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Chapter

Brain Cooling and Cleaning: A New Perspective in Cerebrospinal Fluid (CSF) Dynamics

Hira Burhan and Iype Cherian

Abstract

The function of the cerebrospinal fluid (CSF) has long been considered for mechanical protection and recently attributed to the supply of nutrients to the brain. However, we hypothesize that the brain is a water-cooled and water-cleaned system. Recent studies on the glymphatic pathways and the introduction of cisternostomy as a surgical procedure for traumatic brain injury reveal a vast and in-depth functionality of the CSF, which works in synchrony with the cardiopulmonary rhythms to act as a buffer for optimum cerebral function. The nasal sinuses are located around the suprasellar cistern, and the evaporating wet mucosa within them during the breathing contributes to local cooling, whereas the nocturnal activation of AQP4 channels allows CSF-ISF exchange. The resultant "cooling and cleaning" of the brain not only maintains a physiological equilibrium but also opens doors for understanding and treating pathophysiology underlying common degenerative and neuro-inflammatory diseases. This chapter describes the novel theory of brain cooling and cleaning and the clinical and experimental evidence to support this hypothesis.

Keywords: glymphatic pathway, cisternostomy, CSF shift, Virchow Robin spaces, subarachnoid cisterns, hydrocephalus, aquaporin-4

1. Introduction

The cerebrospinal fluid (CSF) is an ultrafiltrate of plasma, which resides in two compartments within the central nervous system (**Figure 1**). The ventricular system comprises four interconnected cavities in the brain and contains a network of ependymal cells forming the choroid plexus which has been believed to be the site of production of the CSF. The ventricular system is continuous with the central canal of the spinal cord (from the fourth ventricle) and allows the CSF to continuously bathe the cranium and the spine. The subarachnoid spaces form openings termed as subarachnoid cisterns which separate the arachnoid and the pia mater, thereby creating an anatomic space between the two meninges. These cisterns are filled with cerebrospinal fluid and form the second compartment where the CSF flows within the cranial cavity.

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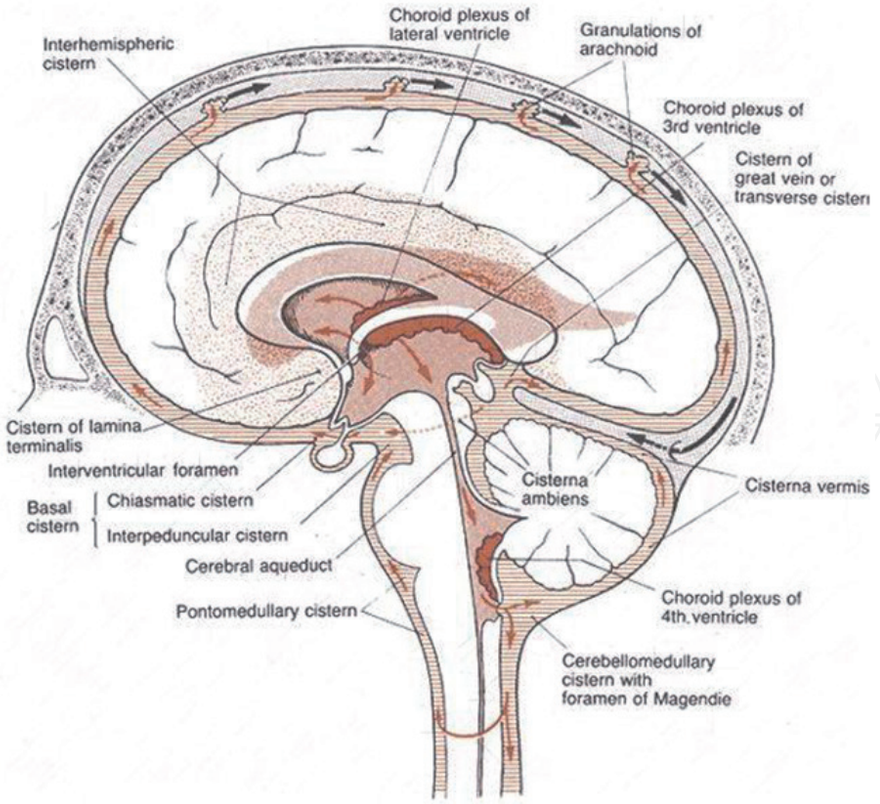

Figure 1.
The anatomy of the fluid compartments of the brain: ventricular and cisternal systems.

2. Cerebrospinal fluid: dynamics and function

Adult CSF volume is estimated to be 150 ml with a distribution of 125 ml within the subarachnoid spaces and 25 ml within the ventricles. This difference in the volume of CSF between the two compartments is important to understand the function of the CSF in a unique perspective.

The CSF secretion varies between individuals, usually ranging between 400 and 600 ml per day in an adult. The constant secretion of CSF contributes to a four to five times turnover per 24-h period. This turnover is of immense importance in exploring the functions of the CSF which have not yet been understood quite well. While the CSF has been considered as a source of nutrition and waste removal and a mechanically buoyant substance, cushioning the brain, the newer insights of the glymphatic pathways have demonstrated a critical role of CSF flow as a physiological buffer for brain functioning.

With a closely regulated composition, the CSF is valuable in analyzing cerebral pathologies. Alterations in the regulation of localized temperatures, malformation of proteins, and impeding clearance of pathologic proteins are the pathophysiological mechanisms for onset and progress of most neurodegenerative disorders as well as secondary brain damage in the setting of trauma. It is, however, interesting to analyze how the impairment of CSF inflow or outflow through the glymphatic system might lead to the cascade of these degenerative and traumatic pathologies.

2.1 The glymphatic pathway and the Virchow Robin (paravascular) spaces

The amount of CSF within the CSF compartments is a consequence of the net filtration and absorption of water through the selectively permeable capillary walls traversing through the brain tissue. This net effect is governed by the physiological

or pathological conditions prevailing within these compartments. The glymphatic system branches along the course of the arteries, arterioles, capillaries, and venules, forming a paravascular cast. This CSF interacts with the end feet of glia and indirectly with neurons to establish an exchange with the brain ISF (**Figure 2**).

The AQP4 channels mediate the bidirectional transport of water in response to passive osmotic and hydraulic pressure gradients [2, 3], resulting in the CSF-ISF exchange [4]. This makes the glymphatic system extremely pressure dependent. Any increase of pressure in the glymphatic system would produce the passage of fluid toward the interstitial space until the pressure in both compartments is equalized. This exchange drives the removal of exogenous molecules from the interstitial spaces of the brain [5, 6] (**Figure 3**).

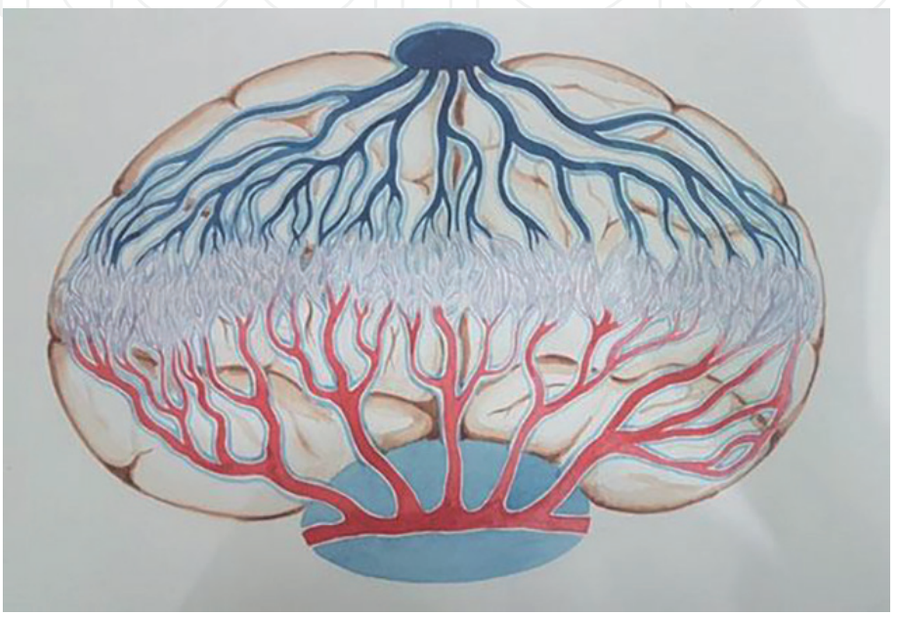

Figure 2.
Artistic representation that depicts the persistence of the paravascular system through the arteries, arterioles, capillaries, venules, and veins. This indicates that just as there is a vascular cast of the brain, there is a paravascular system cast as well. Courtesy: Cherian and Beltran [1].

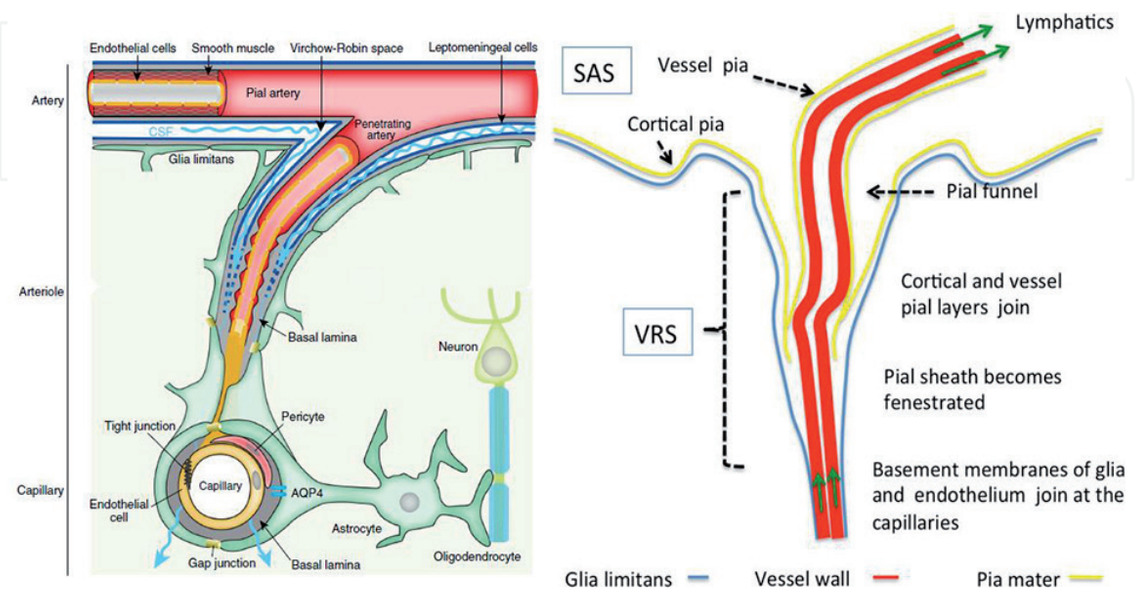

Figure 3.
The anatomy of the Virchow Robin spaces forming an extensive network of communication within the glymphatic pathway. Courtesy: Orešković and Klarica [7].

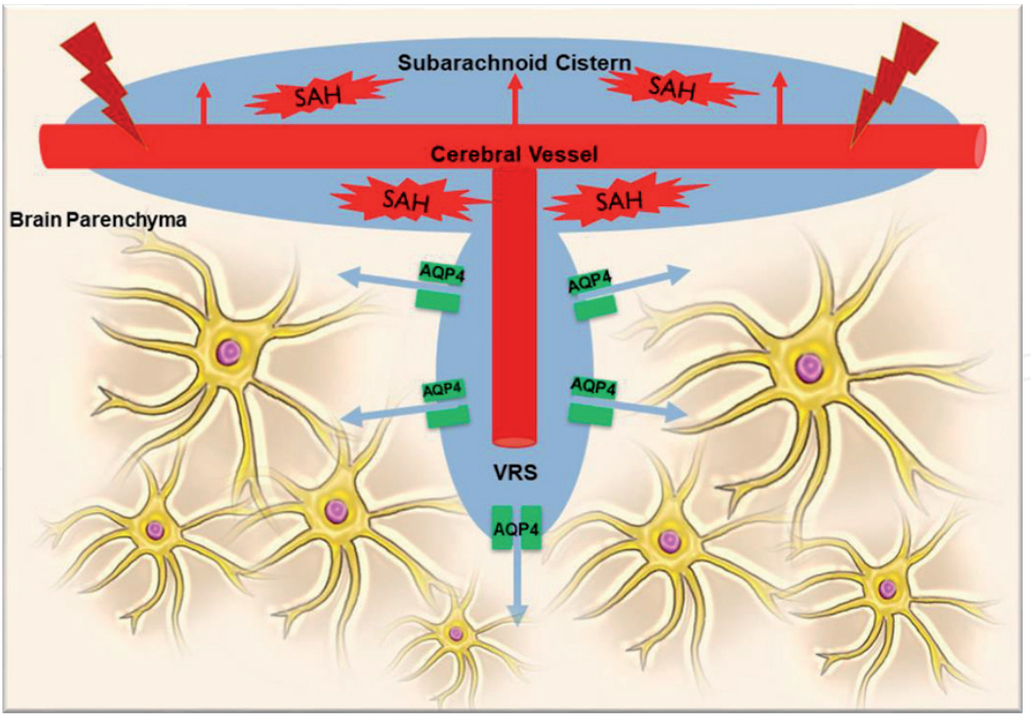

Figure 4.
Schematic representation of the mechanism of CSF-shift edema following traumatic brain injury. The AQP-4 channels on the lining of VRS allow the shift of CSF from the cisterns into the brain parenchyma leading to brain edema.

2.2 Introducing the concept of "CSF-shift" edema

The dependence of AQP4 to pressure gradients in both senses might be the underlying mechanism leading to the recently described "shift edema" following trauma [8] and also would explain the advantages of cisternostomy over craniectomy for the treatment in the short- and long-term follow-up of the patients [9]. Subsequent to subarachnoid hemorrhage, red blood cells are confined to the subarachnoid space and do not enter the VRS as pial membranes between the PVS and the SAS prevent the exchange of large molecules [10] (**Figure 4**).

3. Brain as a water-cooled and water-cleaned system

3.1 The subarachnoid cisterns and paranasal sinuses: anatomical relationships

The brain can be assumed as a water-cooled system with the CSF as a medium of heat removal and the paranasal sinuses as cooling surfaces. The close contact of the PNS with the suprasellar cisterns helps create a radiation system, and the mechanical process of breathing allows the sinuses to deliver the acquired heat from the brain parenchyma which is dumped by the CSF residing in the cisterns. Evaporation at the sinus surface causes cooling effect that is transmitted to the cisterns, dissipating the heat from the CSF which is acquired from the brain parenchyma [1] (**Figure 5**).

This cooling unit can be hypothesized to be a fundamental thermostat, and any hindrance in CSF flow might explain the cascade of protein misfolding secondary to heat accumulation as seen in neurodegeneration. While brain cooling is a passive process that occurs throughout the day, brain cleaning is more pronounced nocturnally. It is believed that brain cleaning is regulated by AQP4 and exchanges between interstitial fluid and CSF have been demonstrated to be more

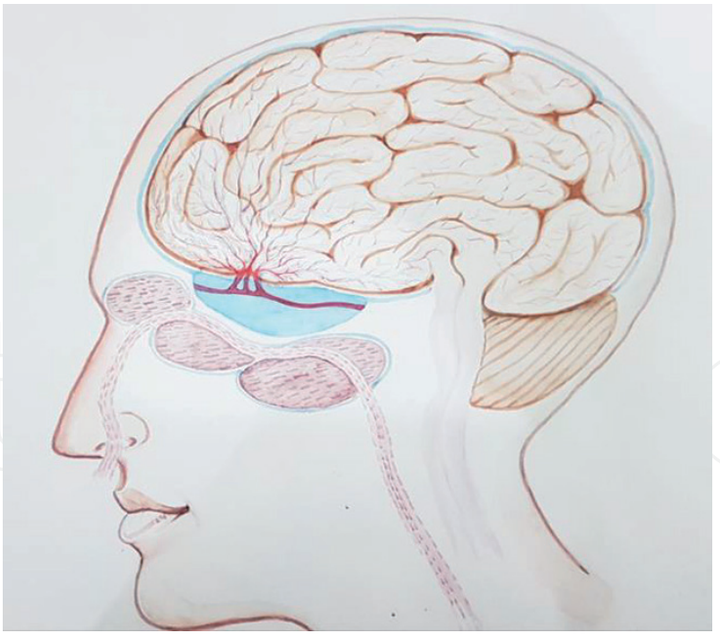

Figure 5.
Close communication of the paranasal sinuses with the cisterns creating a brain cooling unit. Courtesy: Cherian and Beltran [1].

active during sleep due to an expansion of the extracellular space, being increased by 60% during sleep [11], particularly in the lateral position [12]. The increased glymphatic clearance of the metabolic waste products generated by neural activity in the awake brain occurs during sleep, explaining the need to sleep for restoring alertness and activity.

3.2 Hypothesis of the CSF-driven brain cooling and cleaning mechanism

CSF is permanently produced and absorbed in the whole CSF system as a consequence of filtration and reabsorption of water volume through the capillary walls into the surrounding brain tissue. The three- to fourfold turnover rate in CSF production allows for a rigorous cerebral buffering at physiological states which helps maintain brain function. The brain generates tremendous amount of heat throughout the day which needs to be removed essentially to prevent protein misfolding and generation of free radicals. This warrants a system to allow for heat removal in the form of cooling as well as cleaning of metabolic wastes to prevent accumulation of toxic metabolites.

At a physiological state, the difference in arterial and venous hydrostatic and osmotic pressures allows a unidirectional flow of water and other molecules (soluble waste), with water leaving from the arterial end and molecules entering at the venous end. This simultaneous exchange of water and waste at two different ends can thus be regarded as a means of cleaning for the brain [5].

A deeper insight to this simultaneous exchange of water and waste in the blood vessels reveals the orientation of the brain vasculature, which, unlike other organs, runs in an opposite fashion, with the primary arteries lying ventral and more medially, whereas the principal veins run in a dorsal and lateral manner. Additionally, the disposition of white matter tracts creates an anisotropic field that facilitates the direction of fluid and molecules toward the main veins, which is further directed by changes in arteriovenous pressure gradients.

The paravascular system therefore maintains a very intricate and evolved system through extensive branching of vessels in the brain along with its paravascular

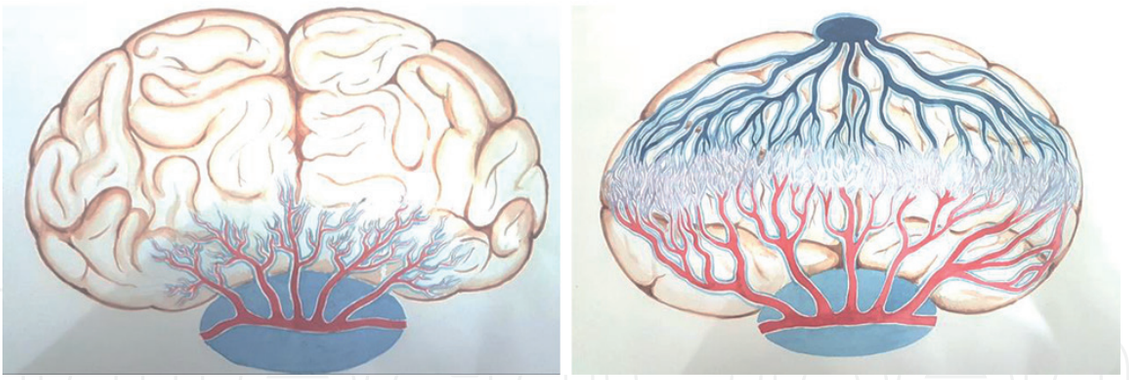

Figure 6.
Schematic representation of the Virchow Robin spaces traveling around the blood vessels from the cisterns into the brain. Courtesy: Cherian and Beltran [1].

system, thus following the vascular cast of the brain. This intricate system is limited by the selectively permeable capillary walls which is only large enough for a red blood cell to permeate through and may indeed be even more intricate than the vessels, since the limiting dimension of the capillaries is 3 in diameter, which is just large enough for a red blood corpuscle to squeeze through (**Figure 6**).

3.3 Role of breathing in brain cooling

The arteriovenous pressure difference described above can lead to the potential role of breathing on the dynamics of CSF flow within the extensive paravascular system. The close relationship of the paranasal sinuses with the basal cisterns provides an excellent radiation chamber that can help in buffering the thermal environment of the brain through continuous evaporation of the mucosa-lined sinus surfaces in contact with the external atmosphere, hence the hypothesis of breathing playing an important role in the cooling of the brain and possibly the clearance of molecules within the paravascular system.

3.4 Sleep and aquaporin-4 in brain cleaning

Attributed to the expression and function of the AQP-4 channels, the brain cleaning mechanism is predominant during sleep. Sleep increases the expansion of the extracellular spaces by up to 60% which allows for a maximal exchange of substances to and fro the CSF and the ISF compartments [11]. This phenomenon is particularly observed in the lateral position [12]. Therefore, the restorative properties of sleep may be linked to increased glymphatic clearance of the metabolic waste products that are generated by neural activity in the awake brain. This might underpin the beneficial effects of sleep, in clearance of metabolic byproducts, the phenomenon of jetlag, and the problems with lack of sleep.

4. Cardiopulmonary regulation of the CSF flow

The primary CSF delivery mechanism, from the subarachnoid space into the paravascular system and along the paravascular space, appears to be arterial pulsatility [6, 13], coupled with brain compliance [2] (**Figure 7**). Arterial pulsatility, coupled with a perivascular compliance, generates successive physical brain compression and expansion, allowing the brain to act like a sponge by virtue of the cycle-dependent systolic-diastolic circulatory movement of blood through

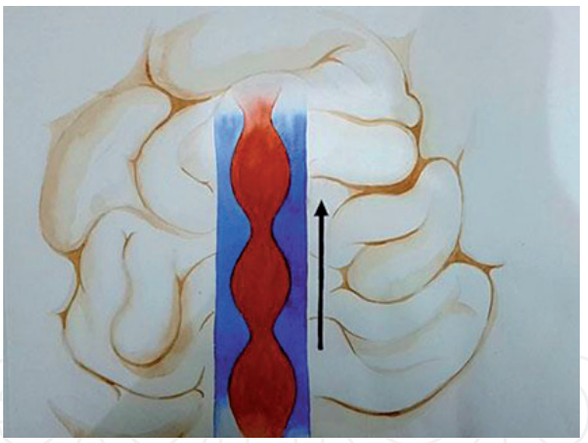

Figure 7.
Graphical representation of pulsations in the artery and veins being the driving force to the CSF in the paravascular pathway.

the brain [14]. This reciprocal movement influences the flow of fluids in the brain parenchyma to initiate a "pumping" effect of CSF around the vessels. These movements are driven by physiological oscillations of arterial and venous blood during craniospinal blood circulation, which are influenced by respiration, body activity, and posture [7].

Loss of arterial elasticity may lead to an impairment of this "pumping" effect in the paravascular system. This is classically seen in small vessel disease or as a consequence of low craniospinal compliance that impedes the expansion of the arteries, as can be seen in normal pressure hydrocephalus, gliosis [15], or post-traumatic hypertension. This would result in a decrease of CSF turnover that hinders the clearance of metabolites [16] and generates excess metabolic heat, thereby contributing to the pathogenesis of neurological diseases.

Aging is a phenomenon that leads to a decline in the exchange efficiency between CSF in the paravascular spaces, and ISF occurs. This can be related to a reduction in the vessel wall pulsatility of intracortical arterioles and the widespread loss of perivascular AQP4 channels [17]. This "hardening" of vessel walls, as a consequence of aging, decreases the drainage of amyloid peptides, which may deposit in the paravascular pathways as cerebral amyloid angiopathy (CAA). These deposits further impede the drainage of ISF along the paravascular spaces, resulting in loss of homeostasis of the neuronal environment that may contribute to neuronal malfunction [15, 18]. The concurrent loss of localized thermal regulation by the paravascular pathway may add to the cascade of damage by modification of proteinaceous components, which are very sensitive to subtle changes in temperature. These structural changes in molecular geometries might disturb solubility and thus the drainage of this metabolic waste, giving rise to a vicious circle.

5. Alterations in the glymphatic system: impaired brain cleaning and cooling

The functional impairment of the paravascular system appears to be an underlying condition of the aging human brain [19], which has also been related to various CNS disorders, such as neurodegenerative disorders that are brought on by the accumulation of misfolded, prion-like proteins (e.g., Alzheimer's or amyloid angiopathy) [17, 20, 21], normal pressure hydrocephalus [19, 22, 23], post-traumatic encephalopathy [24, 25], or neuroinflammatory disorders, such as multiple sclerosis. Furthermore, the presence of the paravascular system would explain the

advantages of cisternostomy over decompressive craniectomy, in the treatment of acute brain trauma [8, 26].

Decreased intracranial compliance leads to increased intraparenchymal pressure, affecting the arterial perfusion of the brain and promoting venous congestion. On the whole, the kinetics of the fluid in the paravascular spaces is impaired. Should there be a loss of AQP4 localization, as seen in reactive astrogliosis and the aging brain, or following trauma or ischemia, or if the CSF outflow is reduced as a consequence of either CSF flow obstruction, cerebral artery pulsatility inefficiency, cerebrospinal venous insufficiency, or lymphatic disorders [27], the localized perivascular CSF recirculation may be impaired.

5.1 Clinical implication

5.1.1 Cisternostomy: the clinical implementation of CSF-shift reversal in TBI

The corresponding author serendipitously uncovered the fact that opening cisterns in severe head trauma had the effect of abating severe brain swelling while drastically reducing the requirement for decompressive hemicraniectomies [24, 28]. His decade-long work on this led him to believe that CSF was ingressing to the brain through the Virchow Robin spaces, producing a condition which has been recently termed as CSF shift edema. Experimental studies on the glymphatic system by Iliff et al. categorically proved the communication of the CSF with the brain through the Virchow Robin spaces, or paravascular spaces, and that this pathway was critical for clearing the brain of metabolites [5, 6]. Perhaps the biggest clinical implication of this finding is the microsurgical opening of the cisterns: cisternostomy, in cases of moderate to severe head injury in order to reverse CSF shift edema, which is the mainstay of the cascade of the TBI damage. This procedure has been discussed in detail in previous publications and prevents progression to diffuse axonal damage or cortical stretch as otherwise seen in decompressive procedures. The phenomenal prognosis in the patients undergoing cisternostomy led the author to investigate the paravascular system in further depth, as well as CSF shifts, and subsequently the likely functionality of the paravascular system (**Figure 8**).

Today, cisternostomy has shown to be efficacious as a primary surgical intervention in moderate to severe traumatic brain injury. While following the principles of reversal of CSF shift edema, cisternostomy has proven to help in the prognosis by decreasing the rates of morbidities and mortalities [22]. It is now being practiced in many neurosurgical centers around the world [25] and has also been accepted

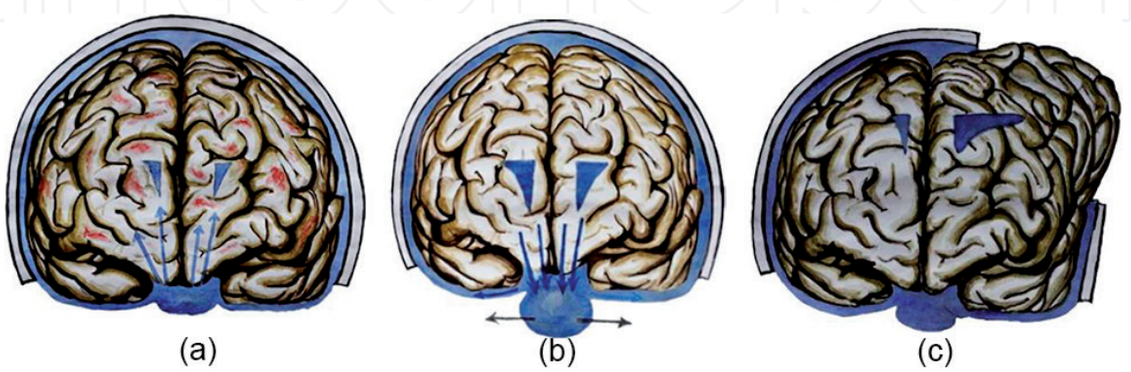

Figure 8.
(a) Raised cisternal pressure due to the traumatic subarachnoid hemorrhage shifts cerebrospinal fluid into the brain, causing raised intracerebral pressure. (b) Opening of the cisterns reverses the cisternal pressure gradient, causing cerebrospinal fluid to flow back into the cisterns, thus decreasing the brain pressure. (c) Decompressive hemicraniectomy allows extracalvarial herniation, leading to further deterioration due to axonal stretch and altered blood flow dynamics. Courtesy: Cherian et al. [24].

as one of the options of surgical intervention in the ongoing Global Neurotrauma Outcomes Study [29].

5.1.2 Road to further research

The paravascular system, its cleaning and cooling properties, and the consequent pathophysiological conditions secondary to the impedance of this system as well as potential treatment measures have not yet been investigated in detail. Reports of an experiment where a bacteriophage is being introduced into the olfactory system of a mouse resulted in the reversal of Alzheimer's symptoms. This could be due to the clearance of the obstructed paravascular system as the phage traveled into the cisterns through the perineural space of the olfactory. This observation opens doors for a paradigm shift in the management of neurodegenerative diseases and warrants extensive research. Further experimental work in this area will include the injection of paramagnetic nanoparticles into the suprasellar cisterns of mice, porcine, or baboon models, where the movement of these nanoparticles may be observed with a T1 W3T MRI.

6. Conclusion

The paravascular system is a branching structure that extensively connects the cells and vessels within the brain. The intricacy of the system and the challenges in performing studies have been a hurdle in exploring this system. However, an in-depth analysis of brain fluid dynamics and its relationship to the cardiopulmonary mechanisms can provide a game changing pathway to the preventive and therapeutic measures of various pathophysiological brain disorders.

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