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Advances in Topographical Neuroanatomy

Michael Besser AM*

Clinical Professor and Lecturer in Surgical Anatomy, Sydney University, Australia

***Corresponding author:** Michael Besser AM, Consultant Neurosurgeon, Clinical Professor, Lecturer in Surgical Anatomy Sydney University, Australia

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ABSTRACT

The classical teaching of the three membranes covering the brain, the pia, arachnoid and dura mater, has recently been redefined by the discovery of a fourth meningeal layer which is immunophenotypically distinct. This has been named the subarachnoid lymphatic membrane (SLYM) by Mollgard and, although only a few cells thick, divides the subarachnoid space into two different spaces bathed in cerebrospinal fluid (CSF). This newly discovered membrane surrounds the blood vessels in the subarachnoid space and is made up largely of immune cells aligning the relationship between the glymphatic system, CSF flow, brain homeostasis and the pathophysiology of neurodegenerative disorders such as Alzheimer's disease [1].

Keywords: Meninges; Lymphatic Drainage; Neuroinflammation; Cerebrospinal Fluid; Sleep

Introduction

The first recorded dissection of a human brain was by Herophilus, a Greek physician, in the third century B.C. As well as documenting the confluence of the dural sinuses he described the arachnoid membrane enclosing the brain. The term "arachnoid" comes from the spider like description, attributed to Ruysch in 1699, made up of an avascular, collagen material separating the pia from the dura, containing the CSF and suspending the brain [2]. The arachnoid membrane is further subdivided by subarachnoid trabeculae, collagen reinforced columns adding further mechanical support to neurovascular structures within the CSF compartment and further stabilization of the suspended brain.

This emerging view of the meninges is now added to the traditional historical opinion of a structural, protective support for the central nervous system (CNS). Evidence currently suggests that specific cells within each meningeal compartment have a differential role in health and neuroinflammatory disease particularly related to brain lymphatic drainage and the neuroimmune interface [3].

It has long been thought that the CNS was immunologically privileged but recent advances in neuroimaging, especially two photon microscopies, has shown immune cells and an elaborate lymphatic drainage system within the meninges [4]. This is aligned with the glymphatic system and is essentially part of a new layer only a few cells thick, named as the SLYM [1]. This layer of myeloid cells is well exposed to the CSF which it can survey and then respond to the inflammation caused by the pathologies of infection or dementia such as Alzheimer's disease [5].

Brain Homeostasis and CSF Flow

The brain differs from other organs of the body due to a unique blood-brain barrier which, although optimal for neuronal function, does not allow for transcapillary filtration. Instead, the brain depends on the cleansing effect of cerebrospinal fluid which washes along the perivascular spaces created by the cells of the glymphatic system and astroglial end feet. These have adluminal aquaporin-4 water channels which facilitate the flow of CSF into the pericapillary spaces and brain parenchyma [6].

Lliff in 2012 using two-photon imaging of fluorescent markers, showed CSF entering the brain parenchyma along perivascular spaces with clearance of interstitial fluid around venous pathways. This group also showed that tagged amyloid-B material was demonstrated within this transport system and deletion of the gene responsible for aquaporin-4 channels dampened the removal of this peptide which is pathogenic in Alzheimer's disease.

The flow of CSF through perivascular spaces in the brain allows removal of metabolic waste and is dependent on arterial pulsation from the cardiac cycle. Hypertension may alter these pulsations and could reduce this flow cycle. This has been linked to accumulation of amyloid-B and hypertension is a known risk factor for Alzheimer's

disease [8]. The cognitive decline often noted with cardiac failure, usually attributed to low oxygenation secondary to low cerebral perfusion, may be due to poor glymphatic flow. This results in incomplete waste clearance and a cycle of aggregation build up with even slower glymphatic function [9].

Drieu and colleagues, in 2022, showed that there also are cellular regulators of CSF flow dynamics. These cells were collectively named parenchymal border macrophages, closely aligned with the brain arterial tree, and play a role in regulation of arterial motion that drives CSF flow. If they are depleted extracellular proteins accumulate with blockage of CSF entry to pericapillary spaces and obstruct adequate brain perfusion. They showed, using single nucleus RNA sequencing, that these cells may be pharmacologically influenced to lessen brain clearance deficiency seen in aging and dementia.

Lymphatic Drainage of The Brain

In 2015 Aspelund and colleagues reported a lymphatic vascular network in the dura mater that drained brain interstitial fluid via the glymphatic system and absorbed CSF from the subarachnoid space. This fluid was subsequently demonstrated to travel through the foramina of the skull base, especially the cribriform plate via the olfactory bulb, to the nasal mucosa and found in the deep cervical lymph nodes [6]. These lymphatic dural vessels were particularly prominent lining the dural venous sinuses and immune surveillance of the brain seems to occur within the meninges [10].

The glymphatic system is a complex, well organized CSF transport system, including export of interstitial fluid and excess proteins, which it shares with the lymphatic vessels. Fluid clearance from the central nervous system via the glymphatic system is structurally distinct using the perivascular spaces of the vascular end feet of glial cells that cover the whole cerebral vascular bed of arteries, capillaries and veins [9]. The astrocytic end feet express the water channel aquaporin-4 which facilitates the flow of CSF into the brain where it aggregates with interstitial fluid [6].

There is a complicated relationship between the functions of the glymphatic system and the meningeal lymphatics. Miscommunication between them may play a significant role in immune and neuroinflammatory disorders of the central nervous system [11]. The meningeal lymphatic vessels have a definitive role in drainage of macromolecules and immune cells from the brain to deep peripheral lymph nodes [12].

Rasmussen and colleagues have speculated, using evidence from experimental models in laboratory animal studies that low glymphatic flow may contribute to the risk of developing neurodegenerative diseases. Certainly inter-individual differences in CSF inflow are seen in healthy humans but CSF clearance is reduced however in all patients with Alzheimer's disease [6].

The meninges without doubt play an important role in brain immunity [4]. The role of the dural venous sinuses seems critical as a neuroimmune interface with brain derived antigens in the CSF having been shown to accumulate around the dural sinuses [13]. However, the precise mechanisms of neuroimmune surveillance are unknown.

Certain CSF cytokines and chemokines (immune molecules) which exert neuromodulatory affect and are biomarkers of neuroinflamatory brain disorders [14] may be affected by the activity of meningeal lymphatics. Altering the accessibility of CSF neuromodulaters to the brain could exert unwanted consequences on the brain parenchyma such as accumulation of the toxic amyloid-B protein [15].

Glymphatic System, Brain Homeostasis and Sleep

It is well established across all biological species, including mankind, that conservation of sleep is vital to ensuring satisfactory brain function. Maintenance of metabolic homeostasis in the brain seems to predominate during sleep [9]. Photon Emission Tomography (PET) has been used to show that amyloid-B accumulates after only a single night of sleep deprivation, particularly in the hippocampus and thalamus [6]. CSF clearance of harmful metabolites such as tau tracers and amyloid-B is reduced in patients with Alzheimer's disease. This is also suggestive that the glymphatic system is mainly active during sleep [6].

Xie and colleagues [16] in 2013, using diffusion two-photon imaging in live mice, showed that sleep was associated with a significant increase in the interstitial space. Convective exchange of CSF with the interstitial fluid also increased with sleep as well as an increased rate of amyloid-B clearance. They surmised that sleep enhanced the removal of neurotoxins that accumulate during the awake phase of the circadian cycle. CSF distribution appeared to be under circadian control and the glymphatic system was much more effective during sleep in animal studies [17].

Functional MRI studies have demonstrated widespread haemodynamic alterations during non-rapid eye movement sleep when combined with simultaneous electroencephalography (EEG) recordings [18]. This is coupled with slow oscillations of neural activity that coincide with dynamic CSF flow into and out of the brain. Fultz and colleagues have demonstrated that the sleeping brain shows waves of CSF flow linked with both neural and haemodynamic rhythms. Clearance of CSF is stronger in sleep patterns associated with low frequency EEG waves [18, 19].

Sleep quality normally diminishes with aging, but an irregular sleep pattern often heralds the start of dementia in neurovascular and neurodegenerative disease [9]. The glymphatic drainage system also decreases in older age and it is most active during sleep to clear protein waste products from the brain. This implies a causal relationship between sleep irregularities and symptomatic progression of degenerative dementia such as Alzheimer's disease which is becoming increasingly common with the aging population [6].

Conclusion

The meninges historically were viewed as only structural support for the brain containing the cerebrospinal fluid which helped protect the brain from trauma. The CSF also bathed the cerebral vasculature whilst supporting the brain. The brain was thought to be a site of immune privilege and, without obvious lymphatic channels, considered to recycle its accumulating protein aggregate waste products [7].

Advances in neuroimaging, particularly two-photon microscopy have revealed an ultra-thin membrane, separate from the pia mater, consisting of just a few cells largely surrounding the cerebral vasculature in the CSF [1]. Brain specific myeloid immune cells largely make up the SLYM and are an integral part of the brain's waste removal glymphatic system.

This newly discovered anatomical structure segregates and assists the control of CSF flow with a role in transporting and removing brain waste but importantly supports the immune defenses of the brain. Disruption of the SLYM may help to explain brain inflammation in traumatic brain injury, meningitis and other neuroinflammatory conditions [9].

Exchange of substances between brain compartments mediated by the SLYM divides the subarachnoid space into functional compartments and acts as a barrier for substances in the CSF greater than three kilodaltons to regulate the movement of pathogens and molecules from CSF to the brain and vice-versa [3]. Glymphatic clearance of metabolic and protein waste is primarily active during sleep when the cardiac and respiratory cycles seem to be most efficient in the propulsive movement of CSF along the perivascular spaces [6].

Waste brain products such as amyloid-B manufactured during the awake cycle of normal circadian rhythm seem only capable of being efficiently cleared during sleep [9]. They are present in higher concentrations during wakefulness and sleep deprivation further increases their levels [6].

It seems clear that the meninges are an essential interface between the brain and its outside boundaries, essential for brain homeostasis and with biological species, including humans, dependent on sleep for satisfactory function of its complex clearance and immune mechanisms. Disruption of the glymphatic and SLYM interdependent systems are likely to be involved in the pathogenesis of the many varied neuroinflammatory and neurodegenerative diseases afflicting mankind [3, 9].

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