). This is known as relapsing-remitting MS (RRMS). In some cases, RRMS progresses to become secondary progressive disease. However, a minority of patients never experience the relapsing-remitting phase and instead, exhibit continuous disease progression from its onset. This is a condition referred to as primary progressive MS (PPMS) (Lassmann, 2019).

MS displays several characteristics commonly associated with inflammatory autoimmune diseases, including disruption of the blood–brain barrier. During acute (relapsing) phases of MS, many patients exhibit plaques, which usually contain substantial inflammatory changes and demyelination within the lesion. Such inflammation primarily involves T-lymphocytes, macrophages and monocytes, which accumulate around blood vessels in the perivascular spaces (PVS), a known glymphatic pathway. When such plaques enter the chronic phase, the lesions tend to show reduced cell expression, with prominent glial scarring and an absence of myelin sheaths (Saade et al., 2018)

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In recent decades, magnetic resonance imaging (MRI) technology has evolved to become a pivotal instrument for diagnosing MS, assessing the prognosis, and monitoring the response to treatment (Filippi et al., 2018; Rocca et al., 2023). The use of MRI enhanced with gadolinium-based contrast agents (GBCA) is a standard monitoring tool for MS, and can show the initial inflammatory stage of MS lesions. Two factors are particularly important for the optimisation of this process: (i) the extent of inflammation around the lesion; and (ii) the time elapsing between intravenous GBCA injection and imaging. Both of these factors influence the extent to which GBCA reach the lesions through the disrupted blood–brain barrier and glymphatic system (Bou Fakhredin et al., 2016). Different MRI sequences can show different MS characteristics and lesion phases. For example, forms of T2-weighted imaging, including both true T2-weighted and FLAIR sequences, can be used to assess the quantity and volume of white matter lesions. However, they do not reliably indicate the activity of such lesions. A T1-weighted sequence without GBCA is useful for identifying late-stage MS lesions, which appear as hypointense on MRI scans and reveal irreversible axonal damage. However, T1-weighted imaging enhanced with GBCA can identify blood–brain barrier impairment and leakage, which occurs during active inflammation (Mallik et al., 2014).

3. Role and function of the glymphatic system

Cserr et al. initially proposed the existence of the glymphatic "perivascular" system and ISF bulk flow by injecting blue dextran 2000 into a rat's caudate. A microscopic examination showed dye distribution by bulk flow along the cerebral blood vessels (Cserr and Ostrach, 1974). Using a horseradish peroxidase infusion in a subsequent study, Cserr and colleagues found perivascular horseradish peroxidase in rat brains 4–8 h post-injection (Cserr et al., 1977). In 1981, isotopes of varying molecular weights injected into a rat's caudate nucleus revealed that despite different diffusion coefficients, all molecules experienced similar clearance rates, thus indicating perivascular drainage via bulk flow (Cserr et al., 1981). Rennels et al. proposed the existence of a perivascular clearance system in dogs and cats (Rennels et al., 1985). Despite this evidence, the hypothesis of CSF perivascular flow was then largely set aside for more than two decades due to limited confirmation from other researchers and technology constraints.

In the last decade, neuroscientific interest in the glymphatic system has intensified. Glymphatic system activity involves the flow of subarachnoid CSF along the PVS surrounding penetrating arteries. The subsequent influx of CSF into the brain interstitium is mediated by the astroglial water channel aquaporin-4 (AQP4), which is mainly expressed at the endfeet of astrocytes that surround the PVS (Iliff et al., 2012). It is proposed that this influx results in the bulk flow of ISF, which then exits along perivenous spaces. Importantly, this bulk flow aids the removal of harmful proteins and waste products from the brain tissue, as shown in Fig. 1 (Iliff and Simon, 2019; Iliff et al., 2012). Brain waste products ultimately drain into the meningeal lymphatic vessels or deep cervical lymph nodes.

Scholars have identified several potential drivers of glymphatic transport including respiration (Helakari et al., 2022), vasomotion (van Veluw et al., 2020), and CSF production and turnover (Rasmussen et al., 2018; Smets et al., 2023). However, cardiac pulsatility seems likely to make the most significant contribution in this regard. In a mouse study, arterial pulsatility declined by 50% following unilateral ligation of the internal carotid artery, whereas dobutamine enhanced penetrating artery pulsatility by 60%. Iliff and colleagues also found that carotid artery ligation reduced the rate of perivascular CSF-ISF exchange, whereas dobutamine increased it. These results indicate the key role of cerebral arterial pulsatility in driving perivascular CSF influx in the brain parenchyma (Iliff et al., 2013b).

Multiple studies have found that tracers, driven mainly by cardiac pulsation, move quickly from the periarterial space into the interstitial spaces, and return to the CSF via the PVS around the veins (Jessen et al., 2015; Yang et al., 2013). The glymphatic system has been shown to transport waste molecules linked to the pathophysiology of Alzheimer's disease (AD), including beta-amyloid protein, a finding supported by the accumulation of such molecules in the brains of transgenic mice in which glymphatic function was compromised owing to the deletion of the AQP4 gene (Iliff et al., 2012). Multiple research studies have indicated that the absence of AQP4 inhibits the distribution and removal of various interstitial substances, including tau (Iliff et al., 2014), lactate (Lundgaard et al., 2017), adeno-associated viruses (Murlidharan et al., 2016) and ApoE (Achariyar et al., 2016). These findings collectively emphasise the significant role played by AQP4 in facilitating both the entry of CSF into brain tissue and the removal of interstitial solutes.

The glymphatic system is primarily active during sleep, shedding light on the longstanding mystery surrounding the function of sleep (Krueger et al., 2016; Reddy and van der Werf, 2020). In a study by Lee et al., glymphatic function was shown to increase predominantly during the slow wave period of sleep and whilst sleeping on one side, rather than in a supine or prone position (Lee et al., 2015). Exercise affects

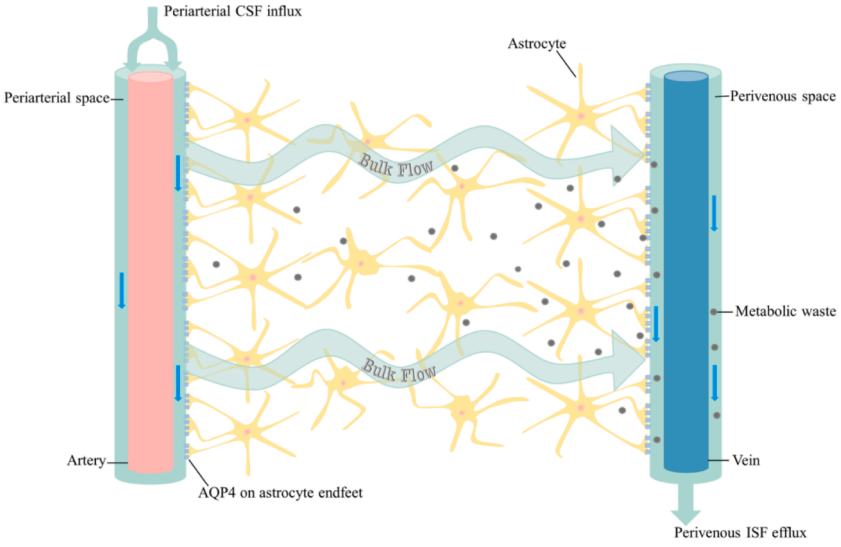

Fig. 1. Schematic diagram illustrating the glymphatic pathway. Adapted from a previous publication (Gao et al., 2023) with permission granted by Dr. Jie Zhu and the publishing journal.

glymphatic clearance positively (He et al., 2017), whereas the effectiveness of glymphatic clearance declines with ageing (Benveniste et al., 2019). Pre-clinical studies have explored glymphatic system activity in multiple diseases. Investigations have indicated that traumatic brain injuries and type 2 diabetes specifically diminish the effectiveness of the glymphatic system (Jiang et al., 2017; Kim et al., 2018; Plog et al., 2015; Simon and Iliff, 2016). A study conducted on rats with type 2 diabetes mellitus found that diabetes significantly slowed the clearance of CSF contrast agents in the hippocampus, leading to cognitive deficits (Jiang et al., 2017).

3.1. Ongoing discussion regarding the glymphatic hypothesis

The glymphatic hypothesis, including the role of AQP4, remains a subject of debate (Abbott et al., 2018; Hladky and Barrand, 2014; Smith and Verkman, 2018). For example, some studies have shown that brain solute transport is dependant on molecular size, suggesting diffusion rather than bulk transport (Pizzo et al., 2018; Smith et al., 2017). Smith et al., found that the deletion of AQP4 had no effect on the transportation of tracers from the subarachnoid space to the brain (Smith et al., 2017). However, five independent research groups re-evaluated the significance of AQP4 in the glymphatic system. They demonstrated that CSF influx was greater in wild-type mice compared to four different Aqp4 knockout lines, as well as in a line lacking perivascular AQP4 localisation (Snta1 KO) (Mestre et al., 2018a).

The clearance of ISF to the perivenous spaces by bulk flow via AQP4 has been challenged, with studies suggesting that ISF solutes are cleared to the intramural peri-arterial drainage system (Albargothy et al., 2018) or brain ventricles (Bedussi et al., 2015) but not to the perivenous spaces. The variability in these results could be attributed to several factors, including the use of different anaesthetic materials, routes of tracer injection, and data analysis methods. For instance, different anaesthetic substances have varying impacts on glymphatic flow. Ketamine/xylazine exhibited the highest CSF tracer penetration, whereas isoflurane exhibited the lowest degree of influx (Hablitz et al., 2019).

Computational models have also challenged the notion that arterial pulsatility drives glymphatic flow (Asgari et al., 2016; Rey and Sarntinoranont, 2018). However, relying on mathematical models for accurate measurements is questionable. For example, these models used histological parameters for perivascular dimensions, which can be affected by the collapse of the PVS during fixation, thus compromising real flow estimations. In vivo studies have shown that PVS are approximately ten times larger than computational model estimates. This potentially explains why computational models concluded that arterial pulsation cannot drive bulk flow (Mestre et al., 2020, 2018c).

4. Imaging the glymphatic system

4.1. Invasive imaging techniques

The first research performed on the glymphatic system employed two-photon laser scanning microscopy (Iliff et al., 2012), a precise and effective technique for examining specific PVS. However, this method is inadequate for conducting brain-wide studies and particularly, for examining the deep brain tissues. In contrast, MRI is capable of dynamic real-time imaging of the whole brain. The glymphatic system can be visualised using the intrathecal injection of GBCA. Gadolinium is a paramagnetic substance that shortens the T1 relaxation time of tissues, making them appear brighter on T1-weighted images. Iliff and colleagues were the first to employ MRI for monitoring glymphatic function in rodents. Their work demonstrated that dynamic contrast-enhanced MRI can effectively reveal the presence of glymphatic pathways(Iliff et al., 2013a). The same MRI technique was applied to assess the impact of a novel AQP4 facilitator, TGN-073, on glymphatic transport. Alghanimy et al., observed that rats treated with TGN-073 exhibited a higher parenchymal uptake of Gd-DTPA in comparison to the vehicles, suggesting the potential of TGN-073 to enhance glymphatic activity (Alghanimy et al., 2023).

The glymphatic system has also been studied in humans. Eide and Ringstad [51] used MRI scans to assess individuals who had received intrathecal injections of GBCA. Four hours after GBCA had been injected into the subarachnoid space, signal intensity in both the grey and white matter of the brain was elevated, suggesting that Gd had entered the human brain through the glymphatic system (Eide and Ringstad, 2015).

Scholars have also examined glymphatic impairment in patients with idiopathic normal pressure hydrocephalus (iNPH). The use, in MRI, of the intrathecal injection of a GBCA as a CSF tracer, accompanied by multiple MRI examinations spanning a 24-hour period, revealed indications of delayed glymphatic clearance in individuals with iNPH when contrasted with healthy controls (Ringstad et al., 2017). The enhancement of glymphatic activity reached its highest point during the night, which was attributed to the activation of glymphatic function during sleep (Ringstad et al., 2017). Another study by Ringstad et al. used repeated MRI scanning to assess glymphatic system activity in individuals with iNPH dementia, revealing brain-wide distribution of a CSF tracer introduced intrathecally. In the iNPH dementia group, clearance of the tracer substance was observed to be slower compared to that seen in healthy individuals, possibly due to compromised glymphatic transport(Ringstad et al., 2018). However, the methods used in these studies were markedly invasive, and are therefore unsuitable for routine clinical imaging.

Nagasawa and colleagues examined the brains of 27 participants who had received intravenous GBCA injections four hours earlier. In the post-contrast MRI FLAIR image, both the PVS and subarachnoid space exhibited elevated signal intensity, indicating the transfer of GBCA to these areas via the glymphatic system (Naganawa et al., 2017). The glymphatic system has been linked to GBCA deposition detected in the dentate nucleus, globus pallidus and pulvinar area of the thalamus (Kanda et al., 2016). Deposition of linear GBCA, e.g. Gd-DTPA, is higher than that of macrocyclic GBCA, e.g. Gd-DOTA (Guo et al., 2018; Radbruch et al., 2015; Saade et al., 2018). Even in individuals with healthy kidney function, residual GBCA is detected not only in the brain but also in other tissues, including the bones, skin and liver, amongst additional organs. It is therefore advisable to avoid the use of GBCA whenever possible (Gibby et al., 2004; White et al., 2006).

Another imaging modality capable of dynamic real-time imaging of the whole brain is positron emission tomography (PET). PET involves the injection of radiolabelled tracers, which are biologically active molecules labelled with a radioactive atom, e.g. carbon-11 (^{11}C) or fluorine-18 (^{18}F). When these nuclei decay, they emit positrons which interact with electrons in the body, resulting in the emission of two gamma rays in the opposite direction. A PET scanner detects these gamma rays and reconstructs an image depicting the tracer concentration. PET imaging has been utilised to evaluate glymphatic clearance in humans.

In vivo dynamic PET studies were conducted to investigate glymphatic flow in patients with AD. Leon et al. utilised two radiolabelled tracers, ^{11}C-PiB and ^{18}F-THK5117, known for their ability to bind to Aβ plaques and tau, respectively. Their findings revealed that individuals with AD exhibited reduced CSF clearance compared to their healthy counterparts (De Leon et al., 2017). They also showed a negative correlation between CSF clearance and the amount of Aβ accumulation in the brain. In another study by Schubert et al., in which ^{11}C-PiB PET was used to assess the CSF dynamics in various patient groups, it was evident that CSF clearance was significantly reduced in individuals with AD when compared to matched controls (Schubert et al., 2019).

4.2. Non-invasive imaging techniques

Ethical considerations preclude the intrathecal injection of GBCA in the majority of human patients. This fact has spurred research into MRI

methods that do not require the injection of GBCA. These techniques, including but not limited to T1-weighted PVS automated segmentation and T2-weighted PVS visual rating, have unveiled potential impairments in the glymphatic system amongst individuals with AD (Joseph et al., 2020; Kamagata et al., 2022; Steward et al., 2019; Vilor-Tejedor et al., 2021) and Parkinson's disease (PD) (Chung et al., 2021; Donahue et al., 2021; Ramirez et al., 2022; Shen et al., 2022, 2021).

The normal structure of PVS, in healthy conditions, is thin, linear and difficult to visualise by MRI. However, in some pathologies PVS dilate and so become easy to detect (Brown et al., 2018). In AD, as in ageing generally, structural MRI scans may reveal dilated PVS. These observations are indicative of potential dysfunction within the glymphatic system (Kim et al., 2022; Taoka and Naganawa, 2021). In MS, the majority of demyelinating plaques are centred around small parenchymal veins, an observation that has been supported by the use of high-strength MRI fields, i.e. 3T and 7T, and T2-weighted sequences. The central vein sign (CVS) is a term used to describe the appearance of a vein within a white matter lesion on T2 MRI sequences. In these sequences, the vein appears as a hypointense feature relative to the surrounding lesion and typically presents as a dot or a fine line situated centrally, running either partially or entirely across the lesion. The CVS is detected in all clinical phenotypes of MS and serves as a valuable imaging biomarker for distinguishing MS from its mimics (Ge et al., 2005; Karussis, 2014; Maggi et al., 2018; Sati et al., 2016). These CVS could suggest glymphatic impairment, as they resemble the dilated PVS found in neurological disorders, such as those observed in mild traumatic brain injuries (Taoka and Naganawa, 2021). Further studies are warranted to explore the relationship between the CVS in MS lesions and potential glymphatic impairment.

Taoka et al. introduced a novel approach that allowed the indirect assessment of glymphatic activity based on diffusion tensor imaging (DTI) (Taoka et al., 2017). This method uses mathematical techniques to eliminate the impact of major white matter fibre diffusivity in order to assess the minor diffusion component within the orientation of the PVS. This DTI analysis "along the PVS" (DTI-ALPS) serves as an index of diffusivity measured along the direction of the PVS, which is perpendicular to the dominant white matter fibres (Fig. 2). This therefore indicates the extent of diffusion within the white matter adjacent to the lateral ventricle body. Taoka et al. used their novel DTI-ALPS technique to evaluate the human glymphatic system in patients with AD. By analysing diffusivity in specific brain regions, they calculated an ALPS index and correlated it with Mini-Mental State Examination scores. Results showed lower water diffusivity along PVS in more severe cases of AD, which suggests glymphatic system impairment (Taoka et al., 2017). This method has proved robust across various scanners, which indicates a high degree of reproducibility in the context of a consistent imaging protocol (Taoka et al., 2022). Since the introduction of this method, it has been widely used in studies of neurological and metabolic disorders (Andica et al., 2023; Ma et al., 2021; Si et al., 2022; Yang et al., 2020). DTI-ALPS revealed compromised glymphatic function in people with PD (Cai et al., 2023; McKnight et al., 2021; Si et al., 2022). The ALPS index also served as a predictor for accelerated decline in both motor and cognitive functions in this population (He et al., 2023). Several studies have used DTI-ALPS to assess glymphatic function in iNPH (Bae et al., 2021; Georgiopoulos et al., 2023; Yokota et al., 2019). For example, Georgiopoulos et al. conducted DTI-MRI in patients with iNPH who showed significantly reduced ALPS index scores compared to their healthy counterparts (Georgiopoulos et al., 2023). Cacciaguerra et al. found the dilatation of PVS in the centrum semiovale to be more pronounced and the DTI-ALPS index to be lower, in individuals with neuromyelitis optica spectrum disorder compared to healthy subjects, suggesting compromised glymphatic function (Cacciaguerra et al., 2022). Liu et al. investigated glymphatic function in patients with early-stage amyotrophic lateral sclerosis using the ALPS-DTI index, noting that these individuals had substantially lower ALPS index values than healthy controls. Periodic limb movements and sleep efficiency were observed to be predictive factors for the ALPS index (Liu et al., 2023). These findings collectively indicate that the ALPS index holds promise as a tool for the evaluation of glymphatic function.

5. Glymphatic impairment in neurodegenerative diseases

The glymphatic system is responsible for maintaining brain health, and plays an important role in various neurological conditions. Ageing is a factor that significantly increases the risk of various neurological conditions. Studies of both animals and humans have shown a strong connection between ageing and dysfunction of the glymphatic system and meningeal lymphatic vessels (Benveniste et al., 2019; Kress et al., 2014; Zhou et al., 2020). This connection may be attributed to age-related alterations in the cerebral vascular system (Balbi et al., 2015; Frost et al., 2016; Love and Miners, 2016; Sun et al., 2018). With increasing age, cerebral arteries become progressively stiffer, which leads to the retention of fluid in expanded PVS. This, in turn, can block perivascular pathways through the narrow basement membrane, and impair glymphatic system function (Sun et al., 2018; Zhou et al., 2020). Arterial pulsation amplitude also tends to decrease with advancing age. Since arterial pulsations are significant drivers of the glymphatic system, this phenomenon may contribute to glymphatic system disruption (Iliff et al., 2013b).

Glymphatic impairment is closely associated with AD, where it may contribute to an increase in the accumulation of Aβ (Xu et al., 2015) and tau (Harrison et al., 2020; Holth et al., 2019,2017) proteins. Sleep

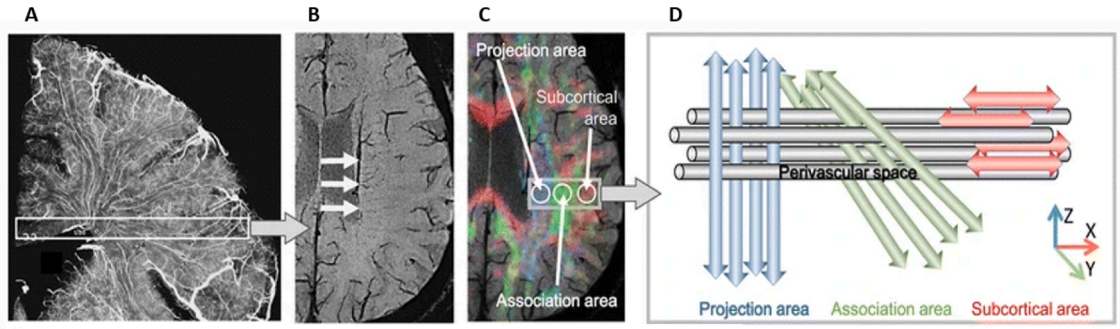

Fig. 2. Diffusion-tensor imaging along the perivascular space.*

*The DTI-ALPS method involves the analysis of diffusion tensor images along the perivascular space. A, a radiograph, shows parenchymal vessels within a brain slice at the level of the lateral ventricle body. B, an axial susceptibility weighted image (SWI), indicates the lateral orientation of parenchymal vessels. C, combines DTI with SWI to show the distribution of different types of fibres, and highlights three regions of interest for the measurement of diffusivity along three directions, x, y and z. D, a schematic, illustrates the relationship between perivascular space and fibre directions, with the perivascular space perpendicular to both projection and association fibres. Adapted from a previous publication (Taoka et al., 2017) with permission granted by Dr. Toshiaki Taoka and the publishing journal.

disturbances accompanying AD pathology may exacerbate glymphatic deterioration through a feedforward process, as the glymphatic system is most active during sleep. This process involves a mutually reinforcing cycle where sleep disturbances and glymphatic system deterioration intensify each other, ultimately accelerating the progression of AD (Winer et al., 2019). Glymphatic impairment has been suggested in PD, potentially as a result of the accumulation of alpha-synuclein protein and decline in dopaminergic neurons (Sundaram et al., 2019; Verghese et al., 2022). Both factors are associated with sleep disruption (Sundaram et al., 2019). Xu et al. investigated the association between age-related hearing loss, i.e. presbycusis, and glymphatic system performance. Their findings revealed that patients with presbycusis and cognitive impairment exhibited significantly compromised glymphatic activity compared to those without cognitive impairment and healthy controls. Additionally, a notable correlation was observed between glymphatic dysfunction and Montreal Cognitive Assessment scores (Xu et al., 2023).

Evidence has also indicated a connection between the glymphatic system and autoimmune demyelinating diseases, e.g. individuals with neuromyelitis optica tested positive for antibodies targeting AQP4 (Pittock and Lucchinetti, 2016). AQP4 water channels are known to have a key mediating role in the glymphatic system (Iliff et al., 2012). Thus, it is reasonable to infer that antibody inhibition of the AQP4 channel induces glymphatic system impairment. This would significantly contribute to the development of the characteristic inflammatory lesions seen in the pathophysiology of neuromyelitis optica. Further research into glymphatic dysfunction in pre-symptomatic neurodegenerative diseases would be of value.

6. Glymphatic impairment in multiple sclerosis

6.1. Altered cerebrospinal fluid dynamics

There is significant research interest in understanding the intricate relationship between CSF dynamics, glymphatic function and the pathogenesis of MS. Scholars have suggested that changes in the flow of CSF within brain tissue may be a factor in the development of MS (Fournier et al., 2018). Using high-resolution MRI scans of the spinal cord from mice injected with GBCA in the cisterna magna, Fournier et al. identified parenchymal CSF circulation within the spinal cord. In a model of MS known as experimental autoimmune encephalomyelitis, they observed a reduction in the spinal cord parenchymal CSF circulation (Fournier et al., 2018). A human study aligns with the previously mentioned animal study. Schubert et al. used dynamic ^{11}C-PiB PET to identify changes in CSF clearance; it was observed that compared to the healthy group, CSF clearance in the lateral ventricle was substantially reduced amongst patients with MS. These findings suggest the presence of pathological alterations in CSF dynamics and glymphatic impairment (Schubert et al., 2019). However, in practice, PET scans are often avoided because they involve the use of ionising radiation, which can pose health risks, especially when repeated scans are required, as is often the case for the ongoing monitoring of patients with MS.

6.2. Altered aquaporin-4 expression

Rohr et al. used the cuprizone model, which replicates several MS characteristics, and found increased AQP4 expression together with a reduction in its polarisation at astrocyte endfeet during toxin-induced demyelination (Rohr et al., 2020). This pattern has also been observed postmortem in the chronic active lesions seen in patients with advanced MS. Rohr and colleagues found that AQP4 expression was decreased around inflammatory brain lesions, especially where peripheral immune cells entered the brain. These observations may be associated with metabolic brain injury and peripheral immune cell infiltration. This research sheds light on the complex role of AQP4 in CNS injury and its potential implications in MS.(Rohr et al., 2020)

In another study, Aoki-Yoshino et al. examined the postmortem brains from patients with MS (Aoki-Yoshino et al., 2005). They found an elevated concentration of AQP4-positive astrocytes around the edges of plaques. They also observed reduced AQP4 polarisation to astrocyte endfeet, with the AQP4 being redistributed along the entire process of the astrocyte (Aoki-Yoshino et al., 2005), findings which may indicate a protective response initiated by AQP4. As previously reported, any impairment in AQP4, whether it is related to its expression or polarisation, can lead to dysfunction in the glymphatic clearing system (Mestre et al., 2018b).

6.3. Potential perivascular space impairment

The astrocyte, a type of glial cell, is fundamental to glymphatic system activity (Iliff et al., 2012). In MS, inflammation and damage to myelin sheaths can impair the normal function of astrocytes and compromise the glymphatic system (Aharoni et al., 2021). A distinguishing pathological feature of MS is the presence of inflammatory lesions in the perivenous spaces, which lead to the formation of demyelinating plaques (Ding et al., 2023; Karussis, 2014). It is important to note that these perivenous spaces serve as an efflux pathway via which the glymphatic system removes waste products. Fig. 3 illustrates the proposed pathological changes in the glymphatic system in MS compared to a healthy glymphatic system.

Many scholars have suggested that PVS dilatation is a marker for glymphatic impairment. PVS enlargement has been associated with conditions, such as AD (Banerjee et al., 2017), stroke (Zhang et al., 2016), cerebral small vessel disease (Laveskog et al., 2018) and MS (Ge et al., 2005). A crucial stage in the pathophysiology and development of MS lesions is perivascular inflammation. Ge et al. described pronounced perivenular areas, i.e. CVS, that seemed to be connected to MS, and proposed that these may prove helpful in distinguishing MS from other white matter disorders, as illustrated in Fig. 4 (Ge et al., 2005). In postmortem research, Vos et al. identified greater levels of blood-brain barrier disturbance in active demyelinating MS lesions than in chronic inactive lesions (Vos et al., 2005). Both focal and diffuse white matter lesions observed on postmortem MRI were linked to enlarged PVS which, on histological examination, contained infiltrated leukocytes (Verghese et al., 2022; Vos et al., 2005).

Granberg et al. conducted a systematic review and meta-analysis focusing on the visualisation of enlarged PVS (EPVS) using MRI in patients with MS. Their findings indicated that in patients with MS, EPVS were associated with cognitive deficits, MRI lesion enhancement with GBCA, and brain atrophy. However, these results have not been consistently reproduced across all studies. The meta-analysis indicated that patients with MS had a higher prevalence of EPVS and larger EPVS volumes than controls. The paper suggests that individuals with MS tend to have a greater burden of EPVS compared to those individuals without MS (Granberg et al., 2020). A recent case report by Scollato et al. presented a patient diagnosed with PPMS and EPVS. Interestingly, this patient experienced a transient improvement following CSF shunt procedures. This suggests that the use of CSF diversion to alleviate the congestion of PVS may enhance glymphatic function and facilitate the removal of proinflammatory molecules (Scollato et al., 2022).

A recent study compared the occurrence of EPVS amongst patients with MS (Kolbe et al., 2022). Evaluators identified and quantified EPVS on T2-weighted MRI images from three regions of interest, namely the basal ganglia, midbrain and centrum semiovale. They found that patients with late-stage RRMS had more EPVS in the basal ganglia area than those individuals with early-stage RRMS and clinically isolated syndromes. This difference was statistically significant and associated with lesion volume, but not brain atrophy (Kolbe et al., 2022). Notably, it was reported that the relationship between sleep efficiency and PVS volume in both the basal ganglia and the whole brain displayed a negative correlation (Berezuk et al., 2015; Kamagata et al., 2023).

Carotenuto et al. recently conducted a retrospective study in order to

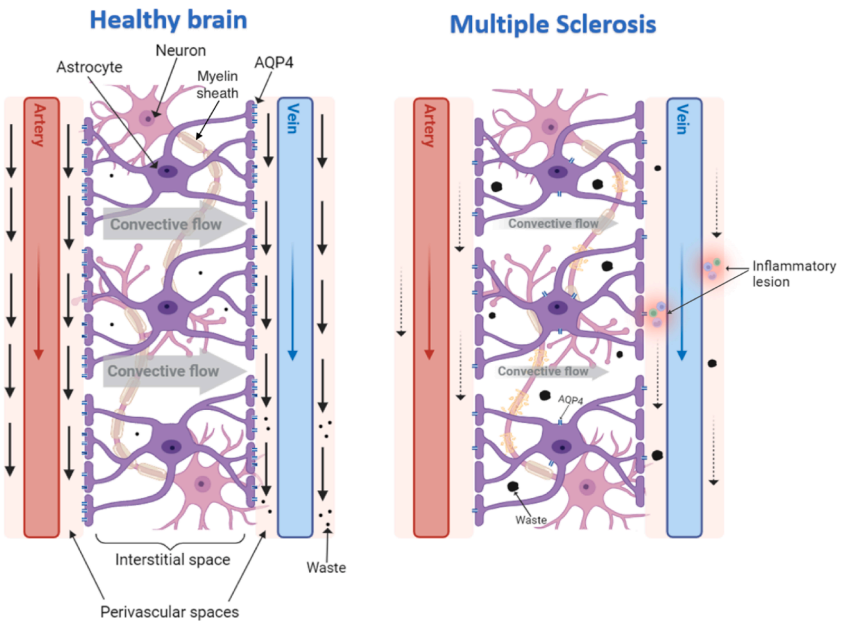

Fig. 3. In a healthy brain on the left, there is a typical glymphatic influx (periarterial) and efflux (perivenous) with high expression of AQP4 at astrocytic endfeet. This facilitates the normal bulk flow of interstitial fluid and maintains the integrity of the myelin sheath. Conversely, in the context of multiple sclerosis on the right, proposed changes include diminished glymphatic influx and efflux, depolarisation of AQP4 away from astrocytic endfeet, reduced bulk flow of interstitial fluid and destruction of the myelin sheath. The existence of inflammatory lesions in the perivenous space may impede the glymphatic efflux pathway.

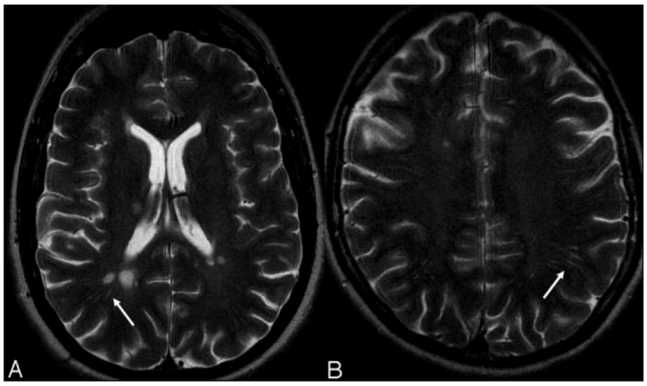

Fig. 4. (A) On a T2-weighted image (TR/ TE, 7900/119) of a 51-year-old patient with relapsing-remitting MS (RRMS), the prominent perivenular space sign (arrow) traces the central course of the veins alongside which the lesions have spread. (B) A 33-year-old patient with RRMS demonstrates the prominent perivenular spaces sign (arrow) on a T2-weighted image which appears to be unrelated to lesions. Image adapted from (Ge et al., 2005) with permission granted by Dr. Yulin Ge and the publishing journal.

explore the role of the glymphatic system in clinical disability, disease progression, demyelination and neurodegeneration in individuals with MS (Carotenuto et al., 2022). Their study included patients with both RRMS and PPMS, together with age- and sex-matched healthy controls. All participants underwent neurological and MRI examinations. Several measurements were taken, including the DTI-ALPS index, a proxy for glymphatic function. Patients with MS generally had impaired glymphatic function compared to healthy controls, with more pronounced impairment seen in those with PPMS as opposed to RRMS. This glymphatic dysfunction was associated with greater disability, demyelination and neurodegeneration, which indicates its importance in the MS disease process (Carotenuto et al., 2022). Additional analysis revealed an inverse relationship between the ALPS index and duration of the disease during the initial 4-year period of MS with no significant correlation subsequently. These findings suggest that dysfunction in the glymphatic system could potentially cause the build-up of neuroinflammatory and neurotoxic substances, leading to the progressive loss of myelin and neurons.

6.4. *Potential meningeal lymphatic vessel impairment*

Shortly after the introduction of the glymphatic hypothesis, studies revealed the existence of meningeal lymphatic vessels within the dura mater, a finding which has further clarified the mechanism responsible for moving fluid from the CSF to the deep cervical lymph nodes (Aspelund et al., 2015; Louveau et al., 2015). Aspelund et al. observed that in transgenic mice lacking these dural lymphatic vessels, the transfer of fluid from the brain parenchyma to the deep cervical lymph nodes was abolished (Aspelund et al., 2015). In mice, dysfunction of the meningeal lymphatics diminishes the paravascular flow of macromolecules and their removal from the ISF, leading to cognitive impairment (Da Mesquita et al., 2018). Meningeal lymphatic vessels have also been identified in humans. These lymphatic vessels are located within the dura mater and are particularly concentrated along the superior sagittal sinus (Absinta et al., 2017; Visanji et al., 2018). The late discovery of meningeal lymphatic vessels may be attributed to their unique and challenging location, thereby contributing to the longstanding belief that the CNS lacks lymphatic vasculature (Aspelund et al., 2015; Jiang, 2019; Louveau et al., 2015).

A recent prospective study by Gabr et al. applied dynamic intravenous contrast MRI, and employed a standard 3T MRI scanner, in order to investigate the dural lymphatic vessels in patients with MS (Gabr et al., 2023). Marked contrast enhancement was seen within these lymphatic vessels, with signal tracking extending for approximately 33 min post-contrast injection, and an average peak enhancement of 109%. In contrast to more invasive techniques, such as intrathecal contrast injection, this approach was minimally invasive and proved effective in facilitating the evaluation of lymphatic function. Potential clinical implications were also considered, with connections between lymphatic signal dynamics, patient age, body mass index and disease characteristics explored. This approach identified correlations between brain atrophy, measured as brain parenchymal fraction, and modified lymphatic enhancement parameters. These correlations may suggest potential

issues related to lymphatic flow linked to MS pathology, age-related cervical lymph node atrophy and capillary hyperpermeability (Gabr et al., 2023). Diminished glymphatic flow may also suggest reduced flow in meningeal lymphatic vessels, potentially leading to the buildup of inflammatory and neurotoxic substances. These include meningeal B and T cells and detrimental cytokines, which could play a role in the development of demyelination (Gardner et al., 2013).

6.5. Potential viral infection

The relationship between MS, the Epstein-Barr virus (EBV) and glymphatic impairment is a subject of ongoing research. Recent evidence suggests that EBV plays a crucial role in the causal pathway of MS (Bjornevik et al., 2022). In a study involving over 10 million participants, Bjornevik et al. found a 32-fold increased risk of developing MS in individuals with prior EBV infection (Bjornevik et al., 2022). Another study showed that individuals who were not infected with EBV had a negligible risk of developing MS, whereas the highest risk for the onset of MS was observed in previously infected individuals (Thacker et al., 2006). Several additional studies also report the existence of EBV in demyelinated lesions in patients with MS (Hassani et al., 2018; Moreno et al., 2018; Serafini et al., 2007). Hawkes et al. proposed that anti-viral agents targeting both the lytic and latent phases of EBV hold promise for preventing MS (Hawkes et al., 2022). It is possible that EBV might depolarise AQP4, leading to impaired glymphatic clearance, thereby potentially initiating or exacerbating MS. Some studies have already proposed a connection between viral infections and altered cerebral AQP4 expression (St Hillaire et al., 2005; Torres et al., 2007; Xing et al., 2017). For instance, infection of the CNS by HIV leads to AQP4 depolarisation, deposition of hyperphosphorylated tau, chronic neuroinflammation and cognitive impairments (Tice et al., 2020). It is worth noting that dementia and tau accumulation are closely linked to glymphatic clearance dysfunction (Da Mesquita et al., 2018; Harrison et al., 2020; Ishida et al., 2022; Peng et al., 2016). Scientific understanding in this area is continually evolving, and further research is needed in order to establish more concrete links between viral infection in MS and glymphatic impairment.

In summary, the existing literature indicates that the glymphatic system plays a critical role in neurological conditions, such as MS. Furthermore, the discovery of meningeal lymphatic vessels has opened new avenues for understanding fluid transport within the brain and their relevance to MS. Understanding these mechanisms may advance the interpretation of this disease and pave the way for innovative therapeutic strategies, particularly those aimed at restoring glymphatic function and improving patient outcomes.

7. Disrupted sleep patterns and glymphatic dysfunction in multiple sclerosis

7.1. Role of sleep in the glymphatic system

The glymphatic system is particularly active during sleep, especially during slow wave sleep. The mechanism underlying this phenomenon is a reduction in noradrenaline levels, which are at their lowest during sleep, which, in turn leads to a striking increase in interstitial space. In contrast, during wakefulness, fluid flux and the cleaning process are inhibited due to higher noradrenaline titres, which reduce the volume of interstitial space (Cai et al., 2020; Goldman et al., 2020; Ju et al., 2017). The results of a mouse study indicated that in comparison to when the animals were asleep, clearance of brain solutes reduced by half whilst the mice were awake (Xie et al., 2013). In a human study using PET, Shokri-Kojori et al. investigated the impact of one night of sleep deprivation on the clearance of β-amyloid in the human brain. These researchers found that a single night of sleep loss significantly increased the Aβ burden in the right hippocampus and thalamus, which are important to cognition. They also found mood deterioration after sleep loss (Shokri-Kojori et al., 2018). Lee et al. observed that sleeping in a lateral position rather than supine or prone increased glymphatic activity. This was especially true for the right lateral decubitus posture, in which the heart is positioned slightly higher, potentially improving cardiac stroke volume, lowering sympathetic tone, and ultimately enhancing glymphatic influx (Lee et al., 2015).

7.2. Multiple sclerosis and sleep disturbances: a feedforward relationship

Sleep disorders have gained attention as a significant factor in various neurological conditions, including MS, and emerging research suggests that sleep disorders might play a role in both the onset and progression of MS (Braley, 2017; Marrie et al., 2015; Neau et al., 2012). In 1994, Tachibana et al. reported sleep disorders in nearly half their MS patients (Tachibana et al., 1994). Several types of sleep disorder have been explored in relation to MS; these include narcolepsy, insomnia, sleep apnoea and restless legs syndrome (RLS) (Braley, 2017; Marrie et al., 2015; Neau et al., 2012). Sleep disturbances are common in MS patients and can exacerbate their existing symptoms, including fatigue, cognitive impairment and mood disturbance. Conversely, it is possible that the neuroinflammatory processes in MS contribute to sleep disturbances.

Buratti et al. tested the connection between sleep quality and the clinical development of MS. In the course of a month-long observation, they identified an increased rate of longer-lasting relapses in patients with RRMS who had poor sleep quality as indicated by a Pittsburgh Sleep Quality Index score of 5. These findings support the hypothesis that poor sleep hinders the ability to recover from MS relapses, potentially due to a problem with myelin regeneration (Buratti et al., 2019). One hypothesis is that sleep disorders may trigger or exacerbate inflammation, potentially through increased release of proinflammatory cytokines (Sakkas et al., 2019). In turn, inflammation could affect the progression of MS by promoting neuronal damage and demyelination. Additionally, multiple studies have shown that sleep plays a crucial role in neuroprotection and repair processes, and that disturbances in sleep may hinder the brain's ability to recover from MS-related damage (Buysse, 2014; Eugene and Masiak, 2015; Hughes et al., 2018).

A study by Veauthier et al. found a bidirectional relationship between sleep disorders and MS, in that sleep disturbances could potentially worsen MS symptoms and disease progression, and MS-related inflammation could contribute to sleep problems. This suggests a feedforward process, but the precise interaction remains complex and unclear. It may be that factors, such as disrupted circadian rhythms, immune system dysfunction and alterations in neurotransmitter pathways are involved (Veauthier and Paul, 2014).

7.3. Sleep apnoea, glymphatic dysfunction and multiple sclerosis: a potential connection

Sleep disruptions are often not regularly and carefully studied in the clinical setting and are frequently underestimated (Merlino et al., 2009). This is despite their incidence and possible pathogenetic significance in various clinical disorders, as well as their societal ramifications (Buratti et al., 2018; L. 2017, 2016). Persistent insomnia may be greatly influenced by neurological abnormalities, pain, stiffness, anxiety or depression, which are common symptoms in patients with MS (Braley and Boudreau, 2016). There is strong evidence that sleep apnoea, both central and obstructive, arises frequently in this population (Braley et al., 2014; Hensen et al., 2018). Various factors may cause these conditions, including demyelinating lesions in the spinal cord and brainstem. Such damage can affect breathing control and muscles in the upper airway, leading to an unsteady drive to breathe (Braley et al., 2014; Hensen et al., 2018). Interestingly, glymphatic system impairment has been identified in patients with obstructive sleep apnoea (Lee et al., 2022; Roy et al., 2022; Wang et al., 2023), with a strong correlation between apnoea severity and glymphatic system dysfunction (Lee et al.,

2022). The high occurrence of sleep apnoea in MS patients and their association with glymphatic system dysfunction prompts further investigation into the possible link between MS and glymphatic dysfunction.

7.4. Restless leg syndrome, glymphatic dysfunction and multiple sclerosis: a potential connection

Recently, Park et al. investigated the DTI-ALPS index in patients with RLS and discovered a significant decrease in water diffusivity along PVS compared to healthy individuals (Park et al., 2023). This finding indicates a compromised glymphatic system function in patients with RLS. The evidence suggests a potential link between RLS and MS, although the precise nature of this relationship is not fully understood. Studies have indicated a higher prevalence of RLS amongst patients with MS than in the general population (Aljarallah et al., 2023; Li et al., 2012). Further research is required in order to elucidate the mechanisms involved and connections between RLS, MS and glymphatic dysfunction.

7.5. Periodic limb movement, glymphatic dysfunction and multiple sclerosis: a potential connection

In 1994, during an evaluation of sleep in 25 patients with MS without emotional disorder compared with 25 normal controls, Ferini-Strambi et al. discovered substantially less sleep efficiency, together with greater arousals and periodic limb movements in the individuals with MS, i.e. 36% compared to 8% (Ferini-Strambi et al., 1994). MRI showed that patients with MS and periodic limb movements showed larger infratentorial lesion burdens, i.e. in the cerebellum and brainstem (Ferini-Strambi et al., 1994). Kang et al. documented that individuals with periodic limb movements had notably larger PVS volumes compared to those without such movements, indicating a potential glymphatic impairment (Kang et al., 2018).

7.6. Pain, glymphatic dysfunction, and MS: a potential connection

Neuropathic pain is a prevalent occurrence in patients with MS. Although pain may be manifested as an acute syndrome, chronic pain is experienced by more than 50% of patients with MS at some point during the course of their disease (O'Connor et al., 2008). Chronic neuropathic pain often persists long after the initial MS insult, significantly impacting the quality of life in numerous individuals with MS. Pain is frequently associated with common MS symptoms, such as muscle spasms, optic neuritis, Lhermitte's sign, and sensations of numbness or pins and needles (Racke et al., 2022). Pain may be both a cause and a result of sleep disturbance (Evans et al., 2017; Roberts and Drummond, 2016; Tang et al., 2012). Noradrenergic neurons in the locus coeruleus exhibit activity patterns, being active during wakefulness, and showing reduced activity or near inactivity during non-REM and REM sleep, respectively (Aston-Jones and Bloom, 1981; Haack et al., 2020). Interestingly, pain is linked to higher adrenergic signalling (Taylor and Westlund, 2017) and poor sleep quality (Ferini-Strambi, 2017; Finan et al., 2013). Goldman et al. suggested that chronic pain may suppress the glymphatic system, a phenomenon attributed to disrupted sleep (Goldman et al., 2020).

Although connections between sleep disturbance, glymphatic dysfunction and MS are becoming established, more studies are required to pinpoint the exact mechanisms involved. Managing sleep disturbances in patients with MS may enhance their general quality of life, as well as delay pathological development.

8. Conclusions

MS is a chronic CNS disorder characterised by inflammation and neurodegeneration. The glymphatic system, responsible for waste removal from the brain and most active during sleep, has gained interest in relation to MS. Researchers have introduced various imaging methods in order to explore the glymphatic system in patients with MS, with particular focus on non-invasive MRI techniques, such as DTI-ALPS. Sleep disorders are emerging as significant factors in neurological conditions, including MS. Recent studies suggest that sleep disorders may influence the onset and progression of MS. Notably, sleep disorders that impact the glymphatic system, such as sleep apnoea and RLS, have been studied in the context of MS. These sleep disturbances can worsen existing MS symptoms. However, it is also possible that the neuroinflammatory processes in MS contribute to sleep disorders. The involvement of the glymphatic system in MS is still a relatively new area of research, and so further studies are needed to understand the specifics of this relationship and its potential therapeutic implications in more detail. This relationship could be bidirectional, with MS-related inflammation affecting the glymphatic system, and glymphatic dysfunction exacerbating MS symptoms.

Methods

A comprehensive search was conducted in two primary academic databases, PubMed and Google Scholar, covering articles published from the inception of these databases up until September 30, 2023. In order for an article to be included in the review, it had to meet the following criteria: (i) published in the English language; and (ii) relevant to the topic of MS and its association with the glymphatic system. The following search terms were used to identify relevant articles: "multiple sclerosis"; "MS"; "glymphatic system"; "lymphatic system"; "perivascular space"; "magnetic resonance imaging"; and "MRI". The reference lists of key articles identified during the search process were reviewed thoroughly. This screening process was conducted so as to identify any additional pertinent publications, with a focus on articles published since 2012. Relevant data were collected and compiled from the selected articles in order to provide an insightful and comprehensive review of the current state of knowledge regarding the relationship between MS and the glymphatic system.

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CRediT authorship contribution statement

Alaa Alghanimy: Investigation, Methodology, Writing – original draft, Writing – review & editing. **Lorraine M. Work:** Supervision, Writing – review & editing. **William M. Holmes:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors report no competing interests.

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