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Lymphatic system in the brain

The lymphatic system is an open system, consisting of a mesh of lymphatic vessels, lymph nodes, lymphatic organs, and lymphoid tissue. Besides, immune function, the lymphatic system also equilibrates body fluid, electrolytes, and nutrient levels as, glucose, amino acid, and lipid, with neurotransmitters, guards from foreign invasion, and eliminates waste products. The central nervous system (CNS) does not have any true lymphatic system.

Maiken Nedergaard, a Danish neuroscientist proposed the term 'glymphatic' indicating the role of glial cells (astrocytes, oligodendrocytes, microglia) in waste clearance. Glial cells also play a vital role in nourishing neurons and in immunity function [20]. This parallels with the peripheral lymphatic system, hence named the glymphatic pathway [1].

The brain has four fluid chambers and among them, CSF and interstitial fluid get exchanged constantly. The notion is CSF enters and evacuates through aquaporin-4 after amalgamated with interstitial fluid with the aid of perivascular glial cells. CSF afterward drained into retropharyngeal, cervical, submandibular, and preauricular lymph nodes [3].

First discovered in the year 2012 in a rodent brain model. CSF was traced by fluorescent dye to determine the pathway. CSF is channeled through parenchyma by a perivascular astrocytic end foot followed by leaving the brain through a central deep vein and lateral-ventral caudal rhinal vein [4]. Thus, this system is consisting of-a para-arterial CSF influx route, a perivenous ISF efflux route, with an astroglia water transport-dependent *trans*-parenchymal portion. The glymphatic system shows activity more during the sleeping period than watchfulness and gets rid of neurotoxins including amyloid β. This system slows down due to the physiological aging process [2]. Also, the glymphatic system is regulated by nervous stimulation both sympathetic and parasympathetic, and posture and genetic predisposition [6].

The impaired glial cell-dependent waste clearance pathway of the central nervous system (CNS) gives rise to neurovascular, neurodegenerative, and neuroinflammatory disorders [11]. Glymphatic disorder, perhaps connected to aquaporin-4 water channels (AQP4) expression, has been demonstrated in disorders such as Alzheimer's disease (AD), stroke and traumatic condition, and head injury [5].

Alzheimer's disease is a neurological disorder where the death of brain cells occurs causing memory loss, language difficulty, and impulsive behavior. Sleep boosts mood, brain functionality, and overall wellbeing. Lack of sleep can enhance AD by accelerating the accumulation of misfolded neurotoxins and impairing the glymphatic system. Dislocation of AQP4 also changes the expression and cumulation of proteins [14]. Amyloid β, α-synuclein, and tau protein clearance are hampered due to compromised AQP4 in AD, which is normally cleared by (CSF) flow through perivascular and interstitial spaces. Thus, APQ4 might be a potential medicinal target for AD [7]. Glymphatic activity can be monitored by diffusion images, illustrating the effective association between narrow perivascular space in AD and glymphatic system [13].

Another neurodegenerative disease, Parkinson's disease (PD) also exerts similar disturbance [8]. Inflation of α-synuclein is the primary pathogenesis of PD because of the lack of a functional glymphatic system [9]. Association of the disturbed glymphatic system in PD is proved in diffusion tensor image analysis along with the perivascular space (DTI-ALPS) method where PD exerts a prominent reduction in ALPS index [12]. Sleep disturbance is characteristic of PD causing oxidative stress and metabolic waste(α-synuclein) accumulation [10]. There is an interrelation between pain and glymphatic system due to the presence of norepinephrine [15]. According to diffusion imaging, a positive correlation is established between pain in cancer patients and glymphatic pathway [16].

Headache and sleep disturbance have been reported in traumatic brain injury patients, which is a matter of concern in the USA. Damage to the glymphatic pathway and failure of disposing of neuropeptides are responsible for the effect [17].

Isolated rapid eye movement sleep behavior disorder (iRBD) can be explained by diffusion imaging also to prove the glymphatic system incorporation [18]. In progressive stages of multiple sclerosis, the glymphatic function is disrupted [19].

To avoid unexpected neurological disorders, proper take care of glymphatic system is necessary. Studies found that proper sleep and exercise aid in healthy dumping functionality of the brain. The glymphatic system is a new ray of hope in diagnostic and prognostic aspects of many unexplained diseases with neurotoxins, introducing an unrevealed field of research. Further exploration of genetics, imaging and behavioral patterns can lead to a more conclusive end.

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Declaration of competing interest

None.

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