A Review on

Glymphatic System: A pathway for managing endogenous metabolites in CNS

A project submitted

by

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Dedicated to my parents

Certification Statement

This is to certify that the project titled “Glymphatic System: A pathway for managing endogenous metabolites in CNS” submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy from the Department of Pharmacy, BRAC University constitutes my own work under the supervision of Sabrina Rahman Archie, Lecturer, Department of Pharmacy, BRAC University and that appropriate credit is given where I have used the language, ideas or writings of another.

Signed,

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Counter signed by the supervisor

_____

Acknowledgement

First, I would like to thank the Almighty Allah for giving me the strength and diligence to complete my work.

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Abstract

Glymphatic pathway is one of the recent discoveries of neuro pharmacology which is a brain-wide paravascular system to exchange cerebrospinal fluid (CSF) and interstitial fluid. This system is associated with the clearance of soluble proteins and metabolic neurotoxic waste products from the brain. Along with the elimination of metabolic waste products from the central nervous system, glymphatic system functions as a facilitator to distribute different compounds such as neuromodulators, amino acids, glucose etc. Recently, it has been observed that suppression of glymphatic system plays a pivotal role in different neurodegenerative diseases like Alzheimer's disease, stroke, Parkinson's disease, Huntington. Moreover, scientists have explored the association of glymphatic system with sleep which clearly reflects the importance of sleep and the activation of the glymphatic system during sleep. The effect of aging and traumatic brain injury on the functions of glymphatic system has also been discovered and mentioned in recent researches as well. Since the concept of glymphatic system is relatively a new addition in to the science of neuropharmacology, the present study is aimed to review the structural components, mechanism of action, factors related to glymphatic system and the significance of glymphatic system associated with neurodegenerative diseases. Further characterization and research on glymphatic system may open up new doors for the treatment of different neurodegenerative diseases. Therefore, the aim of this review paper is to assemble available information regarding glymphatic system and present it in a concise and more constructive manner.

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List of acronyms

AD= Alzheimer's disease

apoE= apolipoproteinE

Aβ= Amyloid beta peptide

ALS= Amyotrophic lateral sclerosis

APP= Amyloid precursor protein

AQP4= Aquaporin water channel

CSF= Cerebro spinal fluid

CNS-= Central nervous system

DOTA-GD= Gadoteric acid

GABA= Gamma-amino butyric acid

IF= Interstitial fluid

MCI =Mild cognitive impairment

MS= Multiple sclerosis

MRI = Magnetic resonance imaging

NE = Norepinephrine

PD = Parkinson's disease

SAH= Subarachnoid hemorrhage

Introduction

Clearance of abundance liquid and interstitial solutes is basic in the case of tissue homeostasis. In the peripheral tissues, various dissolvable materials, like proteins and other liquid from the interstitial space come back to the general circulation through the lymphatic framework (Liao & Padera, 2013). This system is extended through all parts of the fringe tissues or peripheral tissues. Moreover, the rate of metabolism is correlated with these lymph vessels. In spite of the fact that the cerebrum and spinal line are portrayed by a high metabolic rate (Weed, L. H. 1997), and synaptic transmission is very sensitive to changes, the focal sensory system or CNS totally needs a functioning lymphatic system. A couple of more researches have talked about that, there could be a lymphatic system-like structures in dura , which might not be lined by endothelial cells. In This paper it is tend to shed light on the theory that, CNS does not have a lymphatic framework and also it has been mentioned that by which way the waste products from CNS is being cleared. At long last ,it is also discussed how recently discovered Glymphatic system, which is hypothesized to mirror the activities of lymphatic system for CNS, might also be regulating proteins and lipids while eliminating waste products (Wang et al.,2012).

1.1 What is lymphatic system:

Lymphatic system being a part of the circulatory system, is also a vital part of our immune system. This system comprises of a web of vessels a clear fluid named lymph is carried throughout our body. This system was first discovered by a scientists named, Olaus Rudbeck and Thomas Bartholin respectively in the late 70^{th} century (Gyton, Hall & Edward, 2005). Our circulatory system, is a closed system but the lymphatic system is not. An average of 20 liters of blood is formed by our circulatory system in every 24 hours. In which, by slim filtration, the plasma is expelled while the platelets remain. Approximately, 17 liters of the plasma are reabsorbed specifically into the veins, while the other three liters remain in the interstitial liquid. One of the prime elements of the lymph framework is to give an embellishment return course to the blood for the surplus three liters (Saladin & Kenneth, 2012). The other fundamental property is that of resistance in the insusceptible framework. In many ways the lymph resembles blood plasma containing lymphocytes and other white platelets. It additionally contains toxic items and cell trash together with microscopic organisms and proteins. Related organs composed of

lymphoid tissue are the destinations of lymphocyte creation (Ma, Ineichen, Detmar, & Proulx, 2009).

Lymphocytes are gathered in the lymph hubs. The spleen and the thymus are the lymphoid organs of the immune system. The tonsils are also lymphoid organs that are connected with stomach framework. The main cells of lymphoid tissues are lymphocytes, while having other sorts of cells for support (Grada & Phillips, 2017). The framework basically incorporates every one of the structures related to generation of lymphocytes which is the cell part of lymph. This system also incorporates the bone marrow, and the lymphoid tissues in the stomach (Ma et al. 2009) This system comprises of lymph related organs, a framework of vessels, and the clear liquid called lymph (Ye, He, Wu, Shang, & Wang, 2017).

1.1.1 Elements of lymphatic framework:

The lymphatic system has different interrelated capacities:

- It discharges interstitial liquid from tissues (Antila et al., 2005).
- Unsaturated fats from the stomach related is transported by this framework (Antila et al., 2005).
- White platelets are transported from lymph ends to the bones (Antila et al., 2005).
- The lymph transports antigen-showing cells, for example, dendritic cells, to the lymph hubs where an insusceptible reaction is invigorated (Antila et al., 2005).

Before it was presumed that the dissemination of interstitial waste from the white matter of brain takes place in the ventricular cerebrospinal liquids in men. Tracers go along with the perivascular spaces to the exterior surface of our brain into the CSF (Kulik *et al.,*2008). Moreover it was said that there are anatomical pathways by which mass liquid waste of our brain could go along to the perivascular spaces from the dark matter. From perivascular spaces to the leptomeningeal courses and afterward into the CSF (Purves , Augustine & Fitzpatrick, 2001). The subarachnoid space may enable directional flow of CSF to happen and anatomical pathways to exist by comperentalisation. Through which specific stream for lymphatic waste of cerebrum interstitial liquid and provocative cells could happen. In any case, In previous studies it is practically demonstrated that human brain contains a drainage framework for this liquids which resembles

the functions of the lymphatic system in other parts of human body (Iliff , Wang , Liao et al., 2012).

1.2 Brain liquids:

The cerebrum comprises of four liquid compartments: cerebrospinal fluid (CSF), interstitial liquid, intracellular liquid, and the blood vasculature (Damkier, Brown, & Praetorius, 2013).

1.2.1 Cerebrospinal fluid:

Cerebrospinal fluid or CSF is a body fluid found in the cerebrum and spinal cord which is almost colorless or. It is originated from the choroid plexuses of the ventricles of the cerebrum. It cradles or cushions the brain as a pad , giving essential mechanical strength and immunological protection to the cerebrum into the coroty (Wright, et al. 2012). The cerebrospinal fluid also works as an essential component by which the cerebral blood flow regulates automatically. The CSF also possesses the subarachnoid space which is located amongst the arachnoid mater and pia mater. It also possesses the ventricular framework around and the brain and spinal line. It constitutes the substance of the ventricles, storages, and sulci of the cerebrum, and additionally the focal trench of the spinal cord (Keep & Jones, 1990).

It has been observed that that here is a probable association from the subarachnoid space to the bony labyrinth of the internal ear by means of the perilymphatic pipe where the perilymph is continious with the cerebrospinal liquid. The CSF resembles blood plasma and is to a great extent like it, aside from the fact that CSF is almost protein-free contrasted to plasma and has some unique electrolyte levels. Moreover CSF has a higher chloride level than plasma, and a proportional sodium level (Damkier, H. H., Brown, P. D & Praetorius, 2013). CSF holds roughly 0.3% plasma proteins, or around 15 to 40 mg/dL, contingent upon the site from where it is sampled. As a rule, lumbar or cisternal CSF contains more albumin like globular proteins than ventricular CSF (Damkier, H. H., & Praetorius,2012). This constant stream into the venous framework weakens the centralization of bigger, lipid-insoluble particles entering the cerebrum and CSF (Iliff, J. J., & Nedergaard ,2013). CSF is ordinarily free of red platelets, and at most contains just a couple of white platelets. Any white platelets are higher in number in CSF it may constitute pleocytosis (Keep & Jones, 1990).

Absorption:

Truly, the assimilation of CSF into the circulating blood is the most striking over the arachnoid villi. From a simply anatomical perspective, CSF most evidently drains into the vascular framework by these arachnoid villi. The thought of the arachnoid villi being the significant site of CSF retention is really in view of the early trials of researchers named Key and Retzius who infused hued gelatin into the CSF space of human corpses (Keep, R. F., & Jones, 1990). They revealed the circulation of the color all through the whole CSF framework and its entry over the arachnoid villi into the venous sinuses (Kulik, Kusano, Aronhime, Sandler, & Winn, 2008). Extensive segments of CSF might be consumed into the cervical lymphatics (Wright, Lai, & Sinclair,. 2012). The perineural subarachnoid space of cranial nerves, which is associated with the cranial CSF space, was recommended as a pathway for the drainage of CSF into the lymphatics of the extracranial delicate tissue at the skull base (Wright et al. 2012).

Properties of CSF:

The cerebrospinal fluid or CSF has several distinctive properties. The primary properties of CSF are mentioned below.

Lightness: Genuinely the human brain weights around 1400– 1500 grams; be that as it may, the cerebrum suspended in the CSF is proportionate to a net weight of 25-50 grams (Prince & Ahn, 2013). The brain in this manner remains in nonpartisan lightness. By this manner the brain can keep up with its thickness and it is not debilitated by its own weight. If the brain was impaired by its own weight then it could turn off blood supply while destroying the brain cells in the areas without CSF (H. H. Damkier, Brown, & Praetorius, 2013).

Protection: This fluid shields the cerebrum tissue from the damage if it gets hit or injured, by giving a liquid cushion that goes about as a safeguard from a few types of mechanical injury (Wright, Lai, & Sinclair, 2012).

Avoidance of cerebrum ischemia: Brain ischemia is avoided by diminishing the measure of CSF in the restricted space inside the skull. This declines the additional weight of the CSF and encourages blood perfusion in the brain (Iliff & Nedergaard, 2013).

Homeostasis: CSF takes into consideration direction of the conveyance of substances between cells of the brain, and neuroendocrine variables, to which slight changes can make issues or harm the sensory system. For instance, high glycine fixation disturbs temperature and pulse control, and high CSF pH causes tipsiness and syncope (Helle Hasager Damkier & Praetorius, 2012).

Waste clearance: CSF takes into consideration about the expulsion of waste items from the brain and is basic in the cerebrum's lymphatic system (Wright, Lai, & Sinclair, 2012). Metabolic waste items diffuse quickly into the CSF and are expelled into the circulatory system as CSF is absorbed (Thrane, Rangroo Thrane, & Nedergaard, 2014).

Source of CSF:

In human brain CSF is produced mainly by a network of blood vessels called the choroid plexus in the lateral, third and fourth ventricles. CSF production is a continuous process. In both people and mice CSF is recreated around four and 12 times in every 24 hours, respectively , and the aggregate volume of CSF in human and in mice is kept steady by expulsion of CSF continuously (Weller, Subash, Preston, Mazanti, & Carare, 2008). It is depleted into the fringe lymphatic framework by efflux through the olfactory globule and along cranial and spinal nerves (Jacobs et al., 2008). The significance of the arachnoid granulations in CSF expulsion has recently been addressed (Helle Hasager Damkier & Praetorius, 2012). Thus, the cranial, spinal nerves and the olfactory courses can be the vita efflux means for CSF (Helle Hasager Damkier et al.2012). From the established or classical model, it can be stated that 80-90% of the total CSF is generated by the choroid plexuses (Christensen, Nguyen, Pedersen, & Damkier,2013). In a rodent study it was found that 6.7% of total amount of proteins existing in choroid plexus, transports ion through membranes. This is a bigger extent than in the kidney, where the extent of proteins evaluated to be engaged with particle transmembrane transport action was 4.8 %. But as the results of experimentations, differs from the classical models of CSF production, a basic new model for CSF hydrodynamics has been developed. Essentially, it has been recommended that CSF production happens by filtration and the fluids are fluxed through capillary walls. and that

the separate volumes of CSF and interstitial liquid chiefly rely upon hydrostatic and osmotic forces between the CSF and cerebrum parenchyma .Which are made by proteins and inorganic particles over the capillary layer (Saunders, Habgood, & Dziegielewska, 1999).In the same way, under physiological conditions, water get separated from capillaries having higher pressure, to the interstitial liquid and Cerebrospinal fluid. Because of low permeability of the electrolytes in the plasma, the retention of electrolytes like Na^+ or Cl^- takes place. Thus an counter osmotic pressure is created which opposes the water filtration (Brown, Davies, Speake, & Millar, 2004).For that reason plasma reaching the low pressure venules, reabsorbs water from CSF and interstitial fluids. As per this more up to date speculation, these two fluids are consistently exchanging and the volume possessed by every compartment relies upon hydrostatic and osmotic powers. Recently some researchers talked about a third speculation that depends on existing experimental information. Their model endeavors to join the two previously mentioned theories and considers the confirmation of the glymphatic pathway discussed below(Kulik, Kusano, Aronhime, Sandler, & Winn, 2008). This scientific model is said to be able to evaluate the impacts the osmolarity of extracellular space, blood, and CSF on water motion in the cerebrum. Which sets up relation amongst osmotic imbalance characteristics and pathological conditions, for example, hydrocephalus and edema (Kulic et al. 2008).This novel approach requires approval, yet could end up providing interesting understanding into CSF flow during typical physiology and pathology (Wright, Lai, & Sinclair, 2012).

1.2.2 Interstitial Fluid:

The interstitial space comprises of connective and supporting tissues and is situated outside the blood vessels, lymphatic vessels and parenchymal cells. Basically the interstitium can be separated into two compartments: the interstitial liquid and the extracellular network/matrix (ECM). The tissue cells of human and other multicellular animals is surrounded by this fluid called ISF or interstitial fluid (Liao & Padera ,2013). The primary component of the extracellular fluid is ISF, while having other components like transcellular fluid, lymph and blood plasma.(Warwick, Roger Peter & Williams,2005) This fluid is found in the spaces amongst the cells. In an average, a man has around 10 liters interstitial liquid, giving the cells with supplements and works as a method of squander elimination. Plasma and interstitial liquid resembles each other (Wang Z & Ying Z,2012).Water molecules, ions, and other small particles

that sequentially and consistently get exchanged amongst plasma and interstitial fluids, are the reasons for their resemblance. These particles get exchanged by the the walls of the capillaries. Plasma, being the significant segment in blood communicates widely with ISF with the help of pores and intercellular clefts in the capillary endothelium. Interstitial fluid is formed by filtration The capillaries form ISF by filtration, and then it is taken away by the lymphatic vessels (Anastasiou, Lorentz, Stein, & Mitchell, 2014).

1.2.3 Brain Vasculature:

The brains arrangement of blood vessels has a few extraordinary highlights that makes it different from the blood arrangement of the remaining parts of the body (Iliff et al., 2012).The whole blood supply of the cerebrum and spinal cord relies upon two arrangements of branches from the dorsal aorta. The vertebral courses emerge from the subclavian arteries, and the inner carotid arteries, which are branches of the regular carotid conduits. The vertebral courses and ten medullary arteries that emerge from segmental parts of the aorta, give the essential vascularization of the spinal cord. While The anterior arteries and the posterior arteries merge to make the medulary arteries (Iliff et al., 2012). In the event that any of the medullary courses are discouraged or harmed, for instance, during stomach surgery. The blood supply to particular parts of the spinal cord might get compromised. The results of neurological harms will be whether the supply to the back or anterior artery is intruded. If the supply in posterior arteries are blocked then it results in reduced sensory capacities, while loss of the front supply frequently causes motor deficits (Kulik, Kusano, Aronhime, Sandler, & Winn, 2008). The blood vessel cerebral dissemination comprises of an anterior cerebral flow and a posterior cerebral flow provided by the interior carotid arteries and the vertebral arteries, respectively. The anterior flow, incorporates the center and front cerebral arteries, which communicate with the posterior blood flow, the basilar artery and back cerebral arteries. This occurs with the help of or via anterior and posterior conveying conduits at the Circle of Willis (Engelhardt & Ransohoff, 2012) **.**From the Circle of Willis, the anterior flow supplies to the neocortex of the brain, in the cerebral hemisphere, while the posterior dissemination supplies the brainstem and cerebellum (Zlokovic, 2011).At the cortical surface, cerebral conduits extends to pial arteries going through the CSF-containing subarachnoid space and the subpial space. In the brain parenchyma the pial arteries

are found, going through a transition and penetrate into arteriols. This creates a perivascular space filled with CSF named Virchow-Robin space (Engelhardt & Ransohoff, 2012).

Research Methodology

Extensive literature review was conducted to extract all the information used in this review paper. Information was obtained from various credible sources including different peer-reviewed journals, online scholarly database, books, newspapers and magazines. Some the various journals from which the information was collected are mentioned below:

- Neurochemical Research
- The journal of Experimental Medicine
- Neurology Reviews
- Neuropathology and Applied Neurobiology
- The Journal of Neuroscience
- Rejuvanation Research
- Lancet Neurol
- Frontiers in Neurology
- Neurological Science
- Current opinion in Neurology
- JAMA: The Journal of the American Medical Association
- Journal of Neurology

3.1 What is Glymphatic system?

The lymphatic pathway system is a very important system which plays immunological functions in our body through fringe organs. This system can function parallel to our blood circulation framework to give an auxiliary flow (Zlokovic, 2011). With the help of this flow, interstitial liquids, proteins and other metabolic waste items from the fundamental tissues, goes into the blood. The proficient expulsion of dissolved proteins from the interstitial liquid is basic to the control of both colloidal osmotic pressure and homeostatic direction of the body's fluid volume. The significance of lymphatic stream can be clearly understood when the lymphatic framework stops functioning properly (Carare et al., 2008). It is believed and proved that the CNS lacks a functioning lymph network. Thus it was a long-asked question that how the delicate neural tissues in the CNS, function without a functioning lymphatic network. Also how the extracellular proteins and other wastes are being cleared. Glymphatic system was at first accepted to be the entire response to this inquiry (Björkhem, Meaney, & Fogelman, 2004).Many researchers have been conducting works and found that actually the dural sinuses and meningeal supply routes are provided with lymphatic vessel like structures which does the work for CNS. and this vasculature forms an interacting pathway to the glymphatic system (Weller, Subash, Preston, Mazanti, & Carare, 2008). In 2012, a two-photon microscopy experiment done in mice first showed the dynamics of the glymphatic system (Hawkes et al., 2011).By infusing CSF marked with fluorescent tracers into the cisterna magna, demonstrated that CSF quickly enters thecerebrum along the cortical pial courses. Then it enters into the Virchow-Robin spaces beside infiltrating arterioles (Hawkes et al., 2011). It was apparent that the CSF tracers, instead of being diffusely and haphazardly circulated in the parenchyma, entered the parenchyma through a periarterial pathway encompassing the vascular smooth muscle cells. and *ex vivo* experiments demonstrated that the tracers quickly left the cerebrum along central deep veins and the lateral, ventral and rhinal veins (Kulik et al., 2008).The accompanying experients demonstrated that the movement of CSF through the brain parenchyma encouraged the clearance of interstitial solutes to perivenous drainage pathways (J. J. Iliff et al., 2012).When CSF moves into the brain parenchyma it regulates interstitial fluid influx inside the brain tissue. Then the interstitial fluid goes to perivenous space. From where it gets excreted out from the brain toward the cervical lymphatic system like structure. This structure that resembles lymphatic system is macroscopic and highly polarized in nature. This system facilitating fluid-fluxes is called or named

Glymphatic system. CSF and interstitial fluid gets rapidly interchanged by this network (Jeffrey J. Iliff & Nedergaard, 2013). As proposed by Dr. Weller and partners such a plainly visible leeway component of interstitial solutes might be of specific significance for neurodegenerative infections including Alzheimer's disease, which is described by the gathering of proteins, including amyloid plaques and tau tangles. (Weller, Subash, Preston, Mazanti, & Carare, 2008).To assess if β amyloid is cleared by the glymphatic pathway, (Iliff et al.,2006) infused fluorescent or radiolabeled amyloid b1– 40 into the mouse striatum, and found that b-amyloid was quickly cleared from the mouse brain along the glymphatic efflux pathway. Thus It was suggested that the paravascular glymphatic system which is driven by AQP4 channels initiates a noteworthy c pathway by which interstitial fluid and other solute gets cleared from the brain tissue (Engelhardt & Ransohoff, 2012).

3.1.1 Anatomy of glymphatic system:

The glymphatic system has parts which are linked with each other in a series (Bell & Gaillard, 2014) :

1. Para-arterial CSF influx pathway
2. Parenchymal pathway
3. Paravenous CSF interstitial fluid clearance pathway

Para-arterial CSF influx pathway:

CSF enters the parenchyma of our brain through the Virchow-Robin spaces. This space is surrounded with arteries that are perforated. The Propulsion of CSF depends on the pulse waves created by the arteries. Influx routes in the pineal gland and pituitary gland ends has been discovered recently located around all penetrating arteries (Engelhardt & Ransohoff, 2012). After that CSF then goes along the arterial smooth muscle basement membrane, that are located around the blood vessels. And from here into the interstitial fluid section of the brain parenchyma (Hu et. al., 2013). Compounds with less molecular weight appears in the CSF that

enters to the interstitial space. While the larger ones gets stuck in the perivascular space (Bell & Gaillard, 2014).

Parenchymal pathway:

Interstitial fluid reaches the veins from the arteries passing along the brain parenchyma (Yang et al., 2013).

Para venous CSF interstitial fluid clearance route:

Drainage of the interstitial fluid from brain parenchyma to the veins needs a driving force. Aquaporin-4 (AQP4) water channels, potassium channels and excitatory amino acid transporter channel works as the driving forces for this transport (J. J. Iliff et al., 2012).

3.1.2 Mechanism of action of Glymphatic system:

CSF gets transported along the periarterial spaces of the brain parenchyma through convective flow. At the same tie ISF exits the perivenous space and flows to the cervical lymph framework or the glymphatic system (Engelhardt & Ransohoff, 2012).This whole process requires energy that comes from various mechanisms. CSF is produced continuously by the choroid plexus that puts a pressure and this pressure directs the fluid movement from the ventricular system to the subrachnoid space. Moreover it is demonstrated by a few professionals that, respiration is not vital in the development of CSF through the water channel (Murfee, Skalak, & Peirce, 2005). Without CSF entering to the perivascular space, ISF– CSF clearance by glymphatic pathway is not possible. Utilizing mice to distinguish arteries from veins, it was exhibited that tracers of CSF goes to the arteries from the pial surface and then to the cortical surface. After that, it goes down to enter the penetrating arteries. Penetrating arteries goes perpendicularly inside the brain and ends up at capillary beds (Zhu, Bergles, & Nishiyama, 2007).Specific to arteries, smooth muscle cells generates pulse waves that drives the CSF along the perivascular space (Stoodley, Brown, Brown, & Jones, 1997). Dobutamine, which is an adrenergic drug, was given to some mice, and it increased the pulsatile effect noticeably (Sohet & Daneman, 2013).Thus larger

amount of CSF was cleared from the perivascular space to the brain tissue. The same group of mice showed the exact opposite effect when arterial pulse waves were destroyed by ligating the arteries. This recommends glymphatic movement, at least to some extent, is driven by blood vessel generated pulse waves and clarifies the reason, why perivascular convergence happens specially around pulsating arteries and not cerebral veins (Sohet & Daneman, 2013).

3.1.3 Various factors affecting the rate of flow:

We have previously known that AQp4 or aquaporin channels are essential or vital for glympgatic activity (Engelhardt & Ransohoff, 2012). In a test done and published on journal of neuroscience, on 2014 used some mice which were genetically designed to not have these auaporin channels. Also some mice which went through traumatic brain injury were used (Zhu, & Nishiyama, 2014). As a result, it was seen that glymphatic activity in both this kind of mice reduced down to 60% than required. And those mice not having aquaporin channels, developed neurodegeneration with time (Zhu, Bergles, & Nishiyama, 2015). Another vital factor found for glymphatic flow is the amount of interstitial space volume, which is proved to be 60-80% greater when we are asleep. Dr. Benveniste said, Normal sleep and certain kind of analgesics significantly increment interstitial space volume (Hawkes et al., 2011).In the same way, when the dozed mice are awake state, it pointedly lessens the glymphatic stream. Some researchers also said , sleep cycle might be an outcome of the increased evacuation of conceivably neurotoxic waste items that amass in the conscious CNS (Jeffrey J. Iliff et al., 2013).It was founf out by Dr. Beneviste and her group that, infusion of norepinephrine antagonists into spinal theca of some mice showed intense glymphatic activity, even when they were awake. They contemplated glymphatic leeway in mice anesthetized with dexmedetomidine, which prompts a state like stage 2 sleep, versus the inhalational isoflurane. Glymphatic activity was considerably more noteworthy in rodents that got dexmedetomidine (Beneviste et al., 2012).

3.1.4 Lipid Transport by the Glymphatic System:

The weight of our cerebrum is 2% of our body's aggregate weight, but it contains more than 25% of our total cholesterol (Bjorkhem & Meaney, 2004). In spite of the brain having higher amount of cholesterol, the blood–brain barrier counteracts the convergence of lipids, lipoproteins and cholesterols, to the cerebrum (Sohet & Daneman, 2013). But the peripheral tissues don't function the same way, while let the cholesterol get secreted by the liver. Our brain tends to synthesize all the cholesterol, starting from the beginning by its own. Hydroxylation to 24-OH cholesterol eliminates over-abundant cholesterol from the brain while circulatory system sinks the excess cholesterol .In-fact Most of the 24-OH cholesterol in the body is found in our cerebrum (J. J. Iliff et al., 2012). Our brain has its very own mechanisms to transmit the excess lipids , using high density carrier particles. These particles transports lipids out from our brain and are secreted from glial cells (Jeffrey J. Iliff et al., 2013). Discharge of these high weight lipoprotein particles from glial cells is reliant on proteins named 'apolipoproteins', mainly E and J. these proteins gets attached with lipids and permits conveyance of lipids, through lymph or circulatory system (Jeffrey J. Iliff et al., 2013).They also clears hydroxylated cholesterol and b-amyloid while the allel 4 of Apolipoprotein is a noteworthy hereditary hazard factor for Alzheimer's disease (Carare et al., 2008). The amount of apolipoprotein is higher around blood vessels and at the pial surface. Choroid plexus also seem to produce some of the amount of this particular protein (Engelhardt & Ransohoff, 2012).Thus we can see that the transportation pathways for these proteins and CSF are basically the same. Which recommends that glymphatic framework plays a vital role in transporting the lipids. Infusions of lipophilic CSF tracers demonstrated that few distinctive lipophilic particles of sizes 1 kDa, and a bigger 3 kDa hydrophobic atom, all entered the cerebrum by means of periarterial courses and left perivenously, like hydrophilic atoms (Jeffrey J. Iliff et al., 2013). Along these lines the glymphatic framework was similar to the lymphatic framework that vehicles the dietary fat, also cholesterol, accumulated in the intestine. In any case, just the 1 KDa lipophilic tracers could diffuse into cerebrum cells though the while the bigger tracers were restricted to the perivascular courses (Murfee, Skalak, & Peirce, 2005) . Thus it can be said that, the glymphatic framework plays an important role distributing the lipid molecules through the brain. And Astrocytes, seems to be playing double role, while releasing Apolipoprotein E, it is keeping up the interstate for lipid appropriation, by the glymphatic framework (Sohet & Daneman, 2013).

3.1.5 Amyloid β transport by Glymphatic system:

In recent studies done on mice proposed that the Aquaporin4 (AQP4) subordinate glymphatic pathway plays a major role in clearing the interstitial space from dissolvable amyloid beta protein. It is also seen that, In mice, Aβ is excreted along perivascular pathways, and Aβ freedom was diminished by 55– 65% in mice with a functioning AQP4 or aquaporin4 water channel while in other mice it happened to be much less (Zlokovic, 2011) also, glymphatic clearance was seen to be diminished by 40% in older mice in respect to young mice, proposing that the glymphatic pathway might be debilitated with age (Zlokovic, 2011). Factors that highly influences glymphatic-ISF flow, incorporate atomic size, blood vessel throb, AQP4 articulation and confinement, lastly sleep. Following subarachnoid infusion, bigger tracer particles diffuse slowly to the parenchyma than the smaller particles. While dissolvable perivascular Aβ can cross the 20 nm astroglial clefts (Jeffrey J. Iliff et al., 2013). The pulse waves created by the blood vessels is basic for disseminating CSF to the interstitium (Pop et al., 2013). On the contrary it can be said that, vascular smooth muscle cells can take up the CSF rich in Amyloid β, within the sight of slower glymphatic flow, which causes for reduced arterial pulse waves. Which on the other hand can result into and protein misfolding and accumulation (Moretti et al., 2012) . This is one way by which Aβ may accumulate in the periarterial space and the subsequent Aβ amassing additionally diminish glymphatic clearance (Irimia et al., 2012). In mice with non-functioning Aqp4, interstitial leeway is lessened by around 70%, bringing about a 55– 65% diminishment in Aβ clearance like in Alzheimer's disease, AQP4 articulation could be diminished, and interstitial Aβ decreases AQP4 expression, which can prompt accumulation of Aβ. In traumatic brain injuries, AQP4 articulation is expanded in, thus mislocalization of AQP4 from perivascular synaptic endings to the astroglial cells happens. Which bring about diminished perivascular AQP4 accessibility, decreasing Aβ expulsion (Jeffrey J. Iliff et al., 2013). Both TBI and AD are related with inflammation of the blood vessels around our brain and these progressions may to some extent clarify the connection between these conditions (Pop et al., 2013). It is seen that in mice, the clearance of Aβ increases two folds while they are asleep (Shaw et al., 2002).This phenomenon of Aβ clearance increases the volume of interstitial space by 60-70%. And it is regulated by an adjustment in astroglial cell volume in response to adrenergic signaling (Mconnel, 2011). This extension of the extracellular space was caused by sleep itself instead of circadian rhythms, as it happened during typical rest, as well as during

anesthesia (Shaw et al., 2002).The current works in this field shows that the glymphatic framework quickens ISF-to-CSF mass flow though it may be incompletely in charge of the expulsion of the Aβ during sleep. The percentage by which glymphatic system assists in this clearance is near 40-45%. This can be computed from the clearance rate consistent data (Carare et al., 2008), while the other 60-55% is believed to be cleared by quickened Blood Brain Barrier transport of Aβ. Also as we have previously discussed that glymphatic system works greatly while the brain is not active, it also flushes the accumulated Amyloid beta towards blood brain barrier during sleep. Because of the glymphatic framework flushing Aβ toward the BBB during sleep, it could in another way clears amyloidbeta through BBB by expanded glymphatic flow (Shaw, Jauch, & Zemlan, 2002).This system may also clears the Aβ through the BBB by means of different systems, for example, sub-atomic changes , as observed with AD-defensive physical and subjective action in mice. These discoveries may mostly clarify how impaired sleep cycle can increase the risk of AD (Jeffrey J. Iliff et al., 2013).

3.2 Glymphatic system works mainly during sleep:

3.2.1 What is sleep?

Sleep is a normally repeating condition of mind and body, portrayed by modified consciousness, moderately restrained sensory activity, restraint of almost all intentional muscles, and diminished interactions with surroundings (National Sleep Foundation, 2006). It is recognized from alertness by a diminished capacity to respond to stimuli, yet is more effectively reversed than the condition of being comatose. Sleep is critical to various brain capacities, including how neurons communicate among themselves. In fact, our mind and body remain surprisingly dynamic while we rest. Everybody needs sleep, however the biological importance is still a secret. Sleep influences practically every sort of tissue and framework in the body, from the mind, heart, and lungs to digestion capacity, mood, immunity and prevention of diseases. By many researches done on human sleeping patterns, it has been found that, constant lack of sleep, or getting low quality sleep, makes a person vulnerable to various diseases, including hypertension, cardiovascular ailment, diabetes, depression , corpulence etc (Madsen et al., 1991).

While asleep, the majority of the body's frameworks are in an anabolic state, restoring the nervous, muscular, immune and sceletal frameworks.thus sleep regulates and helps these are vital procedures that look after mood, memory, psychological execution, also takes part in the execution of endocrine system and immune systems (Seigel, 2005).Recent discoveries shows that sleep plays an vital role by evacuating toxins and other particles in our cerebrum that develops while we are conscious (National Sleep Foundation, 2006).

3.2.2 Relationship between Sleep and Glymphatic system:

The most important physiological changes in sleep occur in the brain. Though why sleep is so important biologically, it is still indistinct (Madsen, et al., 1991). Energy metabolism of our brain decays only by 15– 25 % while we are asleep, which recommends that it does not just occur to save energy metabolism (Xi, Kang & Xu, 1993).But many studies have found a unique feature of sleep. Which is the activation of a system of our brain named glymphatic system. This is system becomes drastically active during sleep, while its capacity is altered during alertness. IN-vivo 2-photon imaging of glymphatic work demonstrated that the CSF flood in the conscious state was lessened by 90 % contrasted with the mice that were anesthetized (Beridge, & Walterhouse, 2003). Keeping in mind the end goal to test if this was particular to the oblivious state or a symptom of the sedative used, a similar test was performed in normally dozed animals. This test of CSF influx demonstrated a noticeable alikeness between evident sleep and anesthetized mice. The sleep wake contrast in glymphatic inrush related with the volume part of interstitial space that was 13– 15 % in the conscious express an extended to 22– 24 % in both rest and sedated mice (O,Donnel, Zappenfeld & Macconnel, 2012). This perception shows that the sleep state is especially helpful for convective liquid motions and consequently to clear the metabolites. Accordingly, a noteworthy activity of sleep is, that it turns on the glymphatic framework and that the brain gets cleared of the neurotoxic molecules accumulated while we are awake. The perception that glymphatic work is exceedingly vital in both anesthetized mice and normally asleep mice yet not in alert mice demonstrates that the activity of glymphatic system differ with sleep versus awake state. But it does not depend on it is circadian rhythms. Norepinephrine being a neuromodulator plays a noteworthy role here (Nilson, Lindman & Owman, 1998).

Some investigations done on this, demonstrated that norepinephrine works as a key controller of glymphatic movement and that norepinephrine may be in charge of concealment of glymphatic function during awake state (Brown, 2005). If a mixture of norepinephrine receptor antagonists is used locally in wakeful mice, it brings about an expansion in CSF tracer inrush which is practically equivalent to that, which is found during sedation or anesthesia (Kress, Iliff & Xia, 2014). Interestingly, norepinephrine application, mirroring the awake state, diminishes the interstitial volume part. The resistance of tissue is decreased during sleep state as the interstitial space volume is increased. This increased space volume facilitates the CSF-ISF exchange. But when the neuromodulator norepinephrine is released it expands the cell volume while reducing the interstitial space volume (Sabbatini, et al., 1999). Thus, the convective exchange of CSF and ISF increments and this outcomes in a concealment of glymphatic motions in the awake state. Norepinephrine likewise acts specifically on choroid plexus epithelial cells and limits the production of CSF (O,Donnel, zappenfeld & Macconnel, 2012).Then again, if the norepinephrine is removed this mimics the sleep state, improves CSF generation . Thus it is seen that nor epinephrine through various mechanisms can regulate the functions of glymphatic system. , and works as a key controller of the switch between the sleep and alert state and solute clearance from the brain (Siegel, 2005).

3.3 Factors affecting the functions of Glymphatic system:

There are some factors that regulate the glymphatic flow and the effectiveness of this system. The primary factors are described below (Jessen, Munk, Lungaard & Nedergaard, 2015):

1. Aging
2. Traumatic brain injury

3.3.1 Aging:

A current evaluation of glymphatic work in aged compared to young mice demonstrated a sensational decrease by 80– 90 % in aged contrasted with young mice (Kress, Iliff & Xia, 2014). This concealment of glymphatic movement included lowered both clearance of CSF tracers as well as radiolabeled b-amyloid and inulin (Sabbatini et al.,1991). The processes of astroglial cells increase in number with aging and could be the reason of lessened glymphatic function with age. We have already known that a distinctive kind of water channel named aquaporin or AQP4 facilitates the exchange of cerebrospinal fluid and interstitial fluid (CSF-ISF) through arterial influx and also facilitates the drainage of interstitial fluid or ISF through perivascular pathways (Fleichman, et al., 2012). These AQP4 channels in younger brains are scattered in astroglial endfeet, thus can function properly. It was also discussed previously that genetically modified mice that do not have AQP4 channels in their brains cannot function properly while it comes to CSF-ISF exchange. This deletion disables CSF– ISF exchange by 65 % and diminishes the β-amyloid clearance by 55 % (Chen, Kassem & Redzic, 2009). Nevertheless, the vascular polarization of astrocytic AQP4 is somewhat lost in responsive astrocytes in old brains, i.e.AQP4 is not present in astrocytic endfeet however are present in parenchymal processes of astrocytes (Fleichman, et al., 2012). Through various works it has been found that aged brain losses the polarizing capacity of the AQP4 channels which in turn reduces the CSF-ISF exchange, sums up that the age related decrease in glymphatic capacity may be to some extent occurs for the imbalance of astrocytic water transfer. Different other factors maybe adding to the lessening of glymphatic action with aging and these can result in decrease in production of CSF by 66 % and CSF weight by 27 % (Madsen, et al., 1999). With increased age the the walls of the blood vesels get hardened and this hardening of the arterial walls results in reduced amount of arterial pulse waves. We have known this arterial pulsation is one of the primary driving force for glymphatic system (Siegel, 2005).The perception of age-related decrease in glymphatic action should be noted as the main reason for many neurodegenerative disease like Alzheimer's disease, is aging. This reduced function of glymphatic framework thus lead to the aggregation of misfolded and over phosphorylated proteins and in this way turns the brain into more vulnerable state towards acquiring a neurodegenerative pathology or may increase the chances of psychological and cognitive dysfunctions (Takalo, Salminen & Soininen, 2013).

3.3.2 Traumatic brain injury:

Traumatic brain injury or TBI is most frequently seen to be affecting the sports persons or people working for the military. TBI increases the risk of Alzheimer's disease and early age dementia (Frosts, Jack & Diamond, 2009). Various studies have demonstrated that, if these traumatic events occur repeatedly or even once, it can cause moderate to severe head injury, prompting dynamic neurodegeneration. Nevertheless, it is still not fully understood that, why a part of a population of individuals tend to develop a chronic neurodegeneration , at the same time many other introduced to the same amount of initial brain trauma does not show any signs or symptoms of encephalopathy and are hardly affected (Palop & Mucke, 2010). Traumatic brain injuries instigate the aggregation of β-amyloid proteins and also of C-tau proteins, which comes proteolytically from MAP-tau. MAP-tau is microtubule protein occurring inside the axons (Jeffrey J. Iliff & Nedergaard, 2013).While C-tau works as a biological marker of cerebrum injury as it is discharged in tremendous amounts and associates with TBI (J. J. Iliff et al., 2012). According to a newer speculation, it is said that the expansive increments of interstitial tau prompts somatic uptake and starts fibrillary accumulation, which increases the amount of tau protein resulting in neurofibrillary tangles. Which eventually forms a prion-like substance of the pathology (Irimia et al., 2012). TBI is connected to development of major astrocytic scars and can initiate intrinsic inflammation of the neurons (Zlokovic, 2011). In various studies, it was noticeable that in cases where events of traumatic brain injury has occurred repetaitively, is impaired of CSF influx, production as well as drainage. The decrease of glymphatic work is persevered until no less than 28 days after damage. The acute decline in glymphatic work was accompanied with glial scars portrayed by hypertrophic GFAP-positive procedures in the ipsilateral hemisphere of the brain. Moreover, AQP4 from vascular endfeet to parenchymal forms was seen to be mislocalized which is similar to AQP4 misallocation seen in aging.By intracortical infusions of human tau could track the clearance pathway of tau protein (Ross & Poirier, 2004). Thus proteins get tau collected around larger veins and also in the tissues. This accumulation of tau around veins and in tissue results in lessening the glymphatic clearance. This proposes CSF-intervened evacuation of tau by means of glymphatic courses is urgent for constraining auxiliary neuronal damage following TBI. Another study utilizing MRI to survey glymphatic work gave further signs that head injury, for example, subarachnoid hemorrhage, extremely impedes glymphatic function, recommending that cerebral drain can cause a broad

hindrance of glymphatic work (Irmia & Wang, 2012). In this model of subarachnoid discharge tissue-type use of plasminogen activator that expels fibrin clumps enhanced glymphatic perfusion (Buerge, 2012). Embolic ischemic stroke delivered a transient hindrance of glymphatic stream in the hours after ischemia, nevertheless, function was recouped at 24 h following transient ischemia (Zeimen, Melenovsky & Kass, 2005). This recommends that improvised restraint of glymphatic work, either by diminished blood vessel throb or impediment of perivascular pathways caused by gentle stroke, can resolve and is linked to enhanced recovery (Zeimen, Melenovsky & Kass, 2005).

3.4. Neurodegenerative diseases associated with Glymphatic system activity:

Glymphatic system in our CNS mirrors the activities of lymphatic system in the rest of the body. This system clears the toxic substances and accumulated proteins from the cerebrum. Thus impairment of this system might increase the risk of neurodegenerative diseases that occurs for the accumulation of various substances in the brain. Some of these diseases are mentioned below that may worsen or occur for the impairment of glymphatic system.

- Alzheimer's disease
- Stroke
- Parkinson's disease
- Glaucoma
- Other diseases (Huntington, MS, ALS)

3.4.1 Alzheimer's disease:

Alzheimer's disease is an interminable dynamic neurodegenerative disease described by three essential groups of indications. The primary group can be termed as cognitive dysfunction and it incorporates memory misplacement, dialect challenges, also executive dysfunction like loss of intellectual coordination skills and etc. The second group contains mental side effects and behavioral aggravations (Burns, Jacoby & leavy, 1990).Delusion, depression, hallucinations, agitation, are some of the collectively termed symptoms (Snowdon et al., 1997). The third group

involves challenges with daily chores, for example, walking, going to the super market, dressing, and eating without any help, etc. The manifestations of Alzheimer's sickness advance from gentle side effects of reduced memory to extremely serious dementia. The conjunction of vascular diseases and Alzheimer's disease is being perceived clinically, pathologically, and epidemiologically now-a-days (Burns, 2005).It is a dynamic brain disorder that harms and inevitably obliterates brain cells, prompting memory loss and changes in memory and other brain capacities. It ordinarily grows gradually and step by step deteriorates as brain work decreases and cerebrum cells in the end get weakened and die. Eventually, Alzheimer's can be lethal, and as of now, there is nothing medical science can do to totally cure the disease (Burns, Jacoby & leavy, 1990). Now-a-days advanced neuroscientific researches are being conducted to create compelling medications and approaches to prevent the malady (Brown, 2005). Specialists are likewise attempting to grow better approaches to care for affected individuals and better approaches to help their families, companions, friends, care givers and others whose lives might be influenced by the patients (Butterfield, 2001).The Alzheimer's Associations are advancing these experimentation endeavors by helping the researchers financially and in other ways who are looking for more answers and new medications, and techniques to limit the disease. for betterment in this area, working together with family members , encouraging overall organizations among researchers, and raising the perceive ability of Alzheimer's as a global health challenge can help(John Hopkins medicines, 2017).

Alzheimer's disease is the most widely recognized sort of dementia, a general term used to depict different illnesses and conditions that harm brain cells. Alzheimer's illness represents 60 to 80 percent of memory realted disorders (Snowdown et al., 1997). Different forms include vascular dementia, dementia with lewy bodies and front temporal dementia. Now and again, a man may have multiple and are said to have mixed dementia. Researchers have recognized a few trademark Alzheimer's cerebrum variations from the norm, including :(Lewis et al., 2001)

- Accumulation of protein pieces called Beta-Amyloid (Olson et al., 2001).
- Tangles of the protein tau (Olson et al., 2001).

- Loss of associations among brain cells that are connected to memory, correspondence and learning these associations, or neural connections, transmit data from cell to cell (Olson et al., 2001).

- Inflammation, activated by the body's immune system (Burns & Iliff, 2001).

- Eventual death of brain cells and serious tissue shrinkage (Burns & Iliff, 2001).

Numerous people demonstrate the early manifestations of the illness when they are in their 60s or mid 70s. Many people think that incidental forgetfulness, such as losing keys or not recalling a name, is an indication of Alzheimer's illness. However, this sort of common memory disturbance does not imply that a person has Alzheimer's malady (Ertekin-Tanner et al., 2000). At first, memory impedances in Alzheimer's infection are not very severe however in the end they start to affect on the life of influenced people, reducing their capacity to work or to function ordinarily. Their symptoms include forgetfulness, asking the same question repeatedly, subsequent to hearing the appropriate response etc. They lose objects, or overlook where they are, the manner by which they arrived and how to return home. They start experiencing difficulty with dialect, judgment, critical thinking and computing numbers (Butterfield, 2001). Their state of mind may change all of a sudden, swinging from quiet to rage and back again inside minutes, without evident reason. Managing these people might be exceptionally troublesome for family members or care givers (John Hopkins medicines, 2017).

These progressions happen gradually and may at first be mixed up for mere carelessness. In any case, in Alzheimer's ailment, patients deteriorate. Treatments can just enhance a portion of the indications (Bales & Gennet, 2002).

3.4.1.1 Risk factors for developing Alzheimer's disease:

On of the main factor for developing Alzheimer’s disease is age. Old people are most susceptible to build up Alzheimer's disease. Around 7% of the population gets this disease after the age of 65. While 35-40% of the population acquires this disease after the age of 80 (Yale et al., 2012). Younger people might also get this disease though this happens rarely. This happens especially in people who have a family history for this condition. There are 3 individual genes which, when transformed, can cause this certain disease (Yale et al., 2012) :

- Presenilin 1 gene
- Presenilin 2 gene
- APP gene (Amyloid precursor protein)

Another gene named ApoE4 gene can also be a risk factor for this disease. This gene might not directly cause the disease. But having copies of this gene makes the elderly people more vulnerable to this disease. These hereditary elements connect in complex ways, which can be best studied or experimented in animal models (Hardy & Dennis, 2010).

3.4.1.2 Diagnosis of Alzheimer's disease:

Alzheimer's ailment is only one of an assortment of types of dementia, the term utilized to depict a decrease in mental capacity. Specialists close-out different reasons for dementia, especially those that can be tackled (Jucker & Walker, 2011). These different sicknesses can frequently impersonate Alzheimer's disease. Medical records, neuropsychological test results, research center examinations and imaging techniques are utilized to upgrade the analysis, however, other than by analyzing cerebrum tissue, there is no real way to test for Alzheimer's malady in living people. With time, especially following a few examinations, the conclusion of Alzheimer's illness turns out to be enough certain (Hardy, Duff & Hardy, 2003).

Different steps are needed to be taken by the doctors to analyze Alzheimer's disease. Such as (John Hopkins medicines, 2017):

• Reviewing the patients' medicinal history
• Assessing the patients physical, neurological and mental condition.
• Conducting neuropsychological studies.
• Evaluating laboratory test results.

At times computerized tomography (CT), magnetic resonance imaging (MRI) or positron discharge tomography (PET) is performed on the individual to preclude other, treatable conditions (Yale et al., 2012). Johns Hopkins Research Center for Alzheimer's Disease and other

specialty centers working with this disease describes these methods to be around 90% precise in affirming Alzheimer's ailment. Though, total diagnosis for verifying this disease must be affirmed by a biopsy of the brain tissue (John Hopkins medicines, 2017).

Alzheimer's disease can have 5 stages with varying symptoms. The steps and their symptoms are discussed in the following table (Butterfield, Swomley & Sultana, 2013).

Stages of Alzheimer's disease: Table 3.1

Stages	Name of the stage	Symptoms
1.	Mild cognitive impairment	• Memory loss • No evidence of the disease • Intact daily life
2.	Mild Alzheimer's disease	• Short term • Memory loss • Repetitive questions • Loss of interest • Problems in daily living
3.	Moderate Alzheimer's disease	• Cognitive deficits • Dementia • Dysexecutive syndrome
4.	Severe Alzheimer's disease	• Severe dementia • Confusion with time or place • Severe anxiety

		• Changes in sleep patterns
5.	Very severe Alzheimer's disease	• Incontinent • Impaired psychomotor skills • Severe dementia

3.4.1.3 Cause of this disease: Amyloid β cascade hypothesis

There are various theories regarding the cause of Alzheimer's disease. One of the primary and simultaneous cause or theory is the Amyloid cascade hypothesis. Alzheimer's (AD) brain experience severe oxidative stress, caused by increased protein oxidation, lipid peroxidation, free radical arrangement, oxidation of nucleic acids, nitrotyrosine levels, and end products of propelled glycation. Among all, the 42-amino peptide or amyloid b-peptide might be the vital element for the pathogenesis of this disease (Butterfield, Swomley & Sultana, 2013).

There are four perceptions that unequivocally support this amyloid theory.

To start with, changes in the gene coding for the tau protein can cause front temporal kind of dementia with a hint of parkinsonism (Balastic et al., 2007). This neurodegenerative disease is described by extreme accumulation of tau in neurofibrillary tangles in the cerebrum, yet no accumulation of amyloid. Thus it is clearly implicated that even the tau accumulation or neurofibrillary tangle formation is severe, these are not adequate to indcite the Amyloid plaque charaqteristic of Alzheimer;s disease (Barone et al., 2011). Secondly, in a study it has been seen that transgenic mice expressed with human mutant APP gene and tau genes experience greater development of tau-positive tangles. Where as those mice only expressed only with tau developes less tau-positive tangles. Though the structure and number of their amyloid plaques are basically the same (Boyd-kimbell, et al., 2006). This results recommends that adjusted APP gene processing starts before tau changes in the pathogenic course of AD (Bush, 2012). Thirdly, when APP transgenic mice is crossed with apolipoprotein E (apoE) inadequate mice, it particularly lessens the brain accumulationin the new born mice (Butterfield, 1997), giving solid

proof that the pathogenic part of hereditary fluctuation at the human apoE locus probably includes metabolism (Butterfield, 1997).

Fourthly, developing proof shows that hereditary changes in catabolism and clearance can influence the onset or starting of AD. Considering these four points, it can be said that accumulation of amyloid in brain works as a prime factor in developing AD and other factors may include the disproportionate production and clearance of tau. Thus they gets tangled and accumulated inside the brain tissue (Butterfield et al., 2006) .

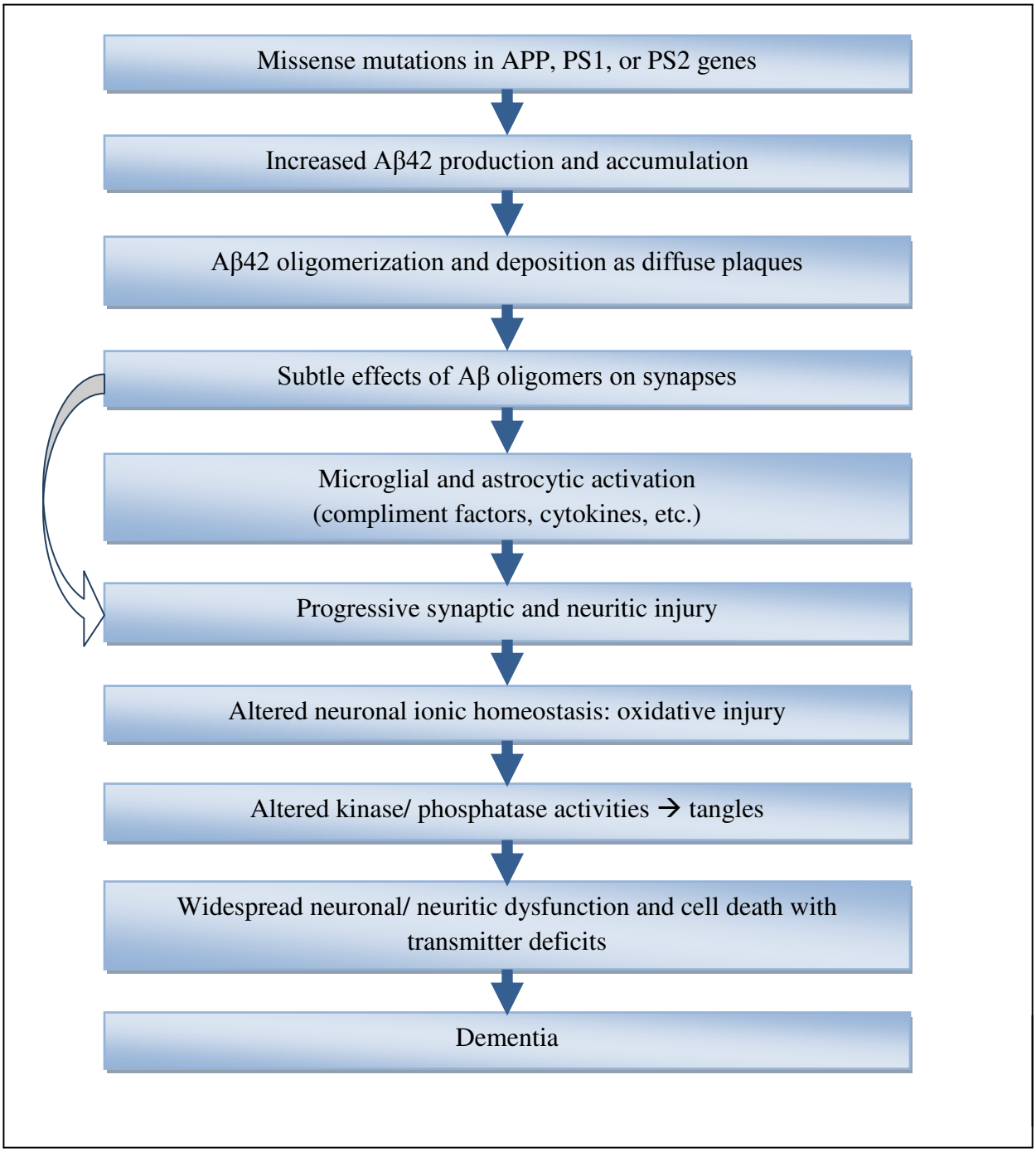

Fig 3.1 Amyloid cascade hypothesis (Butterfield et al., 2006)

3.4.1.4 Role of Glymphatic impairment in the development of AD:

Therefore from the previous discussion we can say that the storage of neurotoxic types of amyloid-β (Aβ) and tau proteins is behind the pathogenesis of Alzheimer disease (AD). This excess Aβ gets accumulated inside the cerebrum as a result of the imbalance of its formation and clearance. At both early-onset and late-onset Alzheimer's disease, clearance of Amyloid beta appears to be hindered at the predromal phase. Likewise Aβ is expelled from the cerebrum by different clearance frameworks: blood-brain barrier (BBB) transport, interstitial liquid (ISF) mass stream, and cerebrospinal fluid (CSF) retention into the circulatory and fringe lymphatic frameworks. Although most extracellular Aβ experiences BBB clearance, we have observed that glymphatic pathway framework plays a noteworthy part in driving Aβ out from the brain. For this reason, impairment of glymphatic function to a large extent incorporates to the development of this disease (Butterfield, Swomley & Sultana, 2013). Additionally The glymphatic framework gets activated while we are asleep and significantly inactivates while we are awake (Szot, 2016)The neurotransmitter norepinephrine is a key controller of the switch amongst sleep and alertness, with low CNS noradrenergic action encouraging sleep and high CNS noradrenergic action producing stimulated alertness (Moretti, 2012).The greater amount of CSF nor epinephrine, found in the elderly might be a reason for the reduced glymphatic function as norepinephrine reduces sleep. This lessened glymphatic function results in accumulation of Aβ and phosphorylated tau, which increases the progression toward Alzheimer's disease (Szot, 2016).

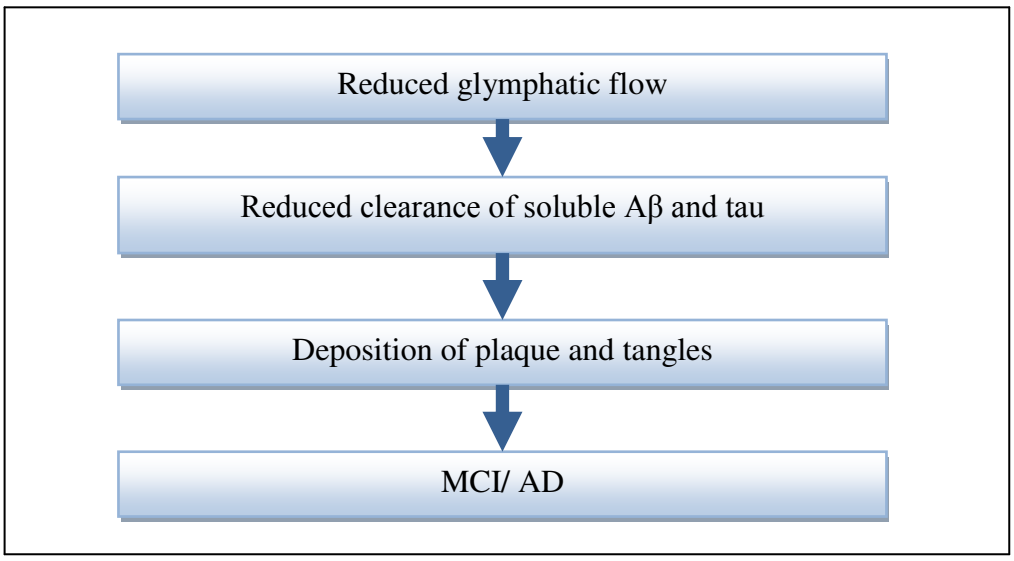

Fig 3.2 Reduced glymphatic flow and progression of AD (Szot, 2016)

3.4.2 What is stroke?

Stroke is a phenomenon which results from loss of oxygenated blood going to our brain. In this occurrence some blood supply to some parts of the brain may get blocked. Without oxygen, our cerebrum cells cannot function properly and starts collapsing in a couple of minutes. If any blood vessels disrupts following any brain trauma and Sudden bleeding occurs inside the brain, this can cause a stroke as well (Adams, Bendixen, kapelle & Biller, 1993). Following these events, brain cells get harmed and may starts to collapse. Thus changes start to occur in parts of the body that are controlled by that certain types of brain-cells. Cases of stroke symptoms incorporate, fatigue, insensibility of the face, hands, or legs (paralysis), inconvenience talking or understanding and inconvenience seeing. A stroke being a serious therapeutic condition requires urgent care. A stroke can cause irreversible harm to the brain tissue, leading to inability and death (Thom *et al.*, 2006).

3.4.2.1 Types of strokes:

There are two major types of stroke. They are ischemic and hemorrhagic .Between these two Ischemic stroke is more prevailing (Wolf, Abott & Kennel, 1991).

If an artery carrying oxygenated blood towards the brain gets blocked, then some parts of the brain might experience oxygen deficiency. This blockage can cause for clotted blood inside the arteries. This blocks the arteries and eventually leads to stroke. This kind of stroke is called Ischemic stroke (Adams, Bendixen, kapelle & Biller, 1993).

If a blood vessels ruptures inside the brain, then internal bleeding occurs. This spilled blood creates a pressure on the brain cells which harms them eventually. Thus hemorrhagic stroke occurs. Hypertension and aneurysms (swelling of the wall of an artery) are conditions that can cause hemorrhagic strokes (Wolf, Abott & Kennel, 1991)

Another condition that is like a stroke is a transient ischemic stroke, likewise called a TIA or 'small scale stroke'. A TIA happens if blood stream to a part of our brain is blocked just for a brief span. But the harm that occurs to the cerebrum cells is reversible (Swieten, 1995).

3.4.2.1. Stroke and Glymphatic system:

The glymphatic framework permits the clearance of the cerebrum interstitial liquid through para-blood vessel efflux and para-venular influx of CSF (Ilifff et al., 2013). Metabolic byproduct generation increases at a greater rate when there has been an episode of neuronal damage. Thus the leeway through the glymphatic framework may play a major role after stroke (Wang et al., 2017). it is assumed through various works that stroke influences the glymphatic framework function. To test this speculation, an invasive infusion technique was designed with gadolinium chelate (dye used in MRI).It was injected inside the cisterna magna of the rats, to check the CSF flow utilizing MRI(Gaberel et al., 2014). In this manner, the capacity of the glymphatic framework after subarachnoid hemorrhage (SAH), intracerebral hemorhage, regular carotid artery impediment, and embolic ischemic stroke was assessed. The present studies exhibits that the glymphatic framework capacity can be assessed in living rats utilizing MRI connected to a minimally invasive infusion of DOTA-Gd (gadoteric acid) in the cis-terna magna. The main finding is that the glymphatic framework is seriously disabled after SAH and in an intense ischemic stroke, but not after intracranial hypertension (Sabri & Macdonald, 2011). Current proof recommends that the glymphatic framework plays a vital role in cerebral waste clearance. Once impeded, the deposition of metabolites inside the parenchyma may prompt brain damage.

This occasion could be especially important in cerebral ischemia happening after SAH (Iliff et. al., 2012). But, to find out if reduced glymphatic function results vasospasm or microcirculatory disability, more works needed to be done. In this cases reestablishing glymphatic perfusion by intraventricular fibrinolysis can work to enhance outcome. During the intense period of ischemic stroke, the decreased of function of glymphatic system might reduce the clearance of excitatory neurotransmitters and may promt death of the nurons. Mechanism behind these occurrence are yet to find , but may comprise (Hanouz et al., 2014)

(1) Reduced production of arterial pulse waves due to vessel occlusion.

(2) The impediment of the perivascular spaces, resulted by intravascular embolism.

As indicated by these two speculations, the glymphatic perfusion seemed typically working , 24 hours after ischemic stroke, when the center cerebral supply route was repermeabilized. Therefore, intravenous thrombolysis may enhance glymphatic flow in the cases of ischemic stroke patients (Artel-ornath et al., 2013).The results came from a current report indicates that, interstitial fluid clearance after micro stroke is lessened in amount. This test was done by utilizing a 2-photon microscopy (Hanouz et al., 2014). In further studies it should be examined if such dysfunctions actually occurs after neurological trauma. Prominently, administration of tissue-type plasminogen activator, either by evacuating perivascular fibrin after SAH or by reestablishing blood vessel patency while there had been an ischemic stroke, the glymphatic perfusion may enhance (Artel-ornath et al., 2013).

3.4.3 Parkinson’s disease:

Parkinson's disease (PD) is a dynamic multi-framework neurodegenerative disease influencing individuals in later years of life(Hughes et al.,1997) It is the second most basic neurodegenerative disorder worldwide with a rising prevalence. Alongside changing population socioeconomics (Pringsheim et al., 2014). The pervasiveness of PD in industrialized nations is assessed at 0.3% of the whole population and around 1% in individuals more than 60 years old (Pringsheim et al., 2014). This illness has particular neuropathological cerebrum changes. There is development of proteinaceous circular structures named lewy bodies, and an spindle or string like structures in the nervous system(Braak, Trediki & Rub, 2005). These lewy bodies in the

somata of the nerve cells, progress topographically in a pre-dictable sequence inside the sensory system (Braak et al., 2004). With advancement of this disorder, substantia nigra and other cores of the midbrain and forebrain end up noticeably influenced (stages 3– 4). It has been proposed that patients create clinical symptoms of the sickness at this stage. At the last stages (5– 6), the processes enters the neocortex with an wide array of clinical indications (Arsland et al., 2009).The deterioration of the neurons in the nigrostriatal pathway which involve dopamine, is viewed as an essential neuropathological associate of motor disability in Parkinson's disease. And this occurs for the accumulation of lewy bodies in the dopaminergic neurons (Arsland et al., 2009). However glutamatergic, cholinergic, GABA-nergic, tryptaminergic, noradrenergic and adrenergic sensory cells may indicate identical damage in their cytoskeleton (Chen, Burton & Webster, 2013). The clinical indications of PD are typically described by the motor disabilities, but there could be problem in other functions of the sensory system as-well (Braak & Braak, 2000)

3.4.3.1. Parkinson's disease and Glymphatic system:

Individuals with neurodegenerative diseases experience the effects of an extensive variety of sleep related issues, including a sleeping disorder (Siegel, 2005).Before it was believed that these unsettling influences were outcomes instead of reasons of brain pathology, either being directly connected to the destruction of sleep related parts of the brain (kress et al., 2014) It can also happen as symptoms of a specific medication regimen or different triggers. It is now presumed that relationship between sleep pattern and neurodegenerative diseases might be more serious. Sleep problems might appear years before there is an actual case of neurodegeneration (Peng et al., 2016). Various studies have actually discovered that the degree of sleep disturbance predicts resulting cognitive dysfunction or disease (Peng et al., 2016). Metabolic waste and free radicals created by our brain can oxidize or break nucleic acid strands and if a section of a DNA or RNA strand breaks, it cannot be supplanted. Our brain tends to recover these things during sleep. We have known above that in these previous few years researchers affirmed the presence of a radical new body framework, the Glymphatic System in our CNS (Mendelson & Larrick, 2013). Which once a day surges our cerebrum with cerebrospinal fluid and washes away the toxic and waste products from our brain cells. It happens once, during profound long sleep cycles mostly at nights (Mendelson & Larrick, 2013). It is known that Parkinson's Disease is a brain issue where

the brain cells that process dopamine in a particular area of the brain known as the the substantia Nigra gets destroyed (Obeso & Rodriguez, 2000).When indications begin to appear in an individual with PD, it is evaluated that 80% of these cells are as of now dead or never again delivering dopamine (Obeso & Rodriguez, 2000). Better quality sleep can enable the cerebrum to clean itself, to detoxify it and make it keep going with the assistance of glymphatic framework (Werner et al.,2013).With impaired sleep, brain disorders, similar to Parkinson's disease, will deteriorate even faster. Since in these neurodegenerative diseases various toxic matters and unwanted molecules gets accumulated in the brain which can worsen the condition. Thus a good quality sleep for such a patient is very important. Also many works in this field regarding neurodegeneration and glymphatic functions, suggest that in early ages a stress less lifestyle with a good amount of daily sleep can keep these neurodegenerative diseases away (Mendelson & Larrick, 2013). Since good sleep lets the glymphatic system work properly getting the brain free from all the toxic substances that harms and deteriorates the brain cells (Peng et al., 2016)

3.4.4 Glaucoma:

Glaucoma is an ophthalmic disorder that destroys or harms our eye's optic nerves. This disease occurs in the cases of fluid deposition in the anterior part of the eye. This accumulated fluid creates an extra pressure on the retina that eventually leads to optic nerve damage (Mckinnon et al., 2002). It is one of the main cause of permanent blindness worldwide (Mckinnon, 2003).

3.4.4.1 Glaucoma and glymphatic system:

The main reasons behind open-angle glaucoma is still not understood clearly. As glaucoma is one of the primary cause of permanent blindness now-a-days, looking for its concealed pathophysiological mechanisms is extremely important and required (Boyd, 2017). In recent times, some works done in this field, talks about existence of an 'ocular glymphatic system' that resembles the glymphatic system of the brain (Brinker et al.,2014)Therefore , this theory of a glymphatic system being in the eye can open up many aspects of the vascular, biomechanical, and biochemical theories of the disease (Giliberti, 2016). Though few research data currently available, is not enough to back up this theory. As nothing conclusive can be said till now, more works should be conducted in this area to fully confirm this hypothesis (Bizrah, Guo & Corderio, 2011). If the existence of a paravuscular transport system in the optic nerve can be confirmed, it

can offer various developed medication and treatment strategies for this devastating disease (Peter et al., 2015).

3.4.5 Other Neurodegenerative diseases associated with glymphatic activity:

Huntington disease: Huntington's disease is a genetic disorder that causes degeneration of nerve cells in the brain. Huntington's disease has a profound impact on a person's functional abilities and daily life. Which includes, movement disabilities, cognitive dysfunction and psychiatric disorders (Frank, 2014).

Multiple Sclerosis: Multiple sclerosis is a viable brain disorder, affecting the CNS. It is a autoimmune disorder where the own immune system of the body attacks the protective covering (myelin) over the nerve fibers (Nakahara, Mayeda, Suzuki, 2012).This disease causes problems in relay actions between the brain and the rest of the body. Finally it leads to deterioration of the nerve cells, and irreversible nerve damage (Tsang & Mcdonnel, 2011).

Amyotrophic Lateral Sclerosis: Amyotrophic lateral sclerosis is a motor neurone disease. It causes the death of brain cells controlling the voluntary muscles (Zarei et al., 2015).

These neurodegenerative disorders like, Huntington disease, Multiple sclerosis (MS), Amyotrophic lateral sclerosis (ALS) and others is found also to have a connection with glymphatic system (Brown, 2015). Since numerous researchers working in this area trusts the disclosure will open new roads not just to understand the reasons for these neurological illnesses yet can contribute to the invention of novel treatments (lundgaard et al., 2014) In neurodegenerative diseases, for example, ALS and Huntington's, a working glymphatic framework is expected to expel those lethal particles from the brain that is caused by these diseases (Brown, 2015) Many thinks, developing medications to reestablish the function of this system can help, despite the reason for the disease (Moore, 2015).

3.5 Advanced aspects of glymphatic system:

With further researches conducted related to this system can open up to newer methods of neurological treatments and diagnosis. Such as,

- A diagnostics test regarding glymphatic function might be developed to identify patients with premature decline in glymphatic activity (Hui, 2015).
- Diagnostic tests can be designed to be done post traumatic brain injury to evaluate the amount by which glymphatic activity has declined. Thus people who are at high risk to develop neurodegenerative diseases can be pinpointed (Jessen, Munk, Lungaard & Nedergaard, 2015).
- A safe and invasive imaging method can be developed to see in which extent CSF fluxes fails in Alzheimer's disease (Iliff, 2013).
- If further studies are conducted, glymphatic system may work as a distribution medium for drugs. As well as cancer drugs inside the brain (Jessen, Munk, Lungaard & Nedergaard, 2015).

Conclusion

Our brain is encompassed by a film called the arachnoid and washed in cerebral spinal liquid (CSF). CSF flows into the cerebrum through an indistinguishable pathway from the arteries that convey blood. This parallel framework is likened to a doughnut like pipe which is located inside another pipe. The inward ring carries blood and the external ring carries CSF. The CSF is taken into cerebrum tissue by an arrangement of conductors that are controlled by a kind of brain cells called glia or astrocytes. The term glymphatic was introduced by merging the two words glia and lymphatic. The CSF that flows through the cerebrum tissue at a rapid speed clears abundant proteins, and other wastes alongside. The liquid and waste are exchanged with a comparative framework having parallel veins which detoxifies the cerebrum and clears the toxins down the spine. From the spine it is transported to the lymphatic framework and from that point to the liver, where it gets metabolized. Questions, like how the brain clears its toxic substances and what happens when these substances get accumulated in the brain, has baffled the scientists for a long time. The discovery of glymphatic system could answer all these questions. Also it is now known that it has critical ramifications for the cure of neurological disorders. Thus diagnostic tests of this system can recognize patients with impaired glymphatic system being more vulnerable to neurodegeneration and neural disorders like Alzheimer's disease. One of the major sign of Alzheimer's disease is the deposition of beta amayloid protein fragments in the cerebrum. And with time these proteins can gather with such density that they are found in the cerebrum as plaques. Thus understanding what part of the glymphatic framework plays in the brain's ability to expel beta Amyloid, could indicate new ways medicines. In particular, regardless of whether certain key 'players' in the glymphatic framework, for example, astrocytes, can be controlled to increase the expulsion of waste. Further studies regarding this system may also identify various functions of CSF fluxes other than waste removal. Also as it has been found that the glymphatic system distributes proteins, lipid, other electrolytes and macromolecules inside the brain, it might also be used as a drug delivery system including cancer drugs inside the brain tissue. Further studies conducted in this area may establish this system as a biomarker also an effective drug delivery system for different diseases.

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