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Research paper

Is cerebral small vessel disease a central nervous system interstitial fluidopathy?

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ABSTRACT

A typical anatomical congregate and functionally distinct multicellular cerebrovascular dynamic confer diverse blood-brain barrier (BBB) and microstructural permeabilities to conserve the health of brain parenchymal and its microenvironment. This equanimity presupposes the glymphatic system that governs the flow and clearance of metabolic waste and interstitial fluids (ISF) through venous circulation. Following the introduction of glymphatic system concept, various studies have been carried out on cerebrospinal fluid (CSF) and ISF dynamics. These studies reported that the onset of multiple diseases can be attributed to impairment in the glymphatic system, which is newly referred as central nervous system (CNS) interstitial fluidopathy. One such condition includes cerebral small vessel disease (CSVD) with poorly understood pathomechanisms. CSVD is an umbrella term to describe a chronic progressive disorder affecting the brain microvasculature (or microcirculation) involving small penetrating vessels that supply cerebral white and deep gray matter. This review article proposes CSVD as a form of "CNS interstitial fluidopathy". Linking CNS interstitial fluidopathy with CSVD will open a better insight pertaining to the perivascular space fluid dynamics in CSVD pathophysiology. This may lead to the development of treatment and therapeutic strategies to ameliorate the pathology and adverse effect of CSVD.

1. Introduction

Cerebral small vessel disease (CSVD) is the umbrella term used to describes various groups of vascular disorders and pathological processes aetiologies following the impairment of the small vessels structural dynamics in the brain including small penetrating arteries, capillaries, and venules (Li et al., 2018; Pantoni and Gorelick, 2014). CSVD is observed in several different ways i.e., showing different pathologies through neuroimaging and clinical presentations such as stroke (ischemic and hemorrhagic strokes), cognitive impairment, vascular dementia, gait disturbances, apathy, and psychiatric disorders (Brown et al., 2018; Duering et al., 2023; Wardlaw et al., 2019). Despite the fact that CSVD has a role in the clinical presentation of patients with cognitive impairment, the relationship between CSVD and Alzheimer's disease is still unclear (Frisoni and van der Flier, 2023). The recent Standards for Reporting Vascular Changes on Neuroimaging 2 (STRIVE-2) provides the latest neuroimaging features of CSVD include recent small subcortical infarct, lacune, white matter hyperintensity, perivascular space, cerebral microbleed, cortical superficial siderosis, cortical cerebral microinfarcts as well as brain atrophy (Duering et al., 2023; Frisoni and van der Flier, 2023).

One major constituent for cerebral small vessel dynamics is the cerebrospinal fluid (CSF), the fluid resident in the central nervous system (CNS) flows within the perivascular spaces around cerebral arteries. It enters interstitial spaces via the water channels controlled by aquaporin-4 (AQP4), which is distributed in the astrocyte foot processes that make

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up the other wall of the perivascular space (Taoka and Naganawa, 2021). The CSF in the interstitial spaces washes away waste proteins accumulated in the brain tissues. Subsequently, the CSF flows into the perivascular space around the vein and flushed outside the brain. This transport system was hypothesized by Iliff et al. (2012). They posited that the CSF and interstitial fluid (ISF) in the perivascular spaces within the brain make up a mass transport system or pathway which links up to the lymphatic system (Iliff et al., 2012). Thus, this system was termed as "glymphatic system" – this name was coined by combining "g" for glia with "lymphatic" system. In the glymphatic system hypothesis, the perivascular space serves as a conduit for the CSF to flow into the brain parenchyma perivascular space (Taoka and Naganawa, 2021).

The brain interstitial system acts as a nanoscale network of continuously connected tubes and sheets surrounding each brain cell that functions as a space for mass transport and intercellular signal transmission. For a better understanding of CSF/ISF dynamics, the general term for the fluids (including blood, CSF, and ISF) submerging the CNS was coined as 'Neurofluids' (Taoka and Naganawa, 2021). Hence, the dysfunction or disruption of the glymphatic system as well as the brain interstitial system which subserves the "neurofluids" can be proposed as CNS interstitial fluidopathy. The driving force for the conduit subserving the cleaning role of the neurofluids is the arterial pulse (Iliff et al., 2013). Any alteration of cerebral pulse which is predominant in CSVD can lead to CNS interstitial fluidopathy. Therefore, this review aims to describe the link between the perivascular space fluid dynamics and CSVD, and to propose CSVD as a form of CNS interstitial fluidopathy.

2. Cerebral small vessel disease (CSVD)

CSVD is the diverse range of disorders with clinical manifestations (as observed through neuroimaging findings) resulting from pathological changes of various etiologies affecting the cerebral small vessels, notably small veins, venules, capillaries, arterioles, and small arteries of the CNS (Mustapha et al., 2019). The cerebral small vessels are essential for the maintenance of adequate blood flow to sub-surface brain structures. Alteration and structural changes of vascular and brain parenchyma may lead to the development and progression of CSVD. CSVD has been described as a precursor to the risks of ischemic strokes, functional loss, disability, and cognitive decline in the elderly (Li et al., 2018).

At present, CSVD is categorized into six distinct types based on to its etiology: (1) arteriosclerosis-related CSVD; (2) amyloid-related CSVD; (3) genetic CSVD (distinct from amyloid angiopathy); (4) inflammatory and immunologically mediated CSVD; (5) venous collagenosis; (6) and other CSVDs (Litak et al., 2020; Pantoni, 2010). The predominant subtypes of CSVD are identified as types 1–3 (as detailed in Table 1), and the remaining subtypes of CSVD were discussed in the comprehensive reviews by Litak et al. (2020) and Mestre et al. (2017).

2.1. Pathogenesis and manifestation

CSVD is caused by several different pathophysiological mechanisms that mostly affect the small blood vessels of the brain. However, the pathogenesis of CSVD is somewhat vague. Many risk factors have been identified, including hypertension, type-2 diabetes mellitus, thrombo-inflammation, dyslipidemia, oxidative stress, endothelial dysfunction, cerebral amyloid angiopathy as well as several genetic disorders (Che Mohd Nassir et al., 2021). Every case of CSVD has its underlying microvascular pathology. Hence, pathophysiology will be discussed based on the subtypes of CSVD.

Increase in the permeability of the blood-brain barrier (BBB) as well as endothelial dysfunction has been found culpable in the development of CSVD (Cuadrado-Godia et al., 2018). BBB leakage has been reported to be a common feature of CSVD with endothelial dysfunction seeming to be a pivotal factor contributing to the genesis of CSVD (Farrall and Wardlaw, 2009). Moreover, the disruption of BBB is a crucial pathological feature of CSVD. BBB is a specialized physiological and physical

Table 1
Classification of CSVD and its relationship with CNS interstitial fluidopathy. (Table Source: Mustapha et al., 2019).

Classification	Characteristics	Pathology	Relationship with CNS ISF
Type I	• Non-amyloidal CSVD • Associated with arteriolosclerosis (age- and vascular risk-factor-related small vessel diseases) • Advances with age • Degenerative microangiopathy • i.e., hypertension, diabetes	• Atrophy of smooth muscle cells in the tunica media (i.e., arteriolosclerosis) • Aggregation of fibro-hyaline material (i.e., lipohyalinosis) • Stenosis of lumen (i.e., microatheroma) • Thickening of vessel wall (i.e., microaneurysms) • Segmental arterial disorganization	• Reduction of the self-regulation ability of CBF (Xu et al., 2023) • BBB integrity failure (Xu et al., 2023) • High pulsations of the arterial walls reducing the net flow in the PVS (Gao et al., 2023) • Decreased or impaired AQP4 polarization (Xu et al., 2023)
Type II	• Amyloidal CSVD • Sporadic and hereditary CAA • Advances with age • i.e. Alzheimer's disease, Down's syndrome	• Accumulation of amyloid-β (Aβ) in the cortical walls (type 1) and leptomeningeal small arteries, but not capillaries (type 2) due to vascular occlusion and rupture • Vasculopathy (i.e., fibrinoid necrosis, loss of smooth muscle cells, wall thickening, perivascular blood breakdown, and microaneurysm) • APOE gene polymorphism (i.e., APOE "2 and APOE "4 allele related to types 2 and 1, respectively)	• Clearance failure due to Aβ deposition in cerebral microvessels (crucial for the drainage of ISF) (Xu et al., 2023) • Increased BBB leakage may be related to APOE genotype (Wardlaw et al., 2022) • Decreased AQP4 polarization in astrocyte endfeet (Xu et al., 2023) • Age-related decline in CSF production (Xu et al., 2023)
Type III	• Genetic-associated CSVD (distinct from amyloid angiopathy) • i.e., CADASIL and Fabry's disease	• Genetic mutations (i.e., glycosphingolipid GB3 in Fabry's disease) • Highly penetrant mutations involve the following genes: NOTCH3, HTRA1, TREX1, GLA, COL4A2 and FOXC1 • Formation of endothelial deposits • Degeneration of smooth muscles • Stenosis of cerebral arterioles	• Protein (i.e., Notch3) aggregation in the PVS causes glymphatic impairment (Mestre et al., 2017) • Abnormally organized AQP4 distribution in the astrocyte endfeet which loss of astrocytic coverage of the vasculature (Mestre et al., 2017)

barrier that protects against the invasion of the brain by circulating immune cells, invading pathogens, and molecules. Thus, damage to BBB allows entry of unwanted molecules, cells, and pathogens and this distorts the function of the brain. With advancing age and the presence of chronic hypertension, there is inability to self-regulate cerebral blood flow (CBF) in response to variations in blood pressure, this coupled with higher arterial stiffness, produces an increased speed and pulsatility of flow in the cerebral arterioles (Cuadrado-Godia et al., 2018). Therefore, damage in the cerebral endothelium of the BBB is inevitable due to the stress occasioned by the hemodynamic changes (Zhang et al., 2017).

Other components of the BBB such as pericytes and oligodendrocyte precursor cells have been reported to be potential contributors to the microvascular damage in CSVD (Cuadrado-Godia et al., 2018). Endothelial dysfunction has also been hypothesized to cause CSVD via various mechanisms: one of which is the reduction in cerebral flow (Armulik et al., 2005). In yet another study, it was reported that increased BBB permeability following endothelial dysfunction subsequently leads to brain parenchyma lesion that led to neuroimaging manifestation such as white matter hyperintensities (WMH) (Wardlaw et al., 2003; Young et al., 2008).

Additionally, evidence of endothelial failure in CSVD are reported to be presented in the form of elevated levels of pro-inflammatory markers (e.g., intracellular adhesion molecule 1), hyperhomocysteinemia, coagulation factors (i.e., fibrinogen, tissue factor pathway inhibitor), serum albumin, and albuminuria as well as serum neurofilament (Cuadrado-Godia et al., 2018).

2.2. Neuroimaging manifestation of CSVD

The onset of CSVD is often neglected due to the no-to-mild symptoms presented and is frequently asymptomatic. Neuroimaging of CSVD is a versatile tool employed in the diagnosis of CSVD. The latest neuroimaging features of CSVD include recent small subcortical infarct, lacune, WMH, perivascular space (PVS), cerebral microbleeds (CMB), cortical superficial siderosis, and cortical cerebral microinfarct (Duering et al., 2023).

Recent studies suggest that WMH are associated with brain atrophy in an additive fashion (Bos et al., 2017). It is reported that in people with WMH, both BBB permeability and mean diffusivity are increased more than what would be expected by aging alone, even in areas of normal-appearing white matter (Caunca et al., 2019). With the aid of magnetic-resonance imaging (MRI), WMH were better observed (Wardlaw et al., 2013c). When viewed in T2-weighted images, the white matter of the brain appears “hyperintense” when compared to homologous healthy tissue due to several pathological processes such as edema, gliosis and demyelination (Caunca et al., 2019). To have a better view of the brain parenchyma, fluid attenuated inversion recovery (FLAIR) prepared imaging is employed. This is to null the signal from CSF, which appears bright on a T2-weighted image. This brightness confounds the identification of lesions.

WMH manifests because of arteriosclerosis of the small vessels that supply the white matter, damage to capillary beds and venous collagenases (Pantoni, 2010; Wardlaw et al., 2013b). Persistent ischemia leads to the release of hypoxia-inducible factors, metalloproteinases and immunological mediators, which cause hyaline wall thickening, smooth muscle cell loss as well as narrowing of the vessel lumen (Fernando et al., 2006). Interference with auto-regulatory adaptations occurs in response to attenuation of cerebral blood flow because of the aforementioned changes. Hence, focal infarction as well as areas of demyelination result is observed as WMH on MRI (Caunca et al., 2019).

Recent small subcortical infarcts are lesions present in the territory of a perforating arteriole resulting from acute severe ischemia of a single arteriole. These lesions are regarded as ovoid cavities or round cavities that are 3 mm to 15 mm in diameter (Zhao et al., 2021). When viewed with MRI, they present hyper-intense on diffusion-weighted imaging (DWI), hypo-intense on the apparent diffusion coefficient map, as well as either normal or hyper-intense to a normal brain on FLAIR/T2 imaging and with less hyperintensity than cerebrospinal fluid on T2 (Zhao et al., 2021).

Perivascular spaces or Virchow-Robin spaces are fluid-filled spaces that surround small arteries and arterioles that perforate the brain surface (Caunca et al., 2019). PVS are commonly microscopic and cannot be viewed on conventional neuroimaging. Nonetheless, they become evident and conspicuous when viewed with greater resolution MRI. Also, PVS are apparent in older patients and associated with other imaging manifestations of CSVD such as WMH and lacunar infarcts (Ding et al., 2017).

Moreover, as reported by Wardlaw et al. (2013a,b,c), PVS are fluid-filled spaces that follow the typical course of a vessel as it travels through deep gray or white matter. PVS could serve as potential MRI marker to help understand the relationship between CVSD and fluidopathy. There is a paucity of information in this regard. PVS may be caused by increased fluid exudation because of greater vascular permeability, obstruction of the lymphatic drainage system or parenchymal atrophy (Caunca et al., 2019). Also, PVS is pathologically related to pro-oxidative enzyme activation and hypertension (Gutierrez et al., 2015).

On the other hand, CMBs are small (measuring up to 10 mm) areas of signal void on T2-weighted imaging (Wardlaw et al., 2013c). Although initially associated with the presence of a concomitant lobar hemorrhage, they have also been discovered in community-based samples (Caunca et al., 2019). They are found to be related to bleeding-prone microangiopathy of various origins. The locations of CMBs differ by etiology. The CMBs detected in cortical location suggests amyloid angiopathy, while those observed in deep locations (such as basal ganglia and thalamus) suggests hypertensive vasculopathy (Greenberg et al., 2009).

CMBs are associated with many processes that weaken cerebrovascular integrity, and thus increase the risk of bleeding. Such processes include elevated blood pressure (especially in deep subcortical regions), carotid stenosis, carotid intima-media thickness as well as arterial stiffness (Del Brutto et al., 2015; Romero et al., 2015). Moreover, multiple studies have reported that the increased prevalence of lobar CMBs is due to the presence of APOEε4 allele, nevertheless a direct causality remains inconclusive (Graff-Radford et al., 2017; Romero et al., 2014).

3. ‘Neurofluids’ dynamic and its network

The glymphatic system is a brain-wide perivascular fluid transport system over which CSF (that surrounds the brain) exchanges with ISF (present within the brain parenchyma) and clears it of waste products. It is analogous to the lymphatic system in the peripheral tissues. This system facilitates proper functioning by limiting accumulation of neurotoxic substances and enabling the flow of nutrients, growth factor and neuromodulator (Young et al., 2019). The glymphatic efflux of ISF is reported to play a significant role in the clearance of several metabolic waste products, such as Aβ and *tau* especially during sleep (Iliff and Nedergaard, 2013).

Recently, the concept of “Neurofluids” (including arterial, venous, CSF, and ISF systems) was proposed as a comprehensive concept for the fluid dynamics of the CNS. The cranium houses numerous space-competing material compartments: the brain parenchyma and the four extracellular fluids, namely arterial, venous, CSF, and ISF. Any disturbance of these fluid compartments can alter the brain dynamics, potentially increasing intracranial pressure, affecting perfusion, and hampering clearance of metabolic waste (Taoka and Naganawa, 2021). These factors all sum up to the CNS interstitial fluidopathy.

For a better understanding of the workings of the neurofluids, glymphatic and brain interstitial systems, let’s look at the various components that make up this clearance system. The glymphatic system is composed of three parts: a para-venous ISF clearance route, a para-arterial CSF influx route and a trans-parenchymal component that is

dependent on astroglial water transport (Suescun et al., 2019). As the macroscopic waste clearance system of CNS, the glymphatic system is responsible for eradicating soluble proteins and metabolites, including Aβ and tau (Iliff et al., 2012).

The neurotoxic compound clearance process within the glymphatic system is described as a three-step serial process. Firstly, the CSF is repeatedly transported from the subarachnoid and Virchow-Robin spaces to the peri-arterial spaces in a bulk flow driven manner; subsequently, CSF is propelled from the peri-arterial compartment into the ISF space. The convection and mixing of CSF and ISF are enhanced by aquaporin 4 (AQP4) in the dense and complex brain parenchyma. Eventually, CSF-ISF fluid mixes with interstitial waste solutes and is subsequently transported to the peri-venous space from the meningeal lymphatic vessels to the lymphatic vessel and circulatory system (Ren et al., 2021).

AQP4 is needed to maintain the glymphatic role and is sufficiently expressed in the end-feet of astrocytes that surround veins and arteries. It is also fastened to the astrocyte's membrane by the carboxyl terminus of α-syntrophin (Ren et al., 2021). Syntrophin-dependent AQP4 mediates the two-way transport of water molecules through the BBB (Amiry-Moghaddam et al., 2003). It is suggested that AQP4 may be responsible for the facilitation of CSF movement from the perivascular space into the interstitial space, thus flushing the ISF (Mestre et al., 2018).

Furthermore, AQP4 reduces the resistance to CSF movement from the perivascular space into the interstitium and subsequently from the interstitium into the peri-venous space. As CSF flows through the glymphatic pathway, there is elimination of metabolic waste products, such as Aβ and lactic acid from deep inside the brain and delivers nutrients or therapeutic drugs to the brain parenchyma. Thus, the glymphatic system acts as a conduit for the distribution of nutrients and therapeutic drugs (Ren et al., 2021).Fig. 1 summarizes the inter-relations of different classification of CSVD with CNS interstitial fluidopathy.

4. CSVD and CNS interstitial fluidopathy

As earlier stated, CSVD is a myriad of diseases affecting various cerebral blood vessels, thus leading to injury to the cerebral matter (both white and gray). These diseases include amyloid angiopathy, arteriosclerosis as well as a host of other hereditary small vessel diseases (Taoka and Naganawa, 2021). These diseases impair CSF/ISF dynamics through the compromise of the integrity of the capillary basement membranes from the pathways through which fluid passes into and out of the brain (Morris et al., 2016). Disruption of the proper flow of "neurofluids" over a protracted period will invariably cause fluidopathy. This is instigated through PVS, hardening of the vesicular smooth muscle wall, presence of Aβ as well as other abnormal proteins in glymphatic pathway (particularly in blood vessels). These are hallmarks of CSVD (see Fig. 2).

4.1. PVS

Perivascular spaces are part of the normal physiological structures that are filled with CSF and coated by pial cells. They surround the wall of arteries, arterioles, veins, and venules as they penetrate the brain parenchyma. PVS are part of the glymphatic system and are involved in waste clearance, energy substrate delivery and blood flow regulation (Duperron et al., 2018).

In CSVD, the PVS becomes dilated or enlarged – detectable on brain MRI. A PVS of more than 3 mm is considered to be dilated (Duering et al., 2023). PVS are shown to be correlated with other MRI markers of CSVD and are also thought to be associated with increased risk of dementia (Zhu et al., 2010). Converging evidence suggests that PVS may have at least partly distinct underlying risk factors, including genetic and clinical consequences depending on their location (Duperron et al., 2018).

The mechanisms surrounding PVS cannot be ascertained. However, it is thought to be caused by astrocytic hypertrophy and loss of perivascular AQP4 polarization, leading to dysregulation of astroglial water transport, as well as BBB dysfunction (Duperron et al., 2018). AQP4 is rheologically involved in regulating the influx and efflux of ISF flow. A recent study utilizing the spontaneously hypertensive rats (SHRs) indicated that an abnormality in glymphatic transport is implicated in the etiology of arteriolosclerotic CSVD due to a combination of PVS and impaired astrocytic AQP4 polarity (Xue et al., 2020). PVS are suggestive of chronic poor perivascular drainage of cerebral arteries, predisposing individuals to impaired or altered meningeal lymphatic drainage and causing defects in amyloid clearance and subsequent cerebral amyloid angiopathy development.

4.2. Endothelial dysfunction

Endothelial cells (ECs) serve as a functional and structural barrier between tissue and blood, modulating circulating components transport, regulating blood flow, and taking part in inflammatory processes. ECs play a significant role in brain tissue as a component of the BBB and the neurogliovascular unit (NGVU). As a result, changes in ECs function or amount are first thought to be an etiological contribution to CSVD. Nonetheless, several investigations have shown that even in severe CSVD, the brain ECs remain microscopically intact, with no evidence of cellular death (Hainsworth et al., 2015; Lammie, 2002). Indeed, the endothelial dysfunction-induced brain injury presents itself in a variety of ways via various pathophysiological mechanisms, leading to the transformation of ECs into an abnormal pro-inflammatory and pro-thrombotic phenotypes (Bai et al., 2022). Both impairment and autoregulation of cerebral blood flow were identified in CSVD patients

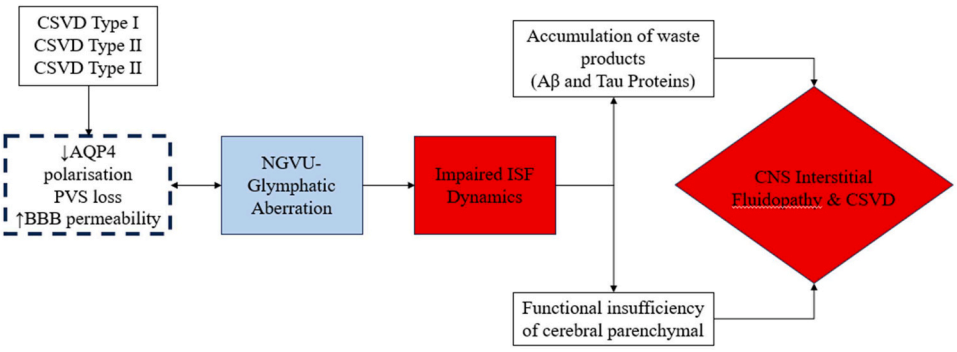

Fig. 1. : The pattern diagram of relationship between cerebral small vessel disease (CSVD) and central nervous system (CNS) interstitial fluidopathy. AQP4, aquaporin 4; PVS, perivascular spaces; BBB, blood-brain barrier; NGVU, neurogliovascular unit.
Figure is adapted from (Che Mohd Nassir et al., 2021).

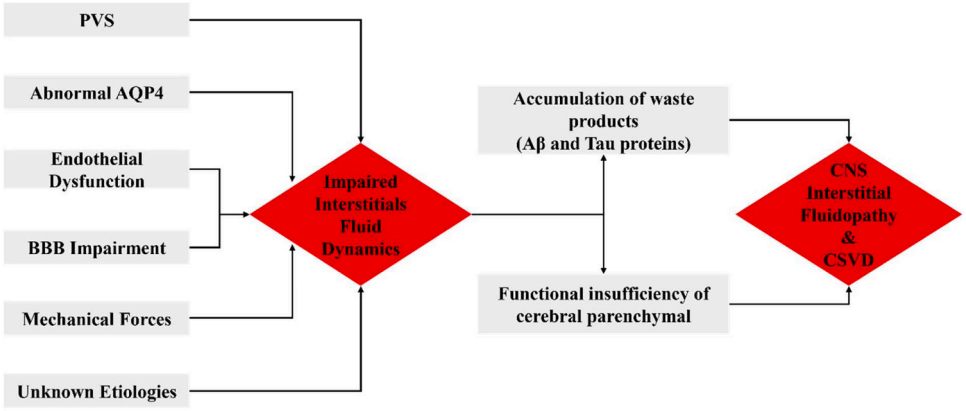

Fig. 2. : Proposed inter-relations of central nervous system (CNS) interstitial fluidopathy with different etiologies related to cerebral small vessel disease (CSVD). AQP4, aquaporin 4; BBB, blood-brain barrier; PVS, perivascular spaces.

utilizing positron emission tomography (PET) and MRI (Poggesi et al., 2016). Because one of the fundamental functions of ECs is to modulate the vascular tone of the vessel wall in cerebral arteries and microvessels, they are clearly engaged in this pathogenic alteration of the ISF dynamics.

4.3. BBB impairment

The endothelial tight junctions, astrocytic end-foot processes ensheathing capillaries, and pericytes embedded in basement membrane are the primary components of the BBB. It controls the passage of ions, chemicals, and cells between the circulating blood and the CSF or brain parenchyma, ensuring normal neuronal activity and safeguarding the brain from toxic substances and pathogens. A breakdown of the BBB allows fluids and other plasma constituents to extravasate, resulting in PVS, localized damage to brain parenchyma such as CMBs, and white matter changes (Gao et al., 2022; Hartz et al., 2012; Ihara and Yamamoto, 2016).

Previous studies suggest that BBB dysfunction is a critical contributor to CSVD pathophysiology is mounting (Wardlaw, 2010). The dynamic contrast-enhanced (DCE)-MRI has recently emerged as a unique method for quantifying BBB permeability in patients. Multiple studies using the DCE-MRI method revealed that BBB integrity was disrupted in CSVD patients, and that the extent of increased BBB permeability was associated with a higher burden of WMH as well as cognitive decline (Li et al., 2018; Walsh et al., 2021). Similarly, there is a strong association between poor functional outcome and higher BBB permeability in CSVD patients has been discovered in a longitudinal investigation (Wardlaw et al., 2013a).

Furthermore, the impairment may increase interstitial fluid volume and thicken and/or stiffen arteriole walls, aggravating vasodilation and impairing oxygen and nutrient transport (Wardlaw et al., 2019). Previously, edemas in white matter lesions were detected in autopsy studies, indicating fluid leaking due to compromised BBB (Black et al., 2009; Feigin and Popoff, 1963). A study that used albumin extravasation to measure BBB integrity found widespread leakage in the ageing brain, which accumulated in severe white-matter lesions (Simpson et al., 2007). This suggest that lack of BBB integrity contributes to the impairment of ISF dynamics.

4.4. Arteriosclerosis

In aging brains, arteriosclerosis is a common small vessel alteration. Cerebral arterial wall stiffening may lead to a reduction in arterial pulsatility as well as facilitating PVS (Iliff et al., 2013). The arterial wall stiffening may alter CSF/ISF dynamics leading to impairment in glymphatic clearance and ultimately fluidopathy. This is because the driving force for spaces subserving the “neurofluids” clearing function is the arterial pulse (Iliff et al., 2013).

4.5. CAA

CAA involves amyloid deposition in the vessel walls in the cerebral cortex as well as overlapping leptomeninges, causing symptomatic intracerebral lobar intracerebral hemorrhage in the elderly. CAA is believed to share Aβ pathology with Alzheimer’s disease. An experimental study demonstrated that CSF inflow and ISF clearance in the brain is suppressed in a mouse model of Alzheimer’s disease. The CSF/ISF dynamics is suppressed prior to the significant accumulation of Aβ (Peng et al., 2016).

Recently, CAA has been suggested in association with MRI-visible PVS in centrum-semiovale, contrary to a more severe MRI-visible PVS in basal ganglia that is frequently seen in chronic hypertension (Charidimou et al., 2017). A study reported that PVS in the cetrum-semiovale, which may suggest impaired ISF drainage, significantly correlated with the existence of cerebral amyloid CAA even in the absence of any lobar hemorrhage (Martinez-Ramirez et al., 2018).

4.6. Hereditary CSVD

Genetic study on CSVD revealed that cerebral autosomal dominant ateriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) which is caused by a mutation of *NOTCH3* gene accounts for the largest number of cases of cerebrovascular disease due to single gene dysfunction. Here, vascular smooth-muscle-cell degeneration ensues in the brain, leading to dysfunction in the CSF/ISF dynamics. This dysfunction prompts the excretion and deposition of granular osmiophilic material (GOM). GOM is believed to be responsible for smooth-muscle-cell degeneration (Taoka and Naganawa, 2021).

Other hereditary small vessel diseases cause CNS interstitial fluidopathy through the effects they exert on vascular, perivascular, and interstitial structures of the brain (Yamamoto et al., 2011). Furthermore, histologic evaluation of brain tissues has revealed irregular thickening, disruption, splitting and fragmentation of the capillary basement membrane together with the accumulation of pools of basement fragments (Nandeesh et al., 2020). Since the cerebral vascular basement membranes form the pathways by which fluid passes into as well as out of cerebral tissues, alterations of the basement membrane by any of the numerous CSVD will probably cause impairment of CSF/ISF dynamics and ultimately lead to fluidopathy.

4.7. CNS interstitial fluidopathy and neurological diseases: its correlation

Alzheimer’s disease (AD), which is characterized by amyloidopathy

or taupathy, is one of the "CNS interstitial fluidopathies". In AQP4 knockout mice, the injection of amyloid-β directly into brain tissue results in a prolonged time course of amyloid efflux implying that ISF dynamics, including AQP4 water channels, play a role in the amyloid-β efflux (Iliff et al., 2012). Another mice model of AD study revealed that glymphatic failure occurred before deposition of amyloid-β in APP/PS1 mice, suggesting it could potentially serve as an early biomarker of AD (Peng et al., 2016). A recent study reported that the TGN-020, a novel AQP4 inhibitor, impaired glymphatic CSF-ISF and tau protein clearance in a mouse model (Harrison et al., 2020). In the context of human studies, a previous radiological study using 11 C-Pittsburgh Compound-B positron emission tomography revealed that AD patients have altered CSF dynamics, suggesting an imbalance between amyloid-B production and discharge (Schubert et al., 2019). Another radiological study of glymphatic system on AD patients, which employed a non-invasive method, the DTI-ALPS reported that the water diffusivity along perivascular spaces was positively correlated with mini mental state examinations (MMSE) score, indicating that glymphatic dysfunction is associated with the severity of AD (Taoka et al., 2017). The latest clinical study reported that the concentration of AQP4 in CSF was higher in patients affected by neurodegenerative diseases compared to unaffected patients, and AQP4 was positively associated with total tau levels in CSF (Arighi et al., 2022).

There is a proposed association between glymphatic dysfunction and the development of Parkinson's disease (PD), which is marked by α-synucleinopathy. An experimental study of PD model mouse that overexpresses mutated human α-synuclein revealed a significant reduction in the glymphatic influx of CSF tracer, which was accompanied by the perivascular aggregation of α-synuclein and a reduction in astrocytic AQP4 expression in the substantia nigra (Zou et al., 2021). In the context of human studies, it has been reported that the visualisation of meningeal lymphatic vessels after intrathecal administration of GBCA was delayed in PD patients, possibly due to impaired glymphatic CSF-ISF and α-synuclein clearance (Ding et al., 2021). In addition to protein accumulation, the combination of aggregated α-synuclein and deteriorated dopaminergic neurons may play a pivotal role in the sleep dysfunction and ISF dynamics in PD (Sundaram et al., 2019). In the study of glymphatic system evaluation using the DTI-ALPS method, the ALPS index was significantly decreased in PD patients with cognitive symptoms and is positively correlated with the severity of PD (Ding et al., 2021; Ma et al., 2021). In this respect, Parkinson's disease may be regarded as one of the "CNS interstitial fluidopathies".

The hallmark of idiopathic normal pressure hydrocephalus (iNPH) is an enlargement of ventricles with normal intracranial pressure. iNPH is a potentially reversible neurodegenerative disease that is classically presented by a triad of dementia, gait and urinary disturbance (Nassar and Lippa, 2016). A recent pathological study of AQP4 immunostaining showed a significant decrease in the perivascular expression of AQP4 in the endoplasmic reticulum of astrocytes along cortical microvessels in the cortical brain biopsies of iNPH patients (Hasan-Olive et al., 2019). In addition, the DTI-ALPS studies have shown that alteration of ISF/CSF dynamics was lower in the iNPH group than the non-iNPH ventricular dilation group (Yokota et al., 2019). Further evaluation by MR spectroscopy shown than peaks of macromolecules were increased in iNPH patients who had gait disturbance and cognitive symptoms, suggesting the impairment of waste drainage in the pathogenesis of iNPH (Akiyama et al., 2021). Of these findings, it is worth noting that idiopathic normal pressure hydrocephalus is associated with "CNS interstitial fluidopathies".

In addition to the clinical scenarios mentioned above, it is noteworthy to highlight that several diseases or conditions, such as sleep disorders, stroke, vascular dementia, traumatic brain injury, and CSVD have been identified to cause disturbances in dynamics of ISF/CSF within the brain (reviewed in Bah et al., 2023 and Gao et al., 2023). The reciprocal relationship between the accumulation of waste products and the dynamics of ISF is established, leading to the formation of viscous cycle within the neural microenvironment. For instance, in AD, the accumulation of amyloid-β causes the dysfunction of the glymphatic system that in turn exacerbates to more severe accumulation of amyloid-β, and thereby establishing this vicious cycle within tissue (Taoka et al., 2022).

Even though the diseases or disorders are unrelated, they share a "CNS interstitial fluidopathy", which could potentially serve as a valuable foundation for the development of treatments and prevention strategies. For instance, the cilostazol treatment has been examined in a clinical trial known as COMCID, involving patients with mild cognitive impairment in Japan (Saito et al., 2016). Cilostazol is presently used as an antiplatelet medication for the symptomatic treatment of peripheral arterial disease, and is utilized for the secondary prevention of ischemic stroke (Saito et al., 2016). While additional research is necessary to establish definitive conclusions, ongoing trials investigating the treatment and prevention of neurodegenerative disorders are suggesting potential enhancements in ISF dynamics.

5. Conclusion

CSVD is a complex disease that encompasses various pathophysiological mechanisms, including endothelial dysfunction, disruption of BBB, increased vascular stiffness, decreased CBF, impaired ISF drainage and inflammation. The presence of enlarged PVS, edema, accumulation of abluminal protein deposits (GOM and Aβ), and the association between CSVD and sleep, indicate that the glymphatic system dysfunction and perivascular pathology may play a significant role in CSVD. Existing hypothesis suggesting that the failure of neurofluids transports via the glymphatic system, play a key role in initiation and progression of CSVD. It is further postulated that the stagnation of glymphatic transport may contribute to the disruption of brain fluid homeostasis, resulting in transient white matter edema, perivascular dilation, and demyelination. Glymphatic MRI is employed for the direct assessment of glymphatic function, and in a recent study by Taoka et al. (2017), an index for DTI analysis along the PVS (ALPS index) was developed, and has demonstrated altered glymphatic function in CSVD (Tang et al., 2022). Indeed, CSVD is frequently observed with the process of ageing; MRI features include dilated PVS.

In this review, we hypothesize CSVD as a form of, extending beyond its widely recognized microcirculation arteriopathy picture. In these numerous cerebral diseases, impairment of the CSF-ISF dynamics is a common feature. Because of the similarity in their underlying causes, CSVD can be classified as a "CNS interstitial fluidopathy". The advancement of neuroimaging technologies may refine this pathophysiological link further, and a pre-clinical model of CSVD in both sporadic and hereditary forms is necessary to better understand its impact on both normal ageing and pathological disorders involving cerebral small vessels. As they all seem to have the same underlying mechanism, this may at least be mutually beneficial in developing proper treatment and preventive methods.

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Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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