REVIEW ARTICLE

Pathobiology of the Glymphatic System in the Traumatic Brain Injury: A Narrative Review

Juan Jose Beltran-Ruiz[1], Juan Sebastian Reyes-Bello[2], Claudia Marcela Restrepo-Lugo[3], Luis Rafael Moscote-Salazar[4]

Received on: 19 July 2022; *Accepted on:* 28 July 2022; *Published on:* 31 August 2022

Resumen

El sistema glinfático es responsable en el cerebro de transportar sustancias hacia el intersticio y luego fuera de él; es fundamental para el funcionamiento neuronal y más aún tras cualquier lesión cerebral.

Es un sistema frágil; su funcionamiento se ve alterado con la edad, los trastornos del sueño y el daño neuronal como en los traumatismos craneoencefálicos, provocando una disminución en el aclaramiento de sustancias neurotóxicas e inflamatorias, lo que desencadena la neurodegeneración y alteraciones en la neurorreparación, a pesar de tener diferentes mecanismos que permiten el flujo de nutrientes y eliminación de sustancias nocivas para la supervivencia y rehabilitación neuronal.

Este artículo describe la relación entre el traumatismo craneoencefálico y la disfunción del sistema glifático, así como los efectos negativos sobre el parénquima cerebral y la neuroinflamación secundaria. Este sistema no sólo se ve afectado por el cambio en la "polarización" de los 4 canales de acuaporina de los astrocitos sino también por las características de las sustancias del entorno neuronal, que optan por un mecanismo de transporte diferente del Sistema Glinfático.

Palabras clave: Sistema glinfático, Trauma cerebral, Trauma craneoencefálico.

Abstract

The glymphatic system (GS) is responsible in the brain for transporting substances toward the interstitium and then out of it; it is essential for neuronal functioning and even more so after any brain injury.

It is a fragile system, its functioning is altered with age, sleep disorders, and neuronal damage as in head trauma, causing a decrease in the clearance of neurotoxic and inflammatory substances, which triggers neurodegeneration and alterations in neuro repair, despite having different mechanisms that allow the flow of nutrients and clearance of harmful substances for neuronal survival and rehabilitation.

This article describes the relationship between head trauma and dysfunction of the GS, as well as the negative effects on the brain parenchyma and secondary neuroinflammation. This system is not only affected by the change in the "polarization" of the aquaporin (AQP) four channels of the astrocytes but also by the characteristics of the substances in the neuronal environment, that opt for a different transport mechanism from the GS.

Keywords: Brain trauma, Craniocerebral trauma, Glymphatic system.

Panamerican Journal of Trauma, Critical Care & Emergency Surgery (2022): 10.5005/jp-journals-10030-1389

Introduction

The GS is a virtual perivascular network in the brain that has the function of transporting brain substances toward neurons and then toward the exterior of the brain, for neural metabolism and its residue, from the interstitium to the meningeal lymphatic vessel. This system of clearance of residues and the remaining neurotoxic increases its action in situations like the reduction of the state of consciousness, during sleeping, or under the effect of anesthetic agents.[1,2] However, there are scenarios where this flow at the level of a GS can be altered, such as the low pulsatility in the penetrating arteries of the brain with aging or different mechanisms that alter the cerebrospinal fluid (CSF) normal dynamics as the edema, which can be caused by a traumatic or vascular brain injury.[3–5]

The purpose of this bibliographic review is to mention some fundamental aspects associated with the physiology and physiopathology of the GS in relation to the neuroinflammatory response during traumatic brain injury, in addition to the negative effects that inadequate flow in the brain brings in the short-term, as well as in the long term, there can be cognitive and affective alterations, sleeping quality, and even neurodegenerative diseases, so the different factors that can affect this important and fragile system can be emphasized, as

[1,2]Federico Lleras Acosta Hospital, Emergency Department and Hospitalization, Ibagué, Tolima, Colombia

[3]Federico Lleras Acosta Hospital, Neurological Surgery Service, Ibagué, Colombia

[4]Grupo Colombiano de Investigación, Clínica en Neurointensivismo, Bogota, Colombia

Corresponding Author: Juan Jose Beltran-Ruiz, Federico Lleras Acosta Hospital, Emergency Department and Hospitalization, Ibagué, Tolima, Colombia, Phone: +573143285154, e-mail: jjbeltranr@ut.edu.co

How to cite this article: Beltran-Ruiz JJ, Reyes-Bello JS, Restrepo-Lugo CM, *et al.* Pathobiology of the Glymphatic System in the Traumatic Brain Injury: A Narrative Review. Panam J Trauma Crit Care Emerg Surg 2022;11(2):82–87.

Source of support: Nil

Conflict of interest: None

well as its importance in the neurotrauma and some alternatives to enhance it.

Methods and Results

The research and literature review was done up until January 2022 in search engines and databases like PubMed, Cochrane Library, ScienceDirect, Google Scholar, and Redalyc, making use of the words "glymphatic system," "brain trauma injury," "craniocerebral trauma," "glymphatic," and using specific linking words (and, in, or) to optimize the search. This produced more than 16,400 results; after the relevant articles were excluded, the results related to physiology and GS pathology, neuroinflammation secondary to traumatic brain injury, and diseases caused by a malfunction of the glymphatic flow at the brain level.

Discussion

Anatomy and Physiology of the Cerebrospinal Fluid

Cerebrospinal fluid (CSF) is the product of plasma ultrafiltration by the lateral ventricles, which then flows into the ventricles and the spinal cord.[3,6] Its production depends on factors such as the pressure gradient in the nucleus of the fenestrated capillaries of the plexuses, the cerebral perfusion pressure, and the autonomic nervous system.[6] The speed of absorption in the arachnoid villi depends on the intracranial pressure that stimulates the mobilization of CSF into the bloodstream.[7] CSF provides hydromechanical support to brain structures and essential nutrients for neuronal function and homeostasis of interstitial fluid in the brain parenchyma.[8]

Anatomy and Physiology of the Lymphatic System

The lymphatic system is a network of vessels specialized in transporting and exchanging substances filtered by the tissues thanks to an extrinsic tissue pressure gradient.[8] It is distributed throughout the body to provide global drainage that connects the lymphatic vessels of the capillary microcirculation with the systemic circulation and is then eliminated through the kidneys and liver.[8,9]

Lymphatic vessels in the central nervous system (CNS) drain CSF into the arachnoid space, then emerge through the cribriform plate, jugular foramen, lacerum, and petrous section of the carotid artery to merge into deep cervical lymph nodes and finish draining into the venous system.[3,7]

Anatomy and Physiology of the Glymphatic System

Interstitial fluid in the brain is produced from hydrostatic filtration of blood plasma in cerebrovascular endothelial cells with fenestrated capillaries and tight cell junctions.[10] The perivascular space is made up of the para-arterial and paravenous spaces that depend on the convection of the flow and the function that the glial cells exert on the exchange of soluble proteins and other products of metabolism in an articulated manner in a system called "Glymphatic System" (GS) in recognition of the implication that glial function has on cerebral lymphatic drainage.[11]

The GS comprises a transparenchymal pathway and the perivascular space, which allows the flow of nutrients into the parenchyma and the transport of waste from neuronal metabolism.[1,2,3,11,12]

Astrocytes play an essential role in the transparenchymal pathway, facilitating the transport of substances from the arterial perivascular space to the interstitium and then to the venous perivascular space through the AQP-4 channels located in the endings of these cells.[7,11] Due to these channels (AQP-4), a convective flow is generated as the content of the CSF is exchanged through the transparenchymal space.[11,13] On its way out of the brain, the drained content connects with the lymphatic vessels in the deep cervical nodes and subsequently to the systemic circulation.

The behavior of GS has been evidenced with different techniques[14] such as Brain Magnetic Resonance Imaging (MRI) with the use of contrast agents such as gadolinium[15] or intrathecal gadobutrol (low molecular weight contrast, 550 Da), describing its distribution in the CNS,[16] elimination routes of the GS itself such as cervical ganglia,[17] and in peripheral blood.[18] These techniques have become a tool to identify CSF behavior such as CSF leaks (intracranial hypotension), idiopathic normotensive hydrocephalus,[19,20] and some neurodegenerative diseases related to GS changes.[14,16,21] In addition, the use of contrast media such as gadobutrol can be considered safe, despite non-serious adverse events such as headache and nausea, possibly associated with underlying pathology or the lumbar puncture itself.[22] Another type of study that has made it possible to evaluate the activity of the GS is the analysis of diffusion tensor-based images of the cerebral perivascular space, where a diffusion index is determined by analyzing the movement of water molecules in the direction of space perivascular considering the planes of subcortical projection fibers and association fibers in specific regions.[14]

Glymphatic System Regulation

The regulation of the GS is multifactorial. It depends on the proper functioning of various structures such as the meningeal lymphatic system, arterial perfusion, venous drainage,[3,23,24] and factors such as sleep, age, and the presence of brain lesions.[3,25]

GS flow is greater during sleep than during wakefulness due to increased brain extracellular volume that optimizes the perivascular flow of proinflammatory substances and neuronal metabolic debris.[1,26,27] On the other hand, the gravitational effect of the position of the head in the lateral decubitus position during sleep improves the flow of CSF toward the periarterial route, which further promotes convective flow and the elimination of waste at the level of the cerebral interstitium.[3,25,28] In addition, some neurotransmitters influence the GS during the transition from wakefulness to sleep by inactivating the noradrenergic projections of the locus coeruleus, causing a decrease in norepinephrine levels and inhibiting its constricting effect on the interstitial space, which generates the expansion of the extracellular volume and the decrease in tissue resistance that favors the faster entry of CSF into the interstitium.[3,25,29] These effects have also occurred during the effect of some anesthetics.[30] In addition, ultrafast magnetic resonance encephalography has shown that cardiac pulsations, respiratory movements, and low-frequency waves influence CSF flow and, consequently, GS dynamics.[31,32]

Brain injuries such as traumatic brain injury (TBI) generate various neurotoxic substances and greater stimulation of peripheral macrophages by chemokine 2 (CCR2), causing a more significant neuroinflammatory cell response and less neuroplasticity.[2] Older people have a greater effect due to the decrease in the pulsatility of the penetrating arteries of the brain, which negatively influences the circulation of the GS.[3] A study in young mice showed that deletion of the CCR2 receptor reduced macrophage accumulation and improved cognitive function within 1 month.[33]

Traumatic Brain Injury

Cranioencephalic trauma is the sudden exchange of external mechanical energy,[34] triggerings a sequence of damage and response in the affected tissue. Three consecutive and consequent phases have been established: primary, secondary, and tertiary injury[2] where the primary harm is not preventable and the secondary damage is the one that is intervened to reduce the physiological response to the trauma and thus avoid the sequelae that occur found in the tertiary lesion.[2]

The primary injury is generated in milliseconds at the moment of the trauma and is a direct result of external mechanical forces that cause damage to the brain tissue and other structures; whereas, in secondary injury, the disturbed tissue is greater and the damage lasts longer. In this process, there is a complex of events such as the release of damage-associated molecular patterns (DAMPs) such as HMGB1 (high mobility protein 1), glutamate release, cellular calcium, membrane depolarization, inflammation, lipid peroxidation, the release of free radicals and necrosis. These events precipitated the beginning of the inflammatory response of different types of neurons such as microglia and astrocytes, the release of proinflammatory cytokines (IL-1,6,17, TNF-α, INF-γ), addition of immune cells such as neutrophils and lymphocytes that generate chemotactic substances and stimulate nearby neurons to join the neuroinflammatory response.[2,35] During this process, ischemia, neuronal hypoxia, cerebral edema, and increased intracranial pressure, among others that are proportional to the severity of the trauma, can be evidenced.[2]

Secondary Lesion and Glymphatic System

Glial cells, mainly astrocytes, and microglia, have changes in their phenotype during the secondary TBI injury known as astrogliosis and microgliosis, respectively, where the M1 phenotype precipitates neuroinflammation, and the M2 phenotype is reparative.[36]

The prolonged or exaggerated glial response due to the M1 phenotype stimulated by DAMPs is the cause of reactive gliosis, which promotes chronic neuroinflammation, oxidative stress, and neurodegeneration. In addition to inhibiting regeneration, this neuronal profile is the cause of inadequate metabolic regulation, low neuronal survival, and GS dysfunction by reducing the clearance capacity of substances such as B-amyloid, white cells, and other neurotoxic elements.[36,37]

Increased or decreased clearance of substances by the GS is detrimental to neuronal function. An increase in GS flow can remove inflammatory molecules necessary for neuronal recovery, and increase glucose and glutamate levels in the interstitium, thus triggering cell death and dysfunction. On the contrary, if the flow of the GS is reduced, a low circulation of cellular debris toward the paravenous space is generated and thus a more significant secondary neuroinflammatory response.[38] These scenarios can be found during the secondary injury after TBI, beginning with a short period of increased clearance of the GS and then reaching a long period of decreased flow. The dramatic change is given by an increase and persistence of the inflammatory response, present most of the time after TBI during the secondary injury.[38,39]

During secondary trauma injury, the functionality of the GS is reduced by up to 60%, and can be installed in hours and last for weeks or months,[2,33] under the presence of factors such as advanced age, a second traumatic brain event without adequate recovery, cerebral edema, microgliosis or reactive astrogliosis, increased intracranial pressure and alterations in cerebral venous drainage or meningeal lymph.[23,36] The time of dysfunction of the GS will be according to the degree and type of injury; for example, during moderate to severe TBI, the clearance of substances may be reduced from 14 to 28 days, while in vascular noxae such as ischemic or hemorrhagic stroke, especially subarachnoid hemorrhage can be dysfunctional from 3 to 28 days.[40]

Neuroinflammation and neurorepair vary in time and intensity of presentation after trauma. Neuroinflammation is generally established first, followed by neurorepair. However, there are times when these processes coincide. Recovery occurs when neurorepair predominates, or otherwise, if neuroinflammation persists, negative effects are triggered that can be long-lasting and progressive, altering brain homeostasis that is reflected in structural and cognitive changes.[2,34]

The ideal state of the GS after TBI would be increased GS flow inflow with decreased waste outflow, aiding in phagocytosis, infection prevention, and isolation of healthy brain tissue.[38,39] This effect could give the GS a dynamic and independent capacity to alleviate the damage in the affected tissue. Still, it seems that the opening or closing behavior of the flow in the GS is the same for both afferent and efferent, possibly due to the presence of the response of polarization in astrocytes.

Vascular Polarization and Aquaporins

A decrease in the density of AQP-4 channels in the feet of perivascular astrocytes is known as a change in "polarization," which reduces the ability to eliminate cellular debris, increasing the concentration of pro-inflammatory substances in the interstitium, causing a greater neuroinflammatory response and cell damage.[2,33] This polarization change has been found to occur not only during traumatic brain injury but also in vascular brain injuries.[15,40] However, the dependence of the GS for the elimination of cellular debris by means of AQP-4 appears to be partial, and there may be other mechanisms that contribute to the dysfunction of the GS, such as astrogliosis and reactive microgliosis.[5,37]

There are different types of AQP in the brain such as AQP-1, AQP-4, AQP-9, AQP-11,[4] in different locations[3] AQP-4 channels are found in astrocytes, with a 10-fold higher density in the perivascular foot ends than in the soma. The location of these channels was demonstrated in a study where the functioning of AQP-4 was suppressed causing a decrease in the flow of perivascular substances toward the cerebral interstitium.[41]

Apparently, the persistence in the loss of polarization is dependent on the existence of reactive gliosis,[11] in addition to the presence of the release of glial fibrillary acidic protein (GFAP), which has been seen to lead to the loss of the perivascular location of AQP-4, turning GFAP into a potential mechanism of glymphatic dysfunction in this and other pathologies.[3]

Mechanisms linked to changes in the polarization of AQP-4 have been described, such as epilepsy, traumatic or ischemic brain injuries, and neurodegenerative diseases that create a loss of this polarity, while in noxas like bacterial meningitis, the presence of lipopolysaccharides and some brain tumors increases AQP-4 mRNA in the perivascular feet of astrocytes.[4,5,42]

It has also been shown in experimental studies that the suppression of AQP-4 in specimens that underwent TBI did not show defects with the clearance of soluble substances such as B-amyloid, and it showed a protective role of the absence of AQP-4 against cerebral edema,[43] however, this study has different limitations as well as deficiencies: the types of markers and the short time to examine the tissues after the injury. Additionally, other authors

state that the use of invasive mechanisms, suboptimal anesthesia, convergence in the ages of the specimens, and the dynamics of the distribution of the markers changes in *ex vivo* tissue.[44]

It cannot be claimed that AQP-4 is the only responsible for glymphatic flow because some studies still have flaws in their methodology, but this does not mean that not there are mechanisms other than AQP-4 that promote the circulation of the content of GS and removal of soluble substances, such as the interstitial diffusion process.[45] The GS is not only formed by the AQP-4 channels, but also by different diffusion mechanisms in the perivascular routes where solutes and proteins can circulate by paracellular and transcellular diffusion.[3] Recent studies indicate that the flow of the GS is regulated by two mechanisms: diffusion and convection, where the exchange with the interstitium is carried out according to molecular size. The diffusion mechanism occurs in small molecules while convective flow occurs in larger molecules.[42,46] This can be seen in some trials where, despite AQP-4 deletion, the flow of the GS decreases at the same time as the clearance of Tau proteins, amyloid, and other soluble solutes.[4]

Neurotrauma, Traumatic Brain Edema, and Glymphatic System

Cerebral edema is a consequence of polarization, due to the worsening of cytotoxic edema which if it persists, overlaps with vasogenic edema. Cerebral edema can last from days to weeks depending on the extension, the energy of the trauma, and the persistence of astrogliosis and reactive microgliosis. In a study where the hit and run method was applied to cause mild and moderate TBI in rodents, there was an indistinguishable change in polarization in the first week, but after the second week in moderate and severe TBI the change in polarization still persisted.[5,37,47,48] Additionally, after TBI, not only the GS is affected, but also the meningeal lymphatic system, that is, the negative effect of TBI on the clearance of waste substances from the CNS are affected globally and involves the interstitial drainage, meningeal and venous cerebral drainage, which increases edema and intracranial pressure by different mechanisms[24] up to prolonging the damage toward a state of chronic posttraumatic encephalopathy where the dysfunction of the GS is compromised enough to generate irreversible damage to the neuronal tissue.[33] Therefore, the polarization of AQP-4 channels in the perivascular feet of astrocytes is one of the mechanisms involved in cerebral edema due to TBI,[4] which alters the GS and its effect on the elimination and contribution of substances that are important for the functioning of neurons, such as glucose, lipids, amino acids, growth factors, among others, which contributes not only to cell death and perpetuation of the proinflammatory state but also to a longer duration of cerebral edema.[2,27]

Regarding the management targets, we can evaluate options such as the surgical approach to cerebral edema in TBI (moderate to severe) through cisternostomy, with which the CSF that has moved toward the cerebral interstitium gets out from there. The suprasellar cisterns may collapse from edema or blood accumulation, causing the CSF from the cisterns to enter the cerebral interstitium *via* the Virchow-Robin space (perivascular space). Thus, the cisternostomy decreases the pressure inside the cranium besides improving the circulation of the cerebral interstitium with the CSF (it improves the flow of the GS), which leads to better clearance of metabolic waste substances that can prolong the edema and neuronal damage.[49–51] The technicality and the availability of resources required for this surgical method can be a barrier to its performance; On the other hand, cisternostomy has shown an advantage over other procedures that also reduce intracranial pressure, such as decompressive craniectomy. These advantages are postsurgical (a higher Glasgow scale at 6 weeks, lower mortality, and less time on mechanical ventilation).[51,52]

Another option other than surgical management is the modulation of the unbalanced and continuous response of microgliosis. These cells, due to their longevity, can have deleterious effects for a long time, and the replacement of microglia has been shown to promote neuro repair to avoid the consequences of chronic neuroinflammation.[37,53]

The noninvasive management of manual physical therapy in repetitive mild neurotrauma (postconcussion syndrome) contributes to restoring, to some degree, the flow of GS in extracranial structures such as the cervical lymphatic system, obtaining a significant improvement in neurological symptoms and signs. Studies of greater clinical significance are required to determine the impact of manual physical therapy.[54]

Glymphatic System and TAU/Amyloid Proteins

After trauma, glymphatic clearance slows down, making amyloid plaques accumulate and increase in size, which further narrows the perivascular space, worsening amyloid exchange and causing amyloid deposition that over time results in neurodegenerative disease.[15] On the other hand, the high concentration of substances and proteins such as Tau are released up to 40,000 times higher than normal after trauma, causing malfunction of the GS mechanisms[15,48] which generates a greater accumulation of Tau protein phosphorylated, B-amyloid, and other neurotoxic substances in the brain parenchyma that chronically lead to neuroinflammation and reactive gliosis, triggering medium- or long-term neurodegenerative diseases such as Alzheimer's disease (amyloid deposits), in addition to cognitive problems, circadian rhythm,[3,27] punctually alteration in the characteristics of sleep, insomnia, migraine, emotional and behavioral disorders.[27,42,48]

The disposal of substances by the GS depends not only on the adequate flow of GS but also on the characteristics of the waste substances, such as their molecular size and their ability to generate soluble oligomers. The decrease in GS flow increases the oligomerization and the accumulation of B-amyloid in the brain, which increases toxicity and cell damage, and generates greater neurodegeneration.[55] One study showed that some classes of exogenous B-amyloid (Aβ42 greater than Aβ40) take more time to clear due to merging with various types of B-amyloid receptors. Moreover, the amyloid species that took longer to be discarded have vascular effects such as vasoconstriction cause to its neurotoxic effect and high solubility.[55] Also, in another study where there is a decrease in GS in mice after a traumatic brain injury, it was concluded that this event could lead to the accumulation of neurotoxic agents such as Tau and B-amyloid.[13,38,48]

The susceptibility of the GS to trauma is a significant factor contributing to neurodegenerative diseases and neurological disabilities. A recent study evaluated the behavior of the GS after chronic mild TBI *in vivo* in rats by contrast-enhanced dynamic nuclear resonance and determined that both inflow and outflow of the indicator to neurons are restricted. In addition, anatomical regions more vulnerable to the decrease in GS flow were identified, such as the hypothalamus and the olfactory bulb, and at the same time, less affected areas such as the cortex, the hippocampus, and the thalamus, as well as others where the flow did not suffer any change like the cerebellum.[13] Similar

results were evidenced in another study where the TBI was mild and repetitive.[38]

Glymphatic System and Consequences of Neurotrauma

Traumatic brain injury has been associated with long-term cognitive deficits, generating various alterations that include loss of some percentage of memory, execution of movements, emotional lability, sensory deficits, altered attention due to neurodegeneration, and neuroinflammation secondary to trauma.[2] The most frequent posttrauma consequences are headaches and short- and long-term sleep alterations, with a bidirectional and feedback relationship, given that they have pathophysiology and anatomical structures in common, such as the thalamus, hypothalamus, brainstem, locus coeruleus, and raphe nuclei.[1,56] Insomnia and drowsiness are common after TBI and can persist for a long time in up to half of people. These symptoms can exacerbate other TBI discomforts such as stress, anxiety, depression, fatigue, chronic pain, headache, and altered cognition.[1,27] Behind the alterations in the initiation and maintenance of sleep, there are presumably changes in the circadian rhythm due to alterations in neurotransmitters and hormones in certain brain areas, such as melatonin,[33] galanin, and gamma-aminobutyric acid (GAMA) in the ventrolateral preoptic nucleus, tuberomammillary nuclei with orexin and histamine, raphe nucleus with serotonin, and the locus coeruleus with norepinephrine.[1]

On the other hand, mild and moderate brain injuries are usually the main trigger of posttraumatic headache, mainly caused by the release of calcitonin gene-related peptide and the imbalance between the metabolic demand and blood supply in the first instance. Within this loss of homeostasis, an alteration in the quantity and activation of the receptor can be found, as well as the concentration levels of some neurotransmitters such as glutamate and adenosine. Cerebral edema and the increase of intracranial pressure are the cause of acute posttrauma headaches due to the persistence of these mechanisms. However, in most of these patients, headache symptoms improve with symptomatic pharmacological management.[1,56]

Regarding sleep disturbances, regardless of their cause, poor sleep quality has negative effects on the clearance of inflammatory and neurotoxic substances that can prolong the natural disease of TBI, además, puede ser tanto causa como consecuencia del mal funcionamiento del SG postraumático. En modelos preclínicos se ha demostrado en roedores que presentaban una baja calidad en el sueño, luego de sufrir daño en el ADN por estrés oxidativo y activación de la respuesta a proteínas desplegadas.[27]

Conclusion

The GS is an extraordinary substance clearance system at the brain level with important normal and pathobiological implications, which is dependent on AQP-4 and other internal and external mechanisms of the CNS and the GS for its proper functioning, and its dysfunction is presented according to the degree, type, and extent of noxa. Given its characteristics of transport and distribution of substances, GS constitutes a target for future treatments of various diseases such as neurotrauma and neurodegenerative diseases.

More studies are required in specimens with similar brain structures to humans to extrapolate the findings and hypotheses of the behavior of the GS in the field of neurotrauma.

Orcid

Juan Jose Beltran-Ruiz https://orcid.org/0000-0001-6359-3630
Juan Sebastian Reyes-Bello https://orcid.org/0000-0001-6499-8162
Claudia Marcela Restrepo-Lugo https://orcid.org/0000-0003-2063-2825
Luis Rafael Moscote-Salazar https://orcid.org/0000-0002-4180-6962

References

1. Piantino J, Lim MM, Newgard CD, et al. Linking traumatic brain injury, sleep disruption and post-traumatic headache: a potential role for glymphatic pathway dysfunction. Curr Pain Headache Rep 2019;23(9):62. DOI: 10.1007/s11916-019-0799-4
2. Xiong Y, Mahmood A, Chopp M. Current understanding of neuroinflammation after traumatic brain injury and cell-based therapeutic opportunities. Chin J Traumatol 2018;21(3):137–151. DOI: 10.1016/j.cjtee.2018.02.003
3. Plog BA, Nedergaard M. The glymphatic system in central nervous system health and disease: past, present, and future. Annu Rev Pathol 2018;13:379–394. DOI: 10.1146/annurev-pathol-051217-111018
4. Nagelhus EA, Ottersen OP. Physiological roles of aquaporin-4 in brain. Physiol Rev 2013;93(4):1543–1562. DOI: 10.1152/physrev.00011.2013
5. Meyerhoff J, Chakraborty N, Hammamieh R. Glymphatics: a transformative development in medical neuroscience relevant to injuries in military central nervous system. Mil Med 2021;usab344. DOI: 10.1093/milmed/usab344
6. May R, Reddy U. Cerebrospinal fluid and its physiology. Anaesth Intensive Care Med 2020;21(1):60–61. DOI: 10.1016/j.mpaic.2019.10.017
7. Louveau A, Plog BA, Antila S, et al. Understanding the functions and relationships of the glymphatic system and meningeal lymphatics. J Clin Invest 2017;127(9):3210–3219. DOI: 10.1172/JCI90603
8. Martin BA, Heidari Pahlavian S. Chapter 5 - Anatomy and physiology of cerebrospinal fluid dynamics. In:Lonser RR, Sarntinoranont M, Bankiewicz K, editors. Nervous System Drug Delivery: Academic Press; 2019:73–89. DOI: 10.1016/B978-0-12-813997-4.00005-0
9. Breslin JW, Yang Y, Scallan JP, et al. Lymphatic Vessel network structure and physiology. Compr Physiol 2018;9(1):207–299. DOI: 10.1002/cphy.c180015
10. Mogensen FL, Delle C, Nedergaard M. The glymphatic system (En)during inflammation. Int J Mol Sci 2021;22(14):7491. DOI: 10.3390/ijms22147491
11. Iliff JJ, Nedergaard M. Is there a cerebral lymphatic system? Stroke 2013;44(6 Suppl 1):S93–S95. DOI: 10.1161/STROKEAHA.112.678698
12. Da Mesquita S, Fu Z, Kipnis J. The Meningeal lymphatic system: a new player in neurophysiology. Neuron 2018;100(2):375–388. DOI: 10.1016/j.neuron.2018.09.022
13. Li L, Chopp M, Ding G, et al. MRI detection of impairment of glymphatic function in rat after mild traumatic brain injury. Brain Res 2020;1747:147062. DOI: 10.1016/j.brainres.2020.147062
14. Taoka T, Masutani Y, Kawai H, et al. Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. Jpn J Radiol 2017;35(4):172–178. DOI: 10.1007/s11604-017-0617-z
15. Nedergaard M. Neuroscience. Garbage truck of the brain. Science 2013;340(6140):1529–1530. DOI: 10.1126/science.1240514
16. Ringstad G, Valnes LM, Dale AM, et al. Brain-wide glymphatic enhancement and clearance in humans assessed with MRI. JCI Insight 2018;3(13):e121537. DOI: 10.1172/jci.insight.121537
17. Eide PK, Vatnehol SAS, Emblem KE, et al. Magnetic resonance imaging provides evidence of glymphatic drainage from human brain to cervical lymph nodes. Sci Rep 2018;8(1):7194. DOI: 10.1038/s41598-018-25666-4
18. Eide PK, Mariussen E, Uggerud H, et al. Clinical application of intrathecal gadobutrol for assessment of cerebrospinal fluid tracer clearance to blood. JCI Insight 2021;6(9):e147063. DOI: 10.1172/jci.insight.147063

19. Eide PK, Ringstad G. MRI with intrathecal MRI gadolinium contrast medium administration: a possible method to assess glymphatic function in human brain. Acta Radiol Open 2015;4(11): 2058460115609635. DOI: 10.1177/2058460115609635
20. Ringstad G, Vatnehol SAS, Eide PK. Glymphatic MRI in idiopathic normal pressure hydrocephalus. Brain 2017;140(10):2691–2705. DOI: 10.1093/brain/awx191
21. Eide PK, Pripp AH, Ringstad G. Magnetic resonance imaging biomarkers of cerebrospinal fluid tracer dynamics in idiopathic normal pressure hydrocephalus. Brain Commun 2020;2(2):fcaa187. DOI: 10.1093/braincomms/fcaa187
22. Edeklev CS, Halvorsen M, Løvland G, et al. Intrathecal use of gadobutrol for glymphatic MR imaging: prospective safety study of 100 patients. AJNR Am J Neuroradiol 2019;40(8):1257–1264. DOI: 10.3174/ajnr.A6136
23. Roncali L, Virgintino D, Coltey P, et al. Morphological aspects of the vascularization in intraventricular neural transplants from embryo to embryo. Anat Embryol (Berl) 1996;193(3):191–203. DOI: 10.1007/BF00198323
24. Bolte AC, Dutta AB, Hurt ME, et al. Meningeal lymphatic dysfunction exacerbates traumatic brain injury pathogenesis. Nat Commun 2020;11(1):4524. DOI: 10.1038/s41467-020-18113-4
25. Hauglund NL, Kusk P, Kornum BR, et al. Meningeal lymphangiogenesis and enhanced glymphatic activity in mice with chronically implanted EEG electrodes. J Neurosci 2020;40(11):2371–2380. DOI: 10.1523/JNEUROSCI.2223-19.2020
26. Jessen NA, Munk AS, Lundgaard I, et al. The glymphatic system: a beginner's guide. Neurochem Res 2015;40(12):2583–2599. DOI: 10.1007/s11064-015-1581-6
27. Lucke-Wold BP, Smith KE, Nguyen L, et al. Sleep disruption and the sequelae associated with traumatic brain injury. Neurosci Biobehav Rev 2015;55:68–77. DOI: 10.1016/j.neubiorev.2015.04.010
28. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. Science 2013;342(6156):373–377. DOI: 10.1126/science.1241224
29. Lee H, Xie L, Yu M, et al. The Effect of body posture on brain glymphatic transport. J Neurosci 2015;35(31):11034–11044. DOI: 10.1523/JNEUROSCI.1625-15.2015
30. Fuxe K, Agnati LF, Marcoli M, et al. Volume transmission in central dopamine and noradrenaline neurons and its astroglial targets. Neurochem Res 2015;40(12):2600–2614. DOI: 10.1007/s11064-015-1574-5
31. Kiviniemi V, Wang X, Korhonen V, et al. Ultra-fast magnetic resonance encephalography of physiological brain activity - glymphatic pulsation mechanisms? J Cereb Blood Flow Metab 2016;36(6):1033–1045. DOI: 10.1177/0271678X15622047
32. Rajna Z, Kananen J, Keskinarkaus A, et al. Detection of short-term activity avalanches in human brain default mode network with ultrafast MR encephalography. Front Hum Neurosci 2015;9:448. DOI: 10.3389/fnhum.2015.00448
33. Sullan MJ, Asken BM, Jaffee MS, et al. Glymphatic system disruption as a mediator of brain trauma and chronic traumatic encephalopathy. Neurosci Biobehav Rev 2018;84:316–324. DOI: 10.1016/j.neubiorev.2017.08.016
34. Hsieh CL, Niemi EC, Wang SH, et al. CCR2 deficiency impairs macrophage infiltration and improves cognitive function after traumatic brain injury. J Neurotrauma 2014;31(20):1677–1688. DOI: 10.1089/neu.2013.3252
35. Arguello J. TCE - Traumatismo craneoencefálico Foro Iberoamericano de discusiones sobre la Familia de Clasificaciones Internacionales de la OMS (FCI-OMS) 2018 [Available from: https://www3.paho.org/relacsis/index.php/es/foros-relacsis/foro-becker-fci-oms/61-foros/consultas-becker/938-tce-traumatismo-craneoencefalicohttps://www3pahoorg/relacsis/index.php/es/foros-relacsis/foro-becker-fci-oms/61-foros/consultas-becker/938-tce-traumatismo-craneoencefalico.
36. Simon DW, McGeachy MJ, Bayir H, et al. The far-reaching scope of neuroinflammation after traumatic brain injury. Nat Rev Neurol 2017;13(3):171–191. DOI: 10.1038/nrneurol.2017.13
37. Bolte AC, Lukens JR. Neuroimmune cleanup crews in brain injury. Trends Immunol 2021;42(6):480–494. DOI: 10.1016/j.it.2021.04.003
38. Christensen J, Wright DK, Yamakawa GR, et al. Repetitive Mild traumatic brain injury alters glymphatic clearance rates in limbic structures of adolescent female rats. Sci Rep 2020;10(1):6254. DOI: 10.1038/s41598-020-63022-7
39. Killen MJ, Giorgi-Coll S, Helmy A, et al. Metabolism and inflammation: implications for traumatic brain injury therapeutics. Expert Rev Neurother 2019;19(3):227–242. DOI: 10.1080/14737175.2019.1582332
40. Lv T, Zhao B, Hu Q, et al. The glymphatic system: a novel therapeutic target for stroke treatment. Front Aging Neurosci 2021;13:689098. DOI: 10.3389/fnagi.2021.689098
41. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med 2012;4(147):147ra111. DOI: 10.1126/scitranslmed.3003748
42. Christensen J, Yamakawa GR, Shultz SR, et al. Is the glymphatic system the missing link between sleep impairments and neurological disorders? Examining the implications and uncertainties. Prog Neurobiol 2021;198:101917. DOI: 10.1016/j.pneurobio.2020.101917
43. Smith AJ, Yao X, Dix JA, et al. Test of the 'glymphatic' hypothesis demonstrates diffusive and aquaporin-4-independent solute transport in rodent brain parenchyma. Elife 2017;6:e27679. DOI: 10.7554/eLife.27679
44. Mestre H, Mori Y, Nedergaard M. The brain's glymphatic system: current controversies. Trends Neurosci 2020;43(7):458–466. DOI: 10.1016/j.tins.2020.04.003
45. Koundal S, Elkin R, Nadeem S, et al. Optimal mass transport with Lagrangian Workflow reveals advective and diffusion driven solute transport in the glymphatic system. Sci Rep 2020;10(1):1990. DOI: 10.1038/s41598-020-59045-9
46. Ray L, Iliff JJ, Heys JJ. Analysis of convective and diffusive transport in the brain interstitium. Fluids Barriers CNS 2019;16(1):6. DOI: 10.1186/s12987-019-0126-9
47. Ren Z, Iliff JJ, Yang L, et al. 'Hit & Run' model of closed-skull traumatic brain injury (TBI) reveals complex patterns of post-traumatic AQP4 dysregulation. J Cereb Blood Flow Metab 2013;33(6):834–845. DOI: 10.1038/jcbfm.2013.30
48. Iliff JJ, Chen MJ, Plog BA, et al. Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. J Neurosci 2014;34(49):16180–93. DOI: 10.1523/JNEUROSCI.3020-14.2014
49. Cherian I, Burhan H, Dashevskiy G, et al. Cisternostomy: a timely intervention in moderate to severe traumatic brain injuries: rationale, indications, and prospects. World Neurosurg 2019;131:385–390. DOI: 10.1016/j.wneu.2019.07.082
50. Cherian I, Bernardo A, Grasso G. Cisternostomy for Traumatic brain injury: pathophysiologic mechanisms and surgical technical notes. World Neurosurg 2016;89:51–57. DOI: 10.1016/j.wneu.2016.01.072
51. Kanmounye US. The rise of inflow cisternostomy in resource-limited settings: rationale, limitations, and future challenges. Emerg Med Int 2021;2021:6630050. DOI: 10.1155/2021/6630050
52. Cherian I, Yi G, Munakomi S. Cisternostomy: replacing the age old decompressive hemicraniectomy? Asian J Neurosurg 2013;8(3):132–138. DOI: 10.4103/1793-5482.121684
53. Henry RJ, Ritzel RM, Barrett JP, et al. Microglial depletion with CSF1R Inhibitor during chronic phase of experimental traumatic brain injury reduces neurodegeneration and neurological deficits. J Neurosci 2020;40(14):2960–2974. DOI: 10.1523/JNEUROSCI.2402-19.2020
54. Kratz SV. Case report: manual therapies promote resolution of persistent post-concussion symptoms in a 24-year-old athlete. SAGE Open Med Case Rep 2021;9:2050313X20952224. DOI: 10.1177/2050313X20952224
55. Peng W, Achariyar TM, Li B, et al. Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease. Neurobiol Dis 2016;93:215–225. DOI: 10.1016/j.nbd.2016.05.015
56. Doustar J, Danan IJ. Glymphatic system dysfunction in mild traumatic brain injury. Neurology 2022;98(1 Supplement 1):S24. DOI: 10.1212/01.wnl.0000801968.87371.4e