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Fluids and flows in brain cancer and neurological disorders

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Abstract

Interstitial fluid (IF) and cerebrospinal fluid (CSF) are an integral part of the brain, serving to cushion and protect the brain parenchymal cells against damage and aid in their function. The brain IF contains various ions, nutrients, waste products, peptides, hormones, and neurotransmitters. IF moves primarily by pressure-dependent bulk flow through brain parenchyma, draining into the ventricular CSF. The brain ventricles and subarachnoid spaces are filled with CSF which circulates through the perivascular spaces. It also flows into the IF space regulated, in part, by aquaporin channels, removing waste solutes through a process of IF-CSF mixing. During disease development, the composition, flow, and volume of these fluids changes and can lead to brain cell dysfunction. With the improvement of imaging technology and the help of genomic profiling, more information has been and can be obtained from brain fluids; however, the role of CSF and IF in brain cancer and neurobiological disease is still limited. Here we outline recent advances of our knowledge of brain fluid flow in cancer and neurodegenerative disease based on our understanding of its dynamics and composition.

This article is categorized under:

Cancer > Biomedical Engineering

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Keywords

brain cancer; fluid flow; neuroscience

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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1 | INTRODUCTION

1.1 | Brain fluid compartments

The brain interstitial space is a dynamic location between the parenchymal cells and vasculature, which provides the fluid and structural environment to support cellular functions. There are three different types of fluid circulating in the brain involved in maintenance and homeostasis. (1) The cerebral blood, primarily in the cerebral veins and intracranial arteries, plays is important in maintaining proper brain perfusion, providing substrates necessary for proper neuronal function, and removing the waste products of metabolism (Fantini et al., 2016). (2) The cerebrospinal fluid (CSF) is a transparent fluid formed within the cerebral ventricles and exists in both the spinal and intracranial compartments (Davson et al., 1970). The CSF is continuously secreted by the choroid plexus, flowing into the brain ventricular space at a constant rate, and circulates in the subarachnoid space and spinal cord (Brown et al., 2004; Damkier et al., 2013). (3) Interstitial fluid (IF) is a fluid residing within the brain interstitial spaces between the parenchymal cells and extracellular matrix. The IF contains a variety of organic compounds and inorganic substances such as neurotransmitters, sugars, amino acids, coenzymes, hormones, salts, and other cellular products (Nakada & Kwee, 2019).

These three fluids are interconnected, however their roles, actions, and responses can vary in different disease states. In this review, we intend to summarize recent research illuminating how CSF and IF regulate brain function during disease development and progression. Beyond the role of a protective fluid cushion and sink for waste, we will focus on diagnosis, treatment, and prevention in central nervous system (CNS)-related diseases.

1.2 | Physiological function of fluids

The CSF has several important functions including providing physical protection, nourishing cells and tissues within the brain, and removing waste from the CNS (Pollay, 2010). Physical protection by the CSF is most apparent in its function as a shock absorber, buffering the impact of brain movement against the skull during impact (Sakka et al., 2011; Telano & Baker, 2021). The CSF also provides buoyancy to the brain effectively reducing its weight, and allowing the brain to maintain its shape (Telano & Baker, 2021). Since the CSF is continuously produced by the choroid plexus, there is a constant clean source of fluid introduced into the rest of the brain. Waste products that are originally produced through brain cell metabolism or synaptic activity are diluted in CSF and subsequently removed via the glymphatic system (Damkier et al., 2013; Huff et al., 2021; Segal, 1993). The glymphatic system is a major drainage pathway within the cortex that comprises a perivascular network, serving to transport CSF through the parenchyma (Iliff et al., 2012; Nedergaard, 2013). It is closely connected to a downstream extraneural drainage network, including meningeal lymphatics, cranial nerves, and large vessels that exit the skull (Louveau et al., 2015; Ma et al., 2017) (Figure 1). The CSF also flows into the interstitial space along this periarterial glymphatic compartment regulated, in part, by the aquaporin-4 (AQP4) water channel in astrocytic end-feet (Benveniste et al., 2019; Mestre, Hablitz, et al., 2018). The CSF carries glucose, proteins, lipids, and electrolytes, providing essential nutrients to CNS through these routes (Veening & Barendregt, 2010). The main

function of IF is, providing a “bath” around the brain parenchyma cells. Similarly to CSF function, the IF plays a role in transferring the energy needed for brain cell metabolism while also providing the specific mechanical environment for the physiological activities of the interstitial cells and extracellular matrix (Aukland et al., 1994; Cirrito et al., 2003; Hladky & Barrand, 2014; Kvietys & Granger, 2010). Moreover, the IF mixes with CSF as it drives the clearance of metabolites and waste products away from the periarterial space toward the perivenous space, finally excreting it through the meningeal lymphatic vessels to the cervical lymph nodes (Benveniste et al., 2017; Hirose et al., 2021). The nature of the IF flows are still being elucidated and thus, methods to image and analyze all the flows in the brain are essential to an understanding of healthy and diseased brain.

1.3 | Fluid flow measurement

Traditional CSF flow measurement is based on invasive procedures such as intracranial pressure monitoring, radioisotope studies, myelographies or lumbar puncture, all of which offer important information about different disorders of the CNS through detection of CSF abnormalities (Korbecki et al., 2019). The rapid development of imaging technology has provided noninvasive methods for assessing dynamic fluid flow, for example, phase-contrast magnetic resonance imaging (PC-MRI), arterial spin labeling (ASL), and 3D-SPACE. The PC-MRI technique is one of the most common procedures for qualitative and quantitative evaluation of CSF changes (Enzmann & Pelc, 1991; Nitz et al., 1992), and combined with other advanced brain imaging technology, provides a useful tool for measuring fluid flow dynamics in aging (Spijkerman et al., 2019), idiopathic intracranial hypertension (IIH) (Capel et al., 2018), brain atrophy (BA) (Yousef et al., 2016), and syringomyelia (Yeo et al., 2017). In clinical studies, PC-MRI has acquired information on the physiology of the normal CSF circulation, in addition to diseases such as aqueductal stenosis (Mohammad et al., 2019), chiari malformation (Smith et al., 2015) and normal pressure hydrocephalus (NPH) (Bradley, 2015; Tawfik et al., 2017), where flows are disrupted.

The IF is an important part of the brain interstitial system comprising approximately 20% of the total brain volume (C. Shi et al., 2015). Unlike with CSF, which is largely detected in the ventricles or other spaces around the brain, the IF is dispersed throughout the brain parenchyma, making it more difficult to access and image. The IF is dynamically distributed between the interstitial space and the brain microvasculature, within exceptionally confined spaces between the parenchymal cells and extracellular matrix. Additionally, the flow of IF is much slower than that of the CSF, often 100 times so (Mestre, Tithof, et al., 2018). Therefore, measurement of IF flow is more difficult than measurement of CSF flow with current methods. Techniques to measure or image the brain IF flow include tracer-based MRI techniques (Benveniste & Blackband, 2002; Han et al., 2014), intravital microscopy (Bedussi et al., 2018), nuclear medicine (Siekkinen et al., 2020) (e.g., positron emission tomography (PET), single-photon emission computerized tomography (SPECT), autoradiography), and transcranial Doppler (W.-J. Lee et al., 2019) (Table 1). Recently, tracer-based imaging was used in animal models of disease and human patients (Chatterjee et al., 2021; Da Mesquita et al., 2018; Kingsmore et al., 2018; Lv et al., 2017). The IF flow and drainage pathways were measured after injection of gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), and sequential T1-weighted dynamic contrast enhanced MRI

(DCE-MRI) to track IF movement (Han et al., 2012), which was applied in tumor bearing rat and mouse models, and translated to human glioma showing heterogeneous flow paths in and around brain tumors (Chatterjee et al., 2021; Guan et al., 2018; Kingsmore et al., 2018).

2 | FLUIDS AND FLOWS IN BRAIN CANCER

2.1 | Fluid flow and glioma invasion

Fluid flow is in intimate contact with the brain tumor microenvironment, particularly at the invasive edges of these cancers. The role of fluid flow in cancers has been most studied in gliomas, particularly in glioblastoma, the most deadly and common of brain tumors. IF flow has been found to increase and influence tumor cell invasion, proliferation and differentiation in noncentral nervous system cancers (Haessler et al., 2012; Polacheck et al., 2011; Shah et al., 2015). As early as 30 years ago, several investigators measured interstitial pressure of brain tumors finding that it was significantly elevated compared with normal tissues (Boucher & Jain, 1992; Gutmann et al., 1992; I. Lee et al., 1992). This pressure differential results in flow of IF (Munson & Shieh, 2014) from the tumor into surrounding normal tissue. As a result of predicting and measuring, it is estimated IF velocities range from 0.1 to 3 μm/s in animal models, depending on the size and location of tumors (Heldin et al., 2004). Using in vitro models of disease, increased IF velocities at the tumor edges can lead to invasion of tumor cells through two as yet identified mechanisms: gradient formation and mechanotransduction. Transcellular gradients form due to IF flow carrying cell-secreted proteins downstream of tumor cells where they bind to the extracellular matrix (Fleury et al., 2006; Stine & Munson, 2022). This transcellular gradient can promote directional metastasis of glioma cells by a mechanism named “autologous chemotaxis” (Fleury et al., 2006). In glioma, CXCL12 and its receptor CXCR4 have been shown to contribute to this mechanism of IF-mediated invasion both in vitro and in vivo (Cornelison et al., 2018; Kingsmore et al., 2016; Munson et al., 2013). CD44, a major receptor on many glioma cells, can also mediate flow-increased invasion through interactions with the extracellular matrix (Kingsmore et al., 2016). Qazi et al. (2011) demonstrated that fluid shear stress is an important factor influencing mechanotransduction-induced invasion through activation of matrix metalloproteinases (MMPs) leading to matrix degradation and subsequent cellular migration. Taken together, there are multiple governing mechanisms that mediate increases in glioma invasion by elevated IF flow, and likely, these mechanisms work in concert in the brain tumor microenvironment, enhancing malignancy of disease.

The IF constantly exchanges with CSF thus providing a reservoir for pro-tumorigenic proteins secreted by brain cancer cells during glioma progression. A recent clinical study showed that the expression of vitronectin, a known promoter of glioma invasion, in glioma patient tumor samples corresponded to levels detected in CSF samples (Fukushima et al., 2007). This study indicates that not only is the CSF is closely related to brain glioma cells during tumor development, it may provide essential factors that promote tumor spread. In another clinical study of CSF samples, researchers found that MMPs and their derivatives are markedly increased in glioma patients when compared to healthy patients (Friedberg et al., 1998). These findings showed MMP-2 and MMP-9 are directly transmitted to tumor cells via the glymphatic system resulting in increased invasion. Moreover, various activated

complex genes have been identified in the CSF including malignant promoter genes known to promote a more malignant tumor phenotype (Carrano et al., 2021). In terms of glioma invasion, the CSF has not been widely used in clinical practice so far for detection or assessment. However, as our knowledge grows surrounding the interactions of CSF with tumor invasion and progression, it offers a potentially important tool in clinical diagnosis and prognosis.

2.2 | Fluid biomarkers in glioma diagnosis

Conventional diagnosis of glioma relies on clinical presentation, including neuroimaging and histopathological analysis. With the development of technology in the field of neuroimaging, neurosurgery, oncology, and radiotherapy, the survival of glioma patients has improved, though only marginally for the most malignant disease (Osman, 2019; Tan et al., 2020).There is the need and opportunity to identify biomarkers to aid in diagnosis, prognosis and tracking of treatment outcomes. The CSF is an important source of potential molecular biomarkers, mostly collected by lumbar puncture or surgery around the brain area. Most analysis has thus far focused on detecting (1) cells (i.e., detecting circulating tumor cells); (2) cell-free tumor DNA (ctDNA); (3) nonprotein-coding transcripts (microRNA and noncoding RNA); or (4) tumor-related metabolites (Figure 2).

CSF cytology provides important initial information across a spectrum of pathologic conditions in glioma patients. In a recent clinical trial neoplastic meningitis from solid tumor was diagnosed by identification of circulating tumor cells (CTCs) in the CSF, which was analyzed by rare cell-capture technology (Nayak et al., 2013). Large-scale studies have reported several tumor types found through CSF sampling such as primitive neuroectodermal tumors (PNETs), high-grade infiltrating glioma, atypical teratoid/rhabdoid tumors (AT/RTs), and low-grade glioma (Ho et al., 2015). These tumor cells initially discovered in the CSF are the earliest meaningful sign for patients in that their detection can enable to clinicians react quickly with the most relevant therapy at earlier stages in tumor development and treatment.

The CSF is a rich and reliable source of ctDNA, and the analysis of this biomarker can characterize and monitor primary and metastatic brain tumors. The ctDNA is not only present in the CSF but also found in the blood of malignant tumor patients. However, the amount of ctDNA in the blood is limited in primary brain tumor patients, with only a minority of patients yielding detectable levels. Thus, in primary tumor patients, the ctDNA is better collected and analyzed from the CSF (Bettegowda et al., 2014; Zill et al., 2018). According to a recently published report, results leveraging deep sequencing of ctDNA obtained from the CSF of glioma patients, indicated that tumor-specific genes were altered (Pan et al., 2019). Interestingly, these tumor-specific gene alterations matched those obtained from samples of the primary tumor. Therefore, the ctDNA extracted from CSF may be used as a surrogate for tumor typing and analysis.

MicroRNAs (miRNA) are noncoding RNAs (ncRNA) of short length, consisting of 18–25 nucleotides (Lagos-Quintana et al., 2001) and are key biological factors in organism development, cell specialization, and homeostasis. Circulating miRNAs exist in almost all human body fluids including blood, serum, urine, saliva, tears, and CSF (Weber et al.,

2010). A number of clinical studies have shown that heightened expression of specific miRNAs is closely associated with malignant tumors, in particular the miRNAs contained in the CSF of brain tumor patients show promise as diagnostic biomarkers (Grotzer et al., 2015; R. Shi et al., 2015). One study in particular identified that metastatic tumor miRNA (i.e., miRNA-125a, miRNA-125b and miRNA-1290) was over-expressed in CSF samples, corresponding to expression levels in the tumor. These fundamental studies showed that miRNA-125a, miRNA-125b and miRNA-1290 can be diagnostic markers for metastatic tumors. In addition, the levels of miRNA-15b and miRNA-21 in CSF from patients with tumors are highly specific in comparison to the miRNAs collected from healthy patients (Baraniskin et al., 2012). Therefore, there is a particular subset of miRNAs that can readily identify brain tumors in clinical practice.

Cancer metabolism research has rapidly expanded in recent years. Metabolic profiling of CSF is used as a tool for diagnosing cancers in patients. Several different groups have collected samples from biofluids and tissues and have used nuclear magnetic resonance (NMR) or mass spectrometry to profile metabolites (Locasale et al., 2012; Nakamizo et al., 2013). According to this type of metabolic profiling analysis, detected metabolites in the CSF of tumor patients and nontumor patients differ (Hirayama et al., 2009). Similarly, metabolites, including specifically lactic acid and choline, in the CSF from high grade glioma patients were significantly increased compared with low grade glioma (Nakamizo et al., 2013). Together, the metabolite biomarkers identified in the CSF of brain tumor patients could provide clinically relevant biomarkers, assisting with diagnosis and providing valuable information for underlying mechanisms surrounding progression to malignant disease.

2.3 | Fluid flow in glioma therapy

Brain fluid flow as an integral component of the tumor microenvironment, plays an important role in the treatment of tumors. It has been detected and computationally modeled that elevated interstitial fluid pressure (IFP) in solid tumors results in IF flows in the surrounding tumor microenvironment (Boucher & Jain, 1992). High IFP has negative implications for chemotherapeutic treatment in that it can limit transport from the tumor microvasculature into the surrounding parenchyma, termed the blood-tumor barrier. Outward convection can also lead to drug removal from the peripheral regions reducing residence time with tumor cells (Welter & Rieger, 2013). Transport of small molecule (<1 kDa) drugs is diffusion-limited, while larger molecules and nanoparticles are subject to the convective flows induced by IFP gradients. IF flow can also be advantageous in terms of getting larger therapeutics through the interstitial space via convective forces. A method called convection-enhanced delivery (CED) involves the continuous infusion of therapeutic agents under positive pressure via implanted catheters (Anderson et al., 2013; Barua et al., 2013). CED can overcome heightened interstitial pressures, bypass the blood brain barrier, and enhance interstitial transport with minimal systemic toxicity while providing higher dosing to the tumor. These alterations of fluid flow via biophysical intervention offer one avenue for treating cancer and overcoming delivery challenges. Additionally, the molecules related to fluid flow responses of tumor cells may serve as targets for its treatment. Several molecules involving IF flow-enhanced invasion have been identified and are in various stages of development preclinically and clinically (Cornelison et al., 2018; Munson et al., 2013;

Shields et al., 2007). These molecules provide conduits to regulate the negative effects of IF flow on cancer progression. Overall, the CSF and IF are a rich biological information source, including circulating tumor cells, ctDNA, miRNAs, proteins and exosomes. Along with rapidly increasing sensitivity and specificity of these analyses, better understanding of the nature of these flows and interactions with tumor cells, and correlations to clinical parameters we expect in the near future, these clinically relevant markers could potentially translate to therapeutic targets.

3 | FLUIDS AND FLOWS IN ALZHEIMER'S DISEASE

3.1 | The role of fluid flow in Alzheimer's disease

Alzheimer's disease (AD) is a leading cause of dementia, and is pathologically defined by the presence of amyloid-β (Aβ) plaques and Tau-containing neurofibrillary tangles in the brain parenchyma. Aβ is removed from the brain by various clearance systems, including proteolytic degradation (Saido & Leissring, 2012), blood–brain barrier (BBB) transport (Deane et al., 2003), IF bulk flow (Bedussi et al., 2018), and CSF absorption into the circulatory (Bateman et al., 2006) and lymphatic systems (Tarasoff-Conway et al., 2015). As early as 20 years ago, a handful of in vivo studies indicated that the majority of Aβ plaques are removed by the BBB, and only a small amount of them are cleared by IF bulk flow (Shibata et al., 2000). However, through advancement of imaging technology and careful experimental work focused on IF bulk flow through the glymphatic system, the role of IF is larger than previously thought (Hablitz et al., 2020; Iliff et al., 2012; Xie et al., 2013). AQP4, one of the membrane-bound protein family, is expressed in the end-feet of astrocytes (Papadopoulos & Verkman, 2013). AQP4 plays a role in clearing interstitial Tau protein and Aβ and as such, dysfunction of AQP4 interferes with this clearance through changes in IF bulk flow within the glymphatic system in murine models of Alzheimer's Disease (Iliff et al., 2012; Silva et al., 2021). The CSF flow clears large proteins such as Aβ and Tau to the perivenous space through a dilution process with IF, finally removing them from the brain. These flows also clear through the meningeal lymphatics, found surrounding the brain, and into cervical lymph nodes (Eide et al., 2018; D. S. Lee et al., 2020). In animal models of Alzheimer's Disease, these vessels shrink, but delivery of Vascular Endothelial Growth Factor-C, a lymphatic-specific growth factor, can induce vessel growth in aging mice, and restore cognitive function (Da Mesquita et al., 2018).

3.2 | Fluid biomarkers in AD

The clinical diagnosis of AD is usually based on excluding other systemic disease and mainly diagnosed through cognitive ability or behavioral tests (Knopman et al., 2001). Recently, CSF biomarkers have been increasingly used in clinical trials for early diagnosis of AD. The CSF amyloid beta (Aβ)1–42 (Hansson et al., 2019), total Tau (T-Tau) (Schröder et al., 2008), and phosphorylated Tau (P-Tau) (Wattmo et al., 2020) have been assessed in numerous clinical studies. The total concentration of CSF Aβ1–42 decreases over time in AD patients, while the Tau and phosphorylated Tau protein levels in CSF become elevated later in the pathophysiological process (Buchhave et al., 2012). As such, the CSF Tau protein concentration is highly correlated with cognitive impairment as compared to Aβ (Savva et al., 2009). Several large multicenter clinical studies reported by Hansson et al.

(2006), Buchhave et al. (2012) and Mattsson et al. (2009) showed that CSF Aβ42, CSF T-Tau, and CSF P-Tau identify emerging AD with good accuracy, further indicating that these markers could diagnose AD at an early stage.

4 | FLUIDS AND FLOWS IN OTHER DISORDERS

Abnormal CSF circulatory dynamics can be affected in several CNS diseases including increased intracranial pressure (ICP), hydrocephalus (Bradley, 2015), idiopathic intracranial hypertension (Virdee et al., 2020), traumatic brain injury (Buttram et al., 2007), stroke (Simats et al., 2018), post-traumatic syringomyelia (Yeo et al., 2017) and brain tumors (Table 2).

4.1 | Hydrocephalus

Hydrocephalus is the buildup of fluid in the ventricles deep within the brain characterized by excessive accumulation of CSF, the result of disturbances in normal secretion or absorption mechanisms (Rekate, 2009). Early research suggested that hydrocephalus was caused by large ICP differentials between the ventricles and the spinal subarachnoid spaces, named noncommunicating hydrocephalus (Hakim et al., 1976). This elevated ICP caused CSF leaks, leading to abnormal drainage and/or CSF flows. Another type of hydrocephalus is communicating hydrocephalus (normal pressure hydrocephalus), which by definition does not result in increased ICP, but it usually co-exists with noncommunicating hydrocephalus. In adults, hydrocephalus commonly happens in patients with a history of strokes, trauma, infections, hemorrhage or tumors (Bodilsen et al., 2013; Bu et al., 2016; Fischer et al., 2014). In the clinic, physicians mainly use neurological exams and noninvasive brain imaging for diagnosis (Koleva & De Jesus, 2022). The most common treatment for hydrocephalus involves the surgical implantation of a shunt, followed by endoscopic third ventriculostomy. Several studies have indicated that aquaporin channels are involved in the pathophysiology of hydrocephalus through engagement of their role in fluid homeostasis (Desai et al., 2016; Hemley et al., 2012; Verkman et al., 2017). Animal studies have demonstrated that AQP1 can regulate the secretion and osmosis of CSF to control hydrocephalus (Wang et al., 2011). These results support the possibility of targeted gene therapy to provide nonsurgical management of hydrocephalus.

4.2 | Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH) is a syndrome characterized by elevated CSF pressure of unknown mechanism and has a high rate of occurrence. Its pathological characteristics are (1) increased CSF production, (2) reduced CSF absorption, and (3) hormonal dysregulation (Hornby et al., 2018; Mollan et al., 2016). Previous animal studies have reported AQP1 expression is closely related to raised ICP through increased CSF production (Stiebel-Kalish et al., 2013), however there is no direct evidence that AQP1 plays the same role in humans. Blood clotting abnormalities have been reported in IIH patients and may indirectly explain the impaired CSF drainage (Sussman et al., 1997). Moreover, in a recent study female IIH patients present increased hormone levels such as serum testosterone, CSF testosterone and androstenedione (O'Reilly et al., 2019). Androgens are known to modulate CSF secretion via the choroid plexus (Santos et al., 2017), a potential

driver of increased brain pressure, indicating the potential of targeting these hormones to resolve this condition.

4.3 | Traumatic brain injury

Traumatic brain injury (TBI) results when a person suffers a blow to the head often leading to disruption of normal brain function, severe injury or death. One common complication in TBI patients is CSF leakage. CSF leakage occurs most often in patients who have suffered head injuries involving skull fractures (Friedman et al., 2001). Patients with TBI can also develop edema, leading to increased ICP and resultant abnormal CSF flow (Bothwell et al., 2019). In rodent models of TBI, glymphatic flow is disrupted with TBI, with repetitive TBI resulting in accumulation of aberrant protein within the glymphatic spaces (Christensen et al., 2020; Iliff et al., 2014; Li et al., 2020). Similarly, disruption of the meningeal lymphatic drainage, thereby reducing the ability of flow to move through and exit the brain, results in worsened symptomology and damage after TBI (Bolte et al., 2020). To our knowledge, there have not yet been any CSF biomarkers that can be used clinically to diagnose TBI. However, several researchers have reported that inflammatory cytokines, such as IL-6, IL-8, and IL-10 are elevated in CSF after severe TBI (Buttram et al., 2007; Kirchhoff et al., 2008; Semple et al., 2010).

4.4 | Ischemic stroke

Stroke commonly occurs when the blood supply to part of the brain is interrupted or reduced, leading to reduced oxygen and nutrient supply. Fluid flow inherently is disrupted when a stroke occurs, as the blood brain barrier is broken down, often causing influx of blood into the tissue. Disrupted flow often results in cerebral edema (Arbel-Ornath et al., 2013; Dhar et al., 2020), and this has been related to reduced drainage via both glymphatics and the meningeal lymphatics (reviewed in Chen et al., 2021; Ji et al., 2021). The CSF is structurally positioned such that it can reflect the immediate immunological changes occurring within ischemic brain tissue. However, in clinical practice using the CSF for diagnosis of stroke is challenging, primarily limited by collection since it requires an invasive procedure that can be difficult to perform in emergency situations. Nevertheless, CSF evaluation could potentially provide additional information for the further pathogenic alterations that occur post initial event. According to published data, CSF proinflammatory cytokine levels, such as IL-6, IL-1β, and TNF-α, are elevated in stroke patients 6 h after onset as compared to a control group (Beridze et al., 2011). These cytokines can be used to assess the progression of stroke. Moreover, using CT-based imaging techniques to measure the volume of CSF in patients with stroke can be used to indirectly evaluate the progression of stroke via cerebral edema severity at peak swelling (Dhar et al., 2016, 2020). These clinical studies may contribute to a more complete interpretation of stroke pathology through the assessment of the CSF.

4.5 | Syringomyelia

Post-traumatic Syringomyelia (PTS) is a particular type of syringomyelia which along with presence of abnormal fluid filled cavities (syringes) after spinal cord injury. PTS generally develops within 5 years after the initial spinal cord injury and impairs CSF circulation (Carroll & Brackenridge, 2005). As early as the 1990s, the clinical studies have

shown that using MRI diagnosis of PTS with measurement of CSF flow in the cavity (Tobimatsu et al., 1995). The CSF flow can be classified into two main categories in the spinal subarachnoid space: pulsatile caudal and rostral flow (Enzmann & Pelc, 1991). Yeo et al. (2017) performed CSF velocity measurements in patients with a syringe with spinal cord injuries via T1-weighted MRI, and found that the average caudal velocities in the syringomyelia patients were 65% lower than in healthy individuals (Yeo et al., 2017). Several different surgical treatments have been favored for the treatment of PTS including laminectomy and opening-up of spinal CSF pathways to restore normal CSF flow dynamics (Falci et al., 2009; Karam et al., 2014; Vaquero et al., 2017). Overall, the prognosis after surgery is not very reliable with current treatment strategies, and thus further prospective work is required to correlate radiographic measures for diagnosing PTS early in its evolution. Further new therapies are being pursued and necessary including inclusion of stem cell therapies (Vaquero et al., 2017),

5 | CONCLUSIONS AND PERSPECTIVE

Fluid flow is an important part of the brain, both functionally and structurally. Despite studies and clinical trials showing that these fluids play a significant role in the development of brain cancer and neurological diseases, they are still relatively poorly understood and implemented. Thus far, most studies have focused on independent fluid flow either of the CSF or IF. However, the precise mechanisms that underlie CSF-IF exchange are yet to be fully defined though this remains an active area of research. As we gain more precise measurements of CSF and IF flow dynamics via MRI in normal and diseased brains, we may see that tracking fluid flow during brain cancer development or neurodegenerative disease progression may offer a useful tool in the diagnostic arsenal. Recently, Kingsmore et al. (2018) leveraged current MRI techniques by applying mass transport principles to calculate IF rates and directions in and around brain tumors. This was subsequently applied to patients with glioblastoma and showed correlations with survival in glioblastoma (Chatterjee et al., 2021). Similarly, this type of MRI technology can offer insight in other neurological disorders (Da Mesquita et al., 2018).

Compared with IF, CSF analysis has been more actively pursued in the clinic. Biomarkers within the CSF have shown potential in clinical trials. In brain cancer, collection of CSF samples from patients provides a resource for biomarker discovery, with the potential to provide patients with personalized and adaptive treatment. In addition, CSF biomarkers have shown good diagnostic performance for mild cognitive impairment in AD patients (Kang et al., 2014). However, there is still work to be done on standardization metrics for these biomarkers prior to clinical implementation. On the contrary, IF is a unique brain fluid that contains biomarkers that may have clinical utility and physiological implications, but sampling of IF for clinical applications has been limited due to a lack of straightforward methods to collect IF from brain. Moreover, existing in vivo tools do not enable measurement of large rarely encountered molecules, such as proteins and neuropeptides, in the fluid. Thus, generation of a complete picture of the neurochemistry of these fluids would be a foundational advance in the future to better understand the whole profile of fluids in the brain. Together, there is a need for more widespread research on collection of IF and possible future clinical practice required less invasive sampling methods. Such

technological advances can further our knowledge of IF composition and hence, the clinical use of IF for diagnostic and treatment applications. Overall, the view of fluids in the brain holistically is essential to best understanding neurological diseases, including both their flows and their composition. The potential is high for discovery, development, and treatment of numerous conditions by examination of this untapped resource within the brain interstitial and ventricular spaces.

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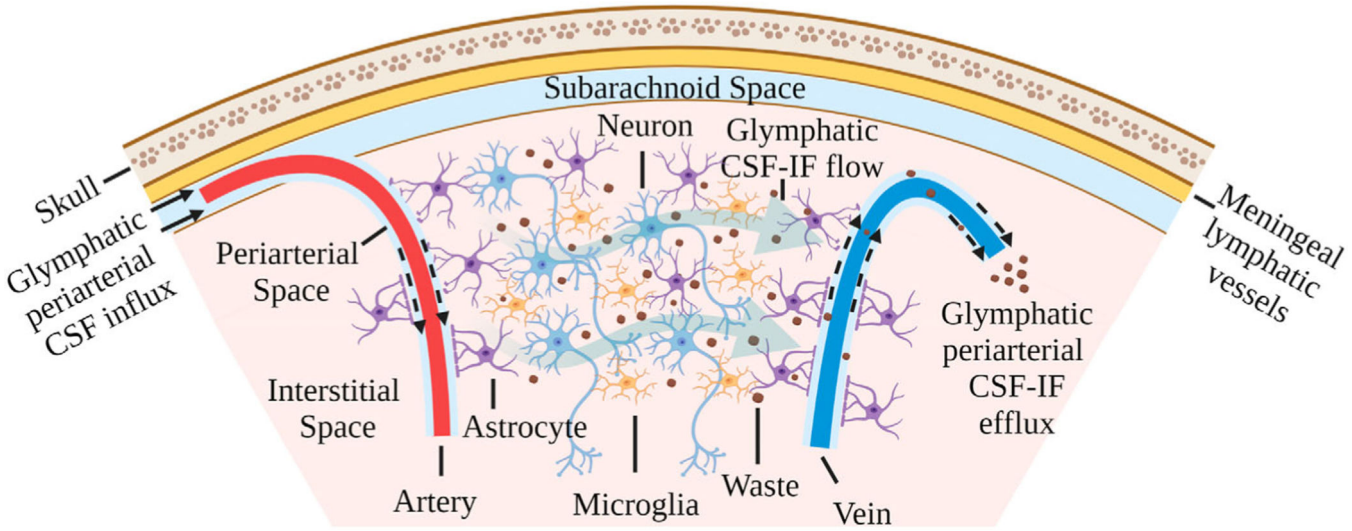

FIGURE 1.

Overview of glymphatic clearance. The glymphatic system drains cerebrospinal fluid (CSF) and solutes through the brain via its periarterial flow pathway, while the CSF is exchanged with IF, allowing interstitial solutes to be cleared out of the parenchyma via the perivenous pathway. Figure was created using Biorender with license to JMM.

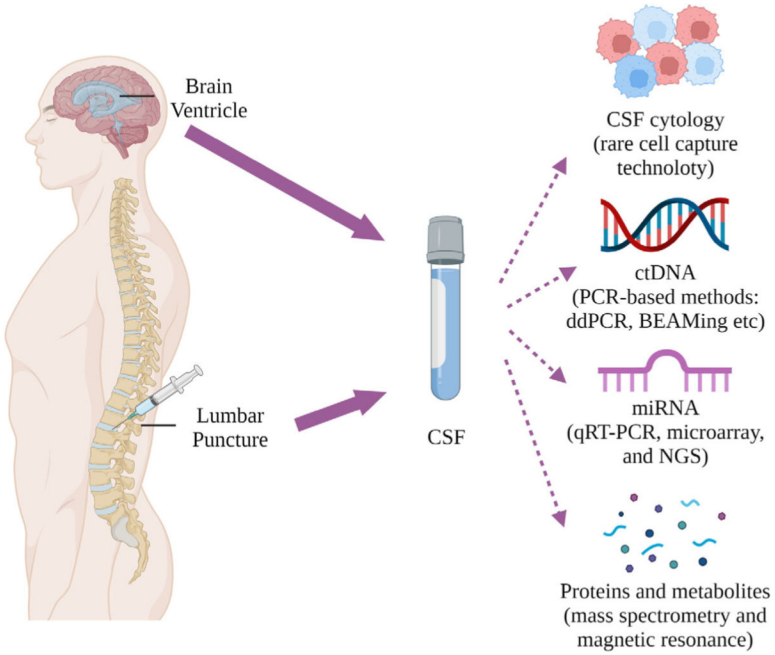

FIGURE 2.

The collection of CSF and potential analytes. The CSF contains several potential molecular biomarkers including cells, DNA, RNA and protein and other metabolites that can be used to diagnose and follow disease. BEAMing, beads, emulsion, amplification, and magnetics; ddPCR, droplet digital PCR; PCR, polymerase chain reaction; qRT-PCR, quantitative real-time-PCR; NGS, next-generation sequencing. Figure was created using Biorender with license to JMM.

TABLE 1

The summarizing the different methods of imaging and sampling

	CSF	IF
Method of imaging	MRI, ASL, 3D-SPACE, PET	MRI, PET, SPECT, intravital microscopy, autoradiography, transcranial Doppler
Method of sampling	Brain ventricle, lumbar puncture	Microdialysis, surgical sampling

Abbreviations: CSF, cerebrospinal fluid; IF, interstitial fluid.

TABLE 2

Fluid flow changes in different brain disorders (as compared to healthy brain)

Type of disease	IF flow rate	CSF flow rate
Alzheimer's disease	↓ (Sykova et al., 2005)	↑ (Attier-Zmudka et al., 2019)
Brain tumor	↑ (Kingsmore et al., 2018)	↑ (Uzair-Ul-Haq et al., n.d.)
Traumatic brain injury	N/A	↓ (Xiong et al., 2014)
Idiopathic intracranial hypertension	N/A	Acute patients ↑, Chronic patients ↓ (Akay et al., 2015; Belal et al., 2020)
Normal pressure hydrocephalus	N/A	↑ (Ahmad et al., 2021; Bradley, 2015; Tawfik et al., 2017)
Ischemic stroke	N/A	↑ (Dhar et al., 2020)
Post-traumatic syringomyelia	N/A	↓ (Yeo et al., 2017)