Review Article

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# ''Impairment of Glymphatic System including Aquaporin-4 (AQP4):a newer perspective of therapy of neurodegenerative diseases /Chronic traumatic encephalopathyIschemic stroke & Vascular dementia: A Review''

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**Abstract**

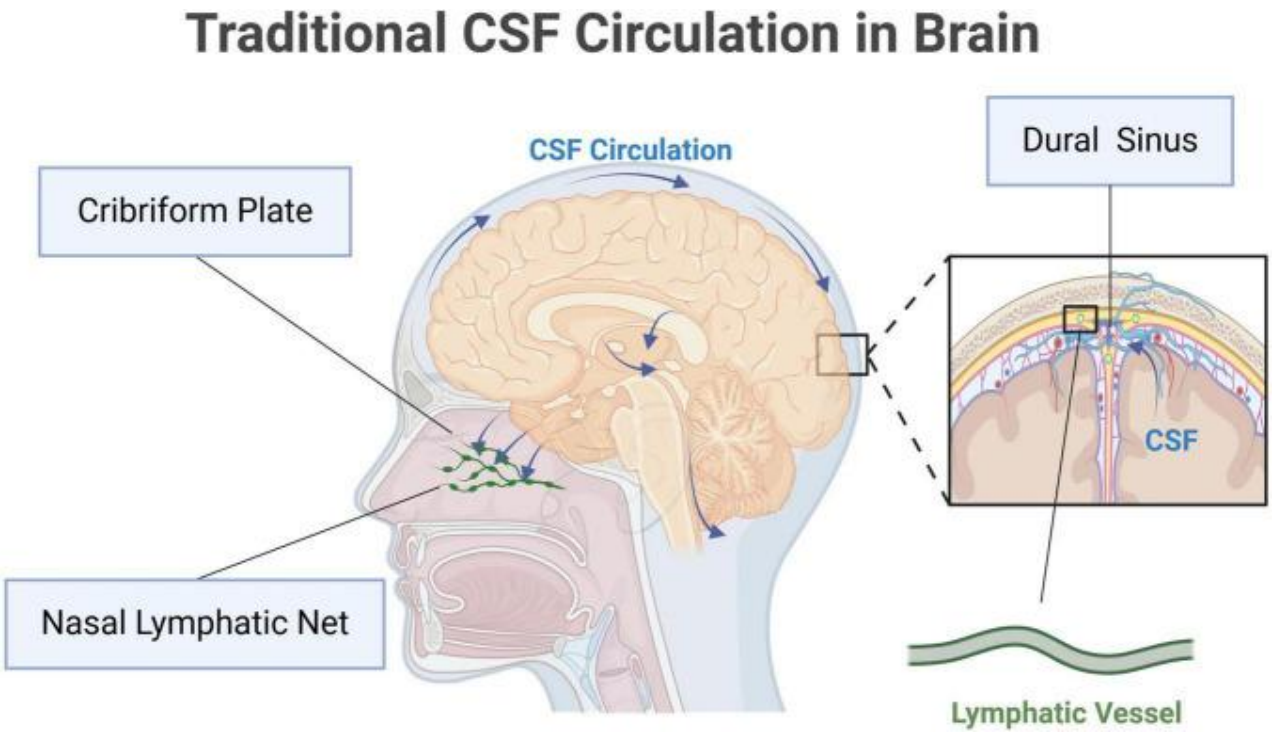
*The glymphatic system theory introduces a new perspective on fluid flow as well as homeostasis in the brain. Here, cerebrospinal fluid(CSF) in addition to interstitial fluid (CSFISF)moves from the perivascular spaces (PVS) of arteries to those of veins for drainage. Aquaporin-4 (AQP4) possesses a pivotal part in driving fluid amongst the PVS.The dysfunctional AQP4 is intricately correlated with the impairment of the glymphaticsystem. The working of the glymphatic system possesses lesser activity at the time of waking however is escalated at the time of sleep. The efficacy of the glymphatic system diminishes with escalation of age. Injury to the glymphatic system would ultimately result in to the generation along with propagation of plethora of brain diseases, for instance Alzheimer's disease (AD),Parkinson's disease (PD), chronic traumatic encephalopathy (CTE), as well as vasculardementia (VaD). Here, we reviewed earlier workcorrelated with theglymphatic system, inclusive of its ideas, fundamental, in addition to impacting factors.We posit that AQP4 possesses the capability of acting in the form of a target for the avoidance of in addition to therapy of certain brain diseases via the controlling ofthe glymphatic system. Previously we had detailed various etiopathogenesis ofAlzheimer's disease (AD),Parkinson's disease (PD),of NDD,here we add impairment of the glymphatic system as another etiologicalfactor.*

**Keywords:** Glymphatic System; Aquaporin-4 (AQP4); cerebrospinal fluid(CSF); interstitial fluid(ISF)

## 1. Introduction to CSF-ISF circulation and glymphatic system in brain

Cerebrospinal fluid(CSF) is a form of clear, colorless fluid, considerably occupying the space amongst the pia as well as arachnoid. CSF is liberated by the choroid plexus amongst the ventricles, in addition to ultimately absorbed via the venous sinuses [1-3] It nourishes in addition to confers protection to the central nervous system (CNS). i) Beginning of CSF circulation takes place from the lateral ventricles, as well as flows via the interventricular foramina into the third ventricle. ii) Subsequently gaining entry into the fourth ventricle via the cerebral aqueduct which gets followed by CSF gaining entry into the subarachnoid space via the median foramen in addition to the two lateral foramina,along with infiltrates via the arachnoid granulations into thedural sinuses[4]. iii) The meningeal lymphatic vessels neighbouring the dural sinuses further absorb a miniscule quantity of CSF. iv) Furthermore, CSF possesses the capability of traversing via the sieve plate encompassing the olfactory nerve, as well as is ultimately absorbed into the cervical lymphatic

vessels in the nasal mucosa [5] .The canonicalCSFcirculation is detailed in Figure 1.

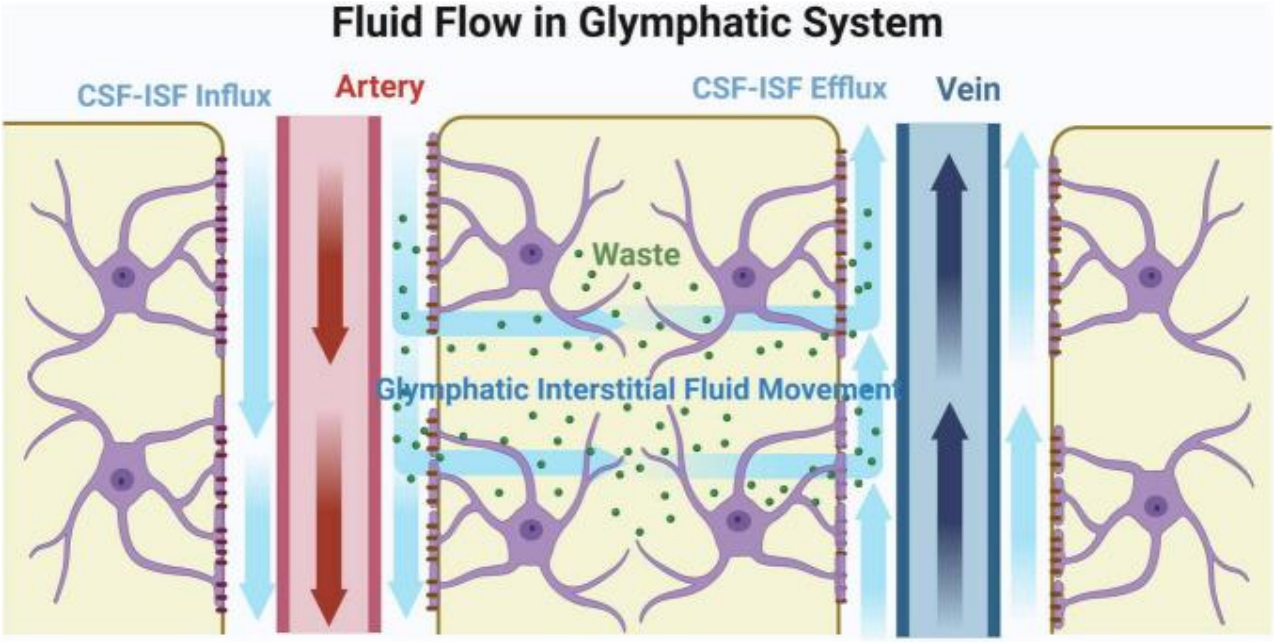



Legend forFigure. 1.
**Courtesy ref no-16** Traditional cerebrospinal fluid (CSF) circulation in brain. Original image by Illustrator (https://app.biorender.com/), modified by the author. CSF isproduced by the choroid plexus and flows from the lateral ventricles into the third ventricle through the interventricular foramen. It then moves intothe fourth ventricle via the mesencephalic aqueduct. From the fourth ventricle, CSF enters the subarachnoid space through the median and lateral apertures. In the subarachnoid space, CSF circulates around the brain and spinal cord, eventually absorbed into the dural sinuses, primarily thesuperior sagittal sinus, through the arachnoid granulations. The meningeal lymphatic vessels near the dural sinuses also take part in the absorptionof CSF. Additionally, CSF can travel along the olfactory nerve through the lamina cribrosa to the nasal mucosa, where it is absorbed by cervicallymphatic vessels.

An escalating quantity of studies detailed new observations in reference to getting insight on the CSF pathway. CSF possesses the capability of traversing the parenchyma from the perivascular spaces (PVS), of the cortex, where the subarachnoid space widens locally. Such broadening contributes to CSF to move with effectiveness as well reaching at the pericellular space (ECS) in the deep brain[6] . At the time ofsuch events , CSF gradually migrates into the interstitial fluid (ISF) at the PVS of small arteries, persistently exchanging matter with blood vessels. This event is further acknowledged in the form of CSF- ISF circulation.At the surface layer, the constitution of CSF in the form of ISF is corresponding;however, owing to CSF flows into deeper brain parenchyma along side thePVS, the free exchange amongst CSF in addition to ISF gets diminished. The alteration in fluid constitution slowly takes place with extensive exchange amongst the PVS, along with brain blood vessels via channels as well as transporters. Apart from yielding the internal mileu for neuronal cells, CSF-ISF further sustains the structure of the ECS in addition to stabilizes brain volume [7] . If the ECS surpasses the normal stretch , the structure of neuronal cells might be injured. Thus , CSF-ISF traversing needs to be controlled amongst a particular stretch.

The terminals of the CSF-ISF circulation are small veins which recycle the fluid into blood circulation [8,9] . This pathway was initially revealed in 2012. Iliff et al's[7], team injected fluorescent tracers into the cisterna magna of mouse, in addition to observed that CSF-ISF circulation works in the form of a self-purification system for brain [7], Neurotoxic wastes, for instance β-Amyloid (Aβ), were observed to be depleted via CSF-ISF flow [7]. Such event is analogous to the peripheral lymphatic system that recycles surplus fluid as well as causes elimination of metabolic wastes generated from tissues. Earlier , it was thought that the brain did not possess lymphatic system. Nonetheless, new observations illustrated that the working of CSF-ISF circulation at the PVS is analogous to the lymphatic system. Aquaporin-4 (AQP4) AQP4, a meaningful water-channel protein that is broadly expressed on the astrocytic end feet in brain, possesses vital part in the controlling

of the CSFISF circulation. Particularly, AQP4 contributes to smooth movement of fluid at PVS. Taking into account the comparable working to the lymphatic system in addition to the robust association with glia, this newly invention of self purification system in brain is referred to in the form of glymphatic system. The pathway of fluid flow in the glymphatic system is detailed in Figure 2.




Legend forFigure. 2.
**Courtesy ref no-16**-Fluid flow in glymphatic system. Original image by Illustrator (https://app.biorender.com/), modified by the author. Cerebrospinal fluid (CSF) to start with flows through the subarachnoid space surrounding the cerebral arteries as well as, into the perivascular spaces (PVS), as pointed by the blue arrow. Upon entering the brain parenchyma, CSF mixes with interstitial fluid (ISF). Aquaporin-4 (AQP4) controls fluid flow in the PVS, promoting the transport ofmetabolic waste products in addition to PVS to the veins for reabsorption. The interstitial fluid which gains entry into the the brain parenchyma ultimately leaves via the perivenous space, efficaciously removing metabolic waste products from the brain

## 2 AQP4: A Central Protein Of Glymphatic System

The AQP4 on the astrocytic end feet physically covers the brain blood vessels in the form of a meaningful aspect of blood-brain barrier(BBB) via binding with a-syntrophin on the perivascular membrane[10]. AQP4 exists in four isoforms: i) two classical forms, M1 as well as M23, in addition to ii) two newly- invented kinds,M1x , along with M23x [11]. The ultrastructure of AQP4 is detailed in the form of orthogonal particle arrays (OAPs) that escalates water permeability along with CSF flow[10].

The distribution of OAPs is basically impacted by the harmony amongst M1 in addition to M23 isoforms. An escalated percentage of M1 possesses the capability of causing dysfunctional OAPs as well as in turn diminishes the water permeability of AQP4 [12]. Additionally, translational readthrough forms a C-terminal extended variant of AQP4x that are inclusive of two readthrough isoforms, M1x in addition to M23x [11,13,14]. AQP4x possesses placement solely encompassing BBB, whereas AQP4-M1 along with -M23are not. Earlier studies have illustrated that AQP4x possesses the capacity of escalating AQP4-medulated glymphatic clearance as well as promoting Aβ elimination in the brain [13,14].

Taken together such observations point that it should be AQP4x thatsustains the fluid movement in the glymphatic system.

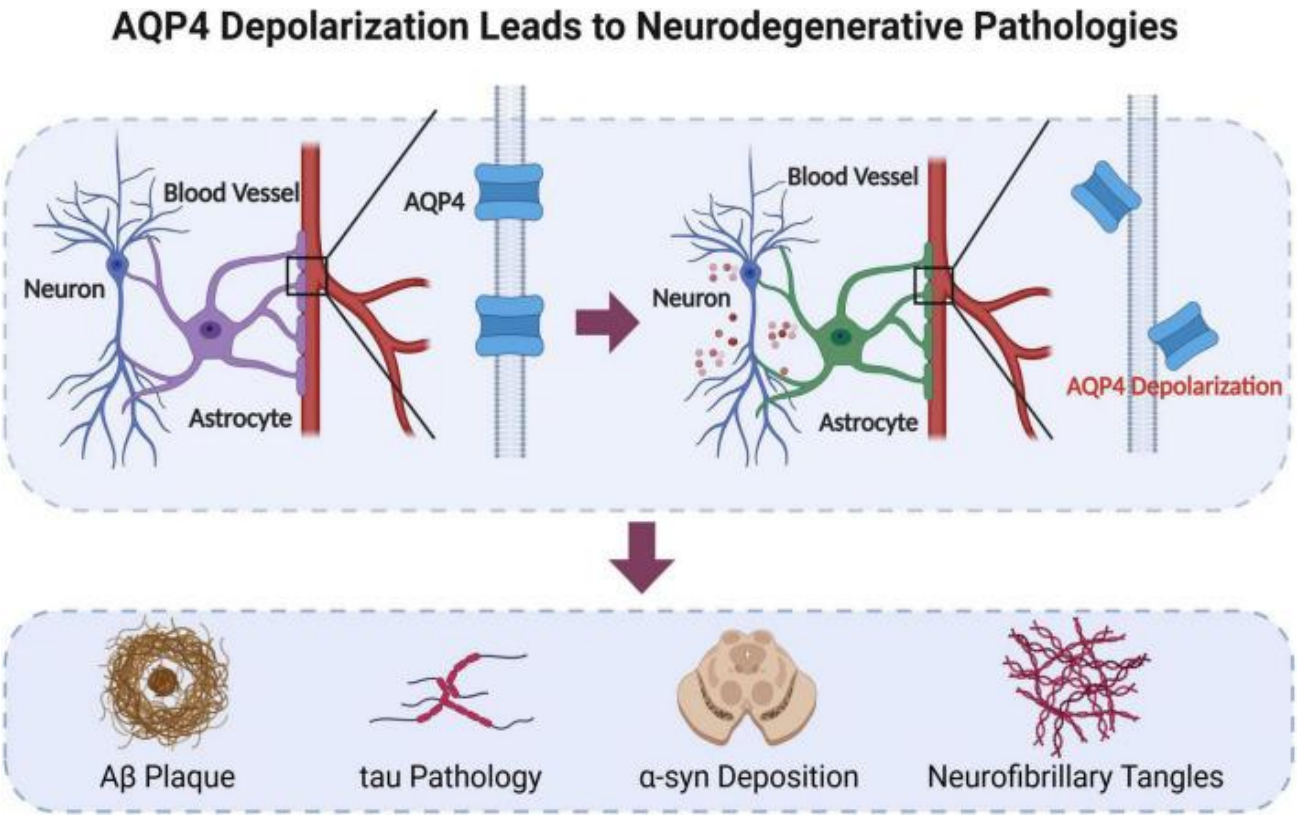
The guiding force of CSF-ISF circulation was earlier believed tobe mechanical force from cerebral artery pulsation, which directly pushes fluid to flow at PVS [15]. Nevertheless, such force lone is not adequately robust to sustain the continuous fluid flow in the glymphatic system. Hence , there must be additional guiding forces apart from the artery pulsation. The chemical force from osmosis modulated by AQP4 is believed to be pivotal in the glymphatic system [16,17]. Particularly, escalated blood pressure(BP) results in fluid efflux in PVS of arteries along with diminished BP result in influx at veins. This events generate an artery-vein gradient of osmotic pressure, guiding fluid flow at PVS. AQP4 yields an efficacious channel for fluid movement embracing as well as is believed to be the origin of the chemical force. The loose fibrous matrix of the PVS yields a low-resistance pathway, allowing fluid to move smoothly. Osmosis is robust enough to guide fluid to permeate with effectiveness from the PVS to ECS, maintainingECS structures [18]. The fluid influx as well as the greater permeability of veins facilitate protein reabsorptionin addition to deletion of neurotoxic

metabolites. Nonetheless, there are studies which question the glymphatic posit by illustrating that transportation of solute in the brain was not meaningfully influenced by AQP4 elimination as well as cardiorespiratory arrest [19].

The conclusions drawn by the researchers was that the perivascular solute transportation promoted just by the simple diffusion autonomous of AQP4 [19]. Accordingly, we embrace the presence of the glymphatic system as well as its working of solute transportation in addition to self- removal . Minimally , the general fluidmovement in the brain is extensively influenced by AQP4. Plethora of, studies have confirmed that the dysfunctional AQP4 might lead to reduction in the effectiveness of CSF-ISF flow [10,19]. AQP4 insufficiency in wild kind animals allowed for a 70% diminished cerebral fluid flow[7,12]. In the animals with medial cerebral artery ligation (MCAO), AQP4 knockout diminished CSF influx into brain tissue. Mice without AQP4 illustrated diminished CSF flow subsequent to MCAO, in addition to did not create cerebral edema amongst 15 min post-MCAO [19]. In a cerebral infarction model, TGN-020, an AQP4 hampering agent , ameliorated CSF- obtained cerebral edema [20]. Furthermore, AQP4 pathologies have been observed to be correlated with the accrual of neurotoxic proteins for instance Aβ as well as α-synuclein (α-syn), pointing that the generation in addition to propagation of neurodegenerative diseases(NDD) should be induced by the disturbance of glymphatic system. Taken together fully the corroboration pointing above collectively implies to the presence of glymphatic system. We think that mechanistic modes that lie beneath would be further clarified with the inception of newer observations with coming time.

The polarized organization of AQP4 encompassing BBB is modulated by the bonds amongst AQP4x as well as α-syntrophin. Transgenic mice without α-syntrophin illustrated AQP4 depolarization surrounding BBB[21]. Whereas mice without AQP4x diminished α- -syntrophin expression by 40%, as well as the perivascular positioning of α- -syntrophin [11,22]. AQP4 polarization is observed to be vital for maintaining the working of the glymphatic system. The clearance rate of glymphatic system meaningfully diminishes with the omission of polarized organization [23-25].

AQP4 depolarization would result in a cascade of neuropathological alteration that is illustrated in Figure 3.




Legend forFigure. 3.
**Courtesy ref no-16** Aquaporin-4 (AQP4) depolarization results in neurodegenerative pathologies. Original image by Illustrator (https://app.biorender.com/), modified by the author. AQP4 is a pivotal protein for maintaining the glymphatic system in the brain. When AQP4 becomes depolarized, the clearance working of glymphatic system decreases. This results in a cascade of pathological alterations, for instance Aβ plaque, α-synuclein deposition, tau pathology as well as neurofibrillary tangles.

Dysfunctional AQP4 along with neurodegenerative pathologies takes place in plethora of brain diseases, for instance i) cerebral infarction, ii) Alzheimer's disease, in addition to iii) traumatic braininjury (TBI) [26].

## 3. Evaluation of glymphatic system

The evaluation of the glymphatic system frequently implicates utilization of tracers as well as in vivo dynamic imaging. In the initial research on the glymphatic system, mice were injected with a fluorescent tracer into the cisterna magna[7].This aided in visualization conveniently of fluid diffusion on the brain surface under two-photon microscopy. Subsequently the brain was sectioned into slices, the fluorescent tracer was found in deep brain tissue in addition to the PVS of arteries along with was absorbed into blood circulation through veins [21]. By injecting a paramagnetic contrast agent, the CSF-ISF flow in the PVS as well as theCSF-ISF exchange in brain parenchyma possesses the capability of getting efficaciously found by utilization of magnetic resonance imaging (MRI) [21].

The gold standard modality technique modality in reference to isolating glymphatic circulation implicated intrathecal injection of a gadolinium contrast agent with contrast-enhanced magnetic resonance imaging (DCE-MRI) [22]. In contrast to two-photon microscopy,MRI possesses the benefit of recording fluid diffusion all through thewhole brain along with is non-invasive [25]. Nevertheless, the resolution of MRI is not that adequate to estimate fluid movement at the microstructural level of the brain. Diffusion tensor imaging along the perivascular space (DTIALPS), an MRI assay, is presently utilized to estimate the glymphatic system non-invasively. Apart from projection fibers as well as association fibers at thelateral ventricular body, DTI-ALPS examines water diffusivity beside the direction of PVS [27]. No contrast agent is needed in reference to methodologies as well as, accounts for outcomes obtained amongst a few minutes [28]. When injury takes place to the glymphatic system, water diffusivity beside the PVS would be diminished [29].

The ALPS index possesses the capacity of asssessment of the working of the glymphatic system [30]. It is capable of delineating the diffusion coefficient beside the vascular trajectory , estimated in the form of the ratio of diffusivity along thePVS to the diffusivity perpendicular to the main fiber bundle in addition to PVS [27,31]. DTI-ALPS is presently utilized to investigate the glymphatic system in the research of age- associated cognitive reduction. The DTI-ALPS index illustrates a robust positive association with mini-mental state examination (MMSE)in addition to Montreal Cognitive Assessment (MoCA) scores, indicating an association amongst cognitive reduction, along with diminished water diffusion beside the PVS [23]. Recently, dynamic infrared imaging has been utilized to determine the glymphatic system [32]. This modality is swifter in contrast to MRI as well two-photon microscopy for attaining images in addition to is further cheaper regarding equipment. Nonetheless, similar to two-photon microscopy, dynamic infrared imaging does not possesses the capacity of visualization of deep brain parenchyma , along with needs a craniotomy at the time of theexperiment [32].

## 4. Glymphatic system at the time of sleep

The working of the glymphatic system possesses lesser activity at the time of waking however escalated at the time of sleep [33]. Such escalation takes place owing to escalated ECS from diminished cell volume at the time of sleep, accounts for larger space for CSF-ISF flow [34].

AQP4 action is influenced by circadian rhythms, in addition to AQP4 knockdown possesses the capacity of depleting such rhythms in the glymphatic system [35]. Glymphatic flow peaks at the time of the transitory period before sleep, the manner illustrated by tracer injections in experimental animals [35]. There is a robust association amongst the working of the glymphatic system as well as sleep phases. CSF-ISFflow in addition to glymphatic clearance meaningfully escalates at the time of slow wave sleep , along with positively associate with δ-wave power [35]. Slow vascular movement at the time of non-rapid eyemovement sleep (NREM) sleep guides fluid flow along with solute transport in the PVS. The PVS escalates subsequent to rapid eye movement sleep (REM) sleep phases, greater at the time of post-sleep awakenings in contrast to pre-sleep awakenings as well, pointing particular PVS dynamics in each sleep cycle phase [33]. One night of sleep deprivation meaningfully escalates Aβ accrual in the right hippocampus as well as thalamus, whereas good -quality sleep facilitatesAβ removal from the brainv [36,37]. Sleep quality is intricately associated with AQP4 working in addition to the rate of removal of glymphatic systemvv[37,38]. Sleep-deprived mice illustratesvAQP4 depolarizationvv[37], alongvwith AQP4 expression in the amygdala as well as dentate gyrus (DG) is meaningfully diminished in mice with fragmented sleep [39]. The mechanistic modes by which clearance of toxins takes place from the brain continues to be uncharted with continuous controversial discussion going on. Compared to previous studies, recent research has displayed that sleep might not escalate the removal of brain toxins. Rather, it results in a meaningful reduction in the removal rate by about 30% [40]. This discrepancy might be credited to differences in experimental methodologies utilized in past studies,making it imperative to carry out performance of further research in reference to deeper understanding [40].

## 5. Influence of aging on glymphatic system

The working of the glymphatic system diminishes with aging.Utilization of DTI-ALPS has been done regarding assessment of the glymphatic system in elderly adults with normal cognition as well as found that the DTIALPSindex diminishes with age [41,42]. At the time of aging, the expression of glial fibrillary acidicprotein (GFAP) is importantly escalated in astrocytes, in addition to AQP4 depolarization at the PVS, resulting in a decrease inCSF influx [43]. Diminishedglymphatic working in view of aging might be an etiological factor in age-associatedneurodegeneration. The clearance of Aβ is diminishedby 40% in agedmice in

contrast to young mice[44].

The diminished working of glymphatic system is attributed to vascular remodeling at the time of aging. Aging causes dysfunctional elasticity of brain blood vessels along with declines the amplitude of arterial pulsations, leading to cerebral vascular sclerosis. Aging in a propagative manner causes inactivation of the Notch3 signaling pathway in the cerebral vasculature, disturbing the controlling of calcium signaling as well as the contractile working of such vessels [45], that might result in i) vasodilatation, ii) tortuosity, along with iii) microaneurysms in brain. Vascular remodeling ultimately diminishes CSF-ISF flow,hindering the working of glymphatic system regarding removal of the wastes from the brain [45-47]. Secondary to that, the accrual of neurotoxic wastes in the brain parenchyma would ultimately result in neurodegenerative pathologies.

Aging-stimulated immune decontrolling causes dysfunctional glymphatic system, along with leading to vascular remodeling.CC-chemokine receptor 7 (CCR7), a vital organizer of the primary immune response, is expressed by i) B lymphocytes, ii) mature dendritic cells (DCs), in addition to plethora of iii) T-cell sub-populations [48,49]. Aging- triggered hematopoietic CCR7 insufficiency possesses the capability of resulting in trauma of glymphatic system in addition to, be inimical for spatial memory[50] .DecreasedCCR7 expression in T cells with aging disturbs meningeal immunity as well as influences the working of astrocytes in addition to microglia in the aging brain. Secondary to that, the expression of polarized AQP4 in astrocytes diminishes [50,51]. CCR7deficiency further results in important alterations in gene expression in the blood endothelial cells (BEC) of brain. Together with diminished AQP4 expression,such alterations possess the capability of causing dysfunctional working of glymphatic system , along with leads to neurodegenerative pathologies[50] .

## 6. Glymphatic System and Brain Diseases

### 6.1 Alzheimer's Disease

The beginning as well as propagation of AD are intricately associated with the dysfunctional glymphatic system. This posit apart from in-depth insight of AD pathogenesis, further emphasizes new therapeutic targets for its therapy [52]. The paradigmatic neuropathological alterations of AD are inclusive of the formation of i) p-tau, ii) Aβ plaques, in addition to iii) neurofibrillary tangles which results in irreversible cognitive injury [21]. (see Figure4) The vital botherations in AD production is the dysequilibrium amongst Aβ generation in addition to removal [53]. AD patients possess a slower rate of Aβ removal, whereas Aβ generation continues to be analogous [54]. The disturbance of glymphatic system is associated with an aberrant size of PVS, as well as in turn, dysfunctional Aβ clearance, leading to the generation in addition to propagation of AD [55,56]. The researchers from team of Iliff et al. (2012) [7], injected Aβ 1-40 via the cisterna magna in addition to found Aβ removal in real time. They observed that Aβ removal was diminished by 55% in AQP4 knockout mice. In APP/PS1 mice, AQP4 knockout does not influence Aβ development however leads to a 25–50% escalation of soluble as well as insoluble Aβ accrual in the brain parenchyma[53]. Such outcomes are owing to diminished CSFISF flow caused by lack of AQP4, which diminishes Aβ removal via the BBB. Certain autopsy studies of AD patients have observed a depolarized organization of AQP4 encompassing blood vessels [53]. Studies dependent on immunohistochemistry have illustrated that enrichment of AQP4 expression in astrocyte end feet encompassing Aβ plaque regions, specifically encompassing vessels with amyloidosis [57,58] . Perivascular AQP4 depolarization has a substantially higher influence on Aβ accrual in contrast to the total elimination of the AQP4 gene in AD propagation [59]. Furthermore, AQP4 depolarization frequently takes place beside astrogliosis, pointing to a plausible association amongst the two pathological alterations[54] . Owing to CSF-ISF possesses the capacity of moving via the "olfactory nerve-nasal mucosa-nasal lymph"pathway, accrual of Aβ might takes place in the olfactory nerve as well as result in axonal injury . Intriguingly, certain AD patients illustrated smell injury in addition to diminished cognitive along with motor impairment[5] .

### 6.2 Parkinson's disease

Parkinson's disease delineate's a neurodegenerative disorderthat possesses the properties by the aberrant accrual of α-synuclein(α-syn) in neurons in addition to the deletion of dopaminergic neurons in the substantia nigra compacta [57] . In case of normal physiological situations , there is a dynamic equilibriumamongst the production , along with breakdown of α -syn. The glymphatic system might possess a vital part in clearing extracellular α-syn as well as its isomers from the brain[58]. Nevertheless, association amongst the glymphatic system in addition to the propagation of PD continues to be uncharted [59]. Restricted corroboration points that the damage to glymphatic system aggravates α-syn accrual along with diminished dopaminergic neurons [60,61] . AQP4 is further involved in the propagation of PD. Autopsy results have illustrated that content of AQP4 expression are negatively associated with α -syn levels in the neocortex of PD patients [62]. In mice with the overexpression of human A53T- α -syn, AQP4 insufficiency exacerbated the pathological accrual of - α -syn as well as facilitated dopamine neuron elimination [63]. DTI-ALPS yields neuroimaging validation of glymphatic system dysfunction in PD patients [64,65] . The DTI-ALPS index is negatively associated with cognitive decline in PD patients [65]. The decline in theDTI-ALPS index canonically starts in the left hemisphere of the brain in addition to transmits to the right hemisphere once PD propagates [65]. Sleep aberration is a frequent clinical manifestation in PDpatients. In the aforementioned manner in Part 4,the glymphatic system possesses the capability of getting escalated at the time of sleep [66]. Hence, it is posited that dysfunctional glymphatic function that results from sleep aberrations is a commonest etiological factor of PD [67]. Particularly, aberrant sleep disturbs CSF-ISF rhythmicity along with diminishes α -syn clearance in the glymphatic system, escalating inimicality to dopaminergic

neurons [35,68] .

### 6.3 Chronic Traumatic Encephalopathy

Traumatic brain injury (TBI) is a frequent phenomenon in sports, falls by mistake , as well as road traffic accidents. Numerous TBI survivors generate clinical manifestations comparable to AD along with PD years subsequent to the injury, inclusive of mood alterations, motor dysfunctions, in addition to cognitive deficiencies [69]. Such chronic neurodegenerative disorder associated with TBI are together labelled in the form of Chronic traumatic encephalopathy (CTE). Greater than 80% of brain donors from the two biggest brain banks for CTE were professional athletes in i) American football, ii) Canadian football, iii) soccer, iv) rugby, v) hockey, along with vi) boxing [70] . This points that CTE is prevalent in professional contact sports. Furthermore, CTE has been found in amateur athletes of contact sports [71]. Whereas athletes usually suffer from concussions at the time of their careers, CTE implicates greater than repetitive concussions. The risk of CTE isintricately associated with the frequency as well as magnitude of head trauma, with 30% of persons experiencing repeated head impacts(RHI) ultimately being diagnosed with CTE [72,73] . The observations of CTE neuropathology date back to an autopsy of a boxer in 1954, who illustrated dementia in addition to dyskinesia subsequent to retirement [74]. The autopsy documented i) cortical atrophy, ii) flattening of the corpus callosum, iii) ventricular dilatation, iv) perforation of the septumpellucidum,along with v) disappearance of the substantia nigra in the midbrain. Microscopically, neurofibrillary tangles (NFTs) wereobserved in the brain tissue, along with a diminishing in the quantity of neurons [74] . With the accrual of autopsy cases, these disfigurements are now believed tobe frequent in long-term survivors of TBI. Furthermore, tau pathologyis found in the brains of CTE patients [73]. Immunohistochemical staining has illustrated p-tau deposits in NFTs,neurons, as well as astrocytes, distributed besides the periphery of small vessels in the deeper aspects of the brain [75].

Additionally, 95% of CTE cases illustrate varying magnitudes of Aβ plaques in the brain [73], in addition to certain studies have further observed dilated PVS in the white matter [73]. The pathogenesis of CTE might be affected by disfigurements in the glymphatic system. A single TBI possesses the capability of resulting in elimination of polarized organization of perivascular AQP4, which later results in dysfunctional clearance working of the glymphatic system [46] . In a model of repeated moderate TBI, ipsilateral hemispheric CSF flow in addition to rate of removal were dysfunctional the day subsequent to the damage,along with the glymphatic system eliminated 60% of its working until 28 days post-injury [76]. This dysfunctionare capable of resulting in escalated agglomeration of tau proteins in the brain which got followed by neurodegeneration [77]. AQP4 knockout possesses the capability of escalating neuroinflammation post-TBI as well as influence post-injury cognitive recovery [78]. The pivotal pathophysiological events of CTE stimulated by repetitive mild TBI (rmTBI) might be inclusive of: (1) mechanical external force injures the BBB) as well as results in the elimination of AQP4 polarization surrounding blood vessels, significantly diminishing the effectiveness of CSF-ISF circulation;
(2) Astrocyte response in the brain parenchyma further escalates the resistance of CSF-ISF flow;
(3) Accrual of large quantity of neurotoxic metabolites takes place in the brain, resulting in i) chronic neuroinflammation, ii) neurodegeneration,
iii) emotional alterations, iv) cognitive in addition to v) dysfunctional memory,along with the beginning of CTE [79,80] .

### 6.4 Vascular dementia

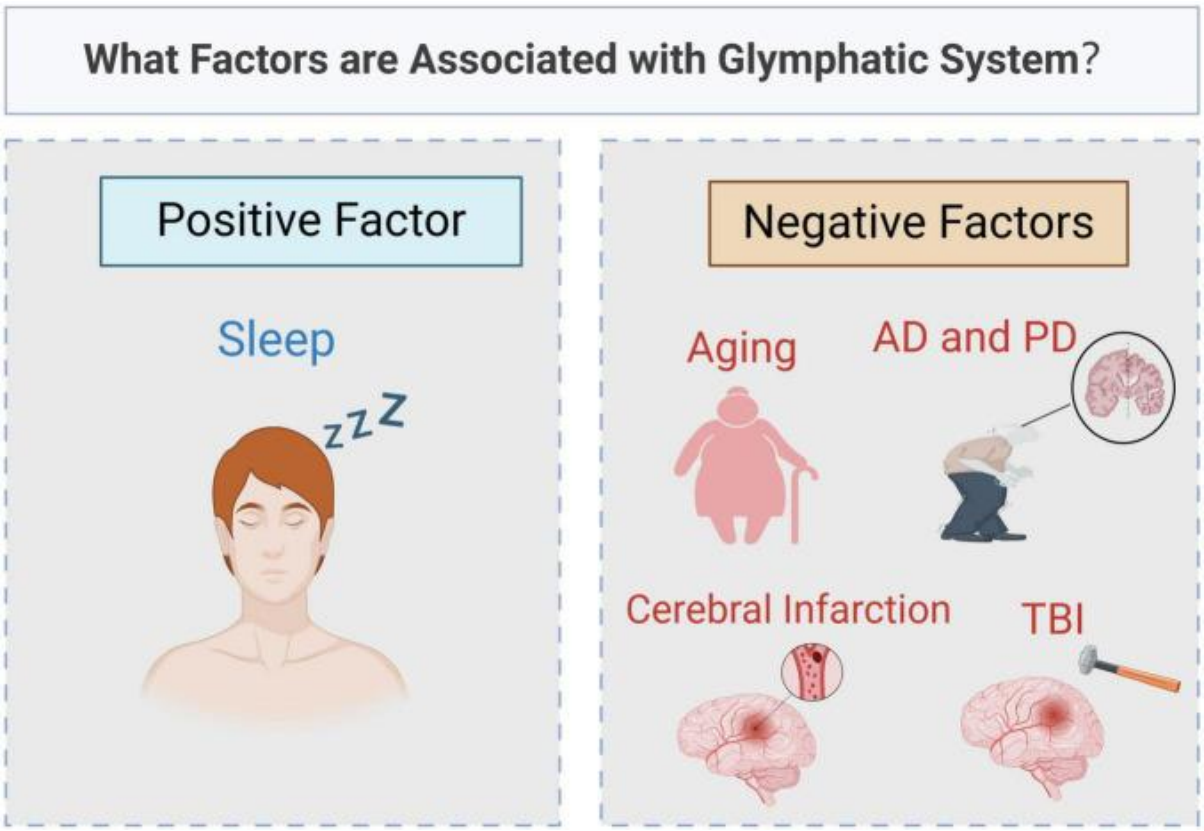
The dysfunctional glymphatic system resulting from cerebral infarction has been observed in rodent as well as non-human primate models of stroke [81], that is believed tobe intricately correlated with the propagation of Vascular dementia (VaD).AQP4 illustrated depolarization at 150 min post-MCAO, in addition to experimental animals illustrate diminished perivascular AQP4 expression [82,83]. The dysfunction would finally result in accrual of neurotoxic wastes in both influenced, along with encompassing brain areas, as well as continue to neurodegeneration in addition to cognitive impairment [84]. Besides, cerebral infarction possesses the capability of influencing the removal of neuroinflammatory mediators.For example, IL-6, generated in the centre of cerebral infarction, is canonically liberated via the glymphatic system. The diminishedglymphatic working impedes the removal of IL-6, plausibly aggravating the neuroinflammatory reaction [85]. Ipsilateral cortical CSF flow diminishes at 3h post-MCAO however itsrectification occurs at 24h post-ischemia-reperfusion [86,87]. Subsequent to 7 weeks MCAO fully , it was found thatthe fluorescent tracer in the infarct centre leaked via the glial scar along with traversed beside the perivascular space [88]. Taken together, dysfunction of the glymphatic system triggered by infarction result in protein agglomeration as well as misfolding, in addition to subsequently initiates i) local inflammation, ii) neuronal elimination, along with eventually iii) dementia [66].

## 7. Conclusions

Previously we reviewed the pivotal part of oxidative stress( OS) in the generation of neurodegenerative diseases(NDD) for instance Amyotrophic Lateral Sclerosis (ALS), Alzheimer's Disease (AD), Parkinson's disease (PD), part of Gut Microbiota dysbiosis in NDD generation as well as ischaemic Stroke development ,Role of Bile Acids in NDD generation inclusive of ALS, AD ,PD , HD in addition to priondisease. Additionally, How adenylyl cyclases (ACs) might be the therapeutic targets regarding neurodegenerative diseases(NDD) ,role of Mitochondrial Melatonergic Pathwayin generation of type 1 diabetes mellitus,& PD ,role of Bile Acids in NDD generation. Here we have further updated the manner dysfunctional glymphatic system is held responsible for the generation of NDD [89-98].

The theorized posit of the glymphatic system yields

innovative understanding into CSF-ISF circulation as well as brain homeostasis. In the glymphatic system, CSF-ISF flows from the PVS of arteries to the ones of veins for drainage. The glymphatic system is imperative for sustenance of CNS working. AQP4 is the primary protein guiding CSF-ISF circulation amongst the PVS of the glymphatic system. Apart from the mechanical force from cerebrovascular pulsation, osmotic forces produced by AQP4 further promoted fluid flow in the glymphatic system. This system possesses a significant part in waste elimination in the CNS, with its working affected by plethora of factors (Figure 4).




Legend forFigure. 4.
**Courtesy ref no-16** What factors are correlated with glymphatic system? Original image by Illustrator (https://app.biorender.com/), modified by the author. The function of glymphatic system is affected by plethora of factors. Sleep is a positive factor, buttressing activity as well as aiding in removal of waste from the brain. Compared to that,aging in addition to brain diseases, for instance Alzheimer's disease (AD), Parkinson's disease (PD), traumatic brain injury (TBI) along with cerebral infarction, possess the capacity of resulting in its diminished working.

Aging negatively influenced affects glymphatic function,while regular sleep enhances glymphatic activity as well as supports long-term brain health. Redistribution or decreased expression of AQP4 impairs glymphatic function in addition to is intricately correlated with NDD for instance AD, PD,along with CTE. We posited that AQP4 possesses the capability of therefore becoming a target for avoidance of in addition to therapy of some brain diseases.

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