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Review

Stagnation and Progression: How Glymphatic Failure Promotes Meningioma Malignancy in Aging

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ABSTRACT: Meningiomas in the elderly present a clinical paradox: despite typically benign histology, they frequently manifest disproportionate peritumoral brain edema (PTBE) and aggressive behavior. Traditional hormonal hypotheses fail to explain this age-specific malignancy. This review articulates a "Neuro-Glymphatic-Tumor Axis" as a working hypothesis, proposing that the senescent collapse of brain clearance infrastructure, rather than tumor genetics alone, may be a key driver of this progression. Specifically, the loss of astrocytic aquaporin-4 (AQP4) polarity and the atrophy of meningeal lymphatic vessels are hypothesized to create a critical "hydrodynamic mismatch." This systemic failure may trap oncogenic toxins, specifically HMGB1 and S100A4, potentially activating RAGE signaling, while simultaneously blocking antigen drainage, which could induce a state of "immunological ignorance." Consequently, the tumor microenvironment may become physically congested and immunologically suppressed. Translating this framework into practice, we suggest that assessing "glymphatic frailty" via functional MRI and exploring microenvironment-targeted strategies, including lymphatic-sparing surgery and AQP4 modulation, represent promising future directions for dismantling the cycle of edema and recurrence in the vulnerable geriatric population.

Keywords: Glymphatic System, Meningioma, Aging, Meningeal Lymphatic Vessels, Peritumoral Brain Edema

1. Introduction

Meningioma is the most common primary intracranial tumor, with incidence peaking in individuals over 85 years of age (Fig. 1) [1–4]. Unlike their younger counterparts, elderly patients often present with an aggressive phenotype characterized by larger tumor volumes, higher pathological grades, and severe, intractable peritumoral brain edema (PTBE) [5–9]. While historical research focused on progesterone receptors in middle-aged women [10, 11], hormonal theories fail to account for this age-dependent escalation in malignancy. This suggests that biological deterioration of the host brain microenvironment, rather than tumor genetics alone, may contribute to disease progression.

Recent discoveries of the glymphatic system and meningeal lymphatic vessels (mLVs) provide a missing link between brain clearance and central nervous system (CNS) homeostasis [12–17]. This network, driven by arterial pulsation and aquaporin-4 (AQP4) polarity within the perivascular space (PVS), clears metabolic byproducts (e.g., Amyloid-β (Aβ, Tau) from the parenchyma [7, 18–

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20] and drains antigens to deep cervical lymph nodes (dCLNs) [21, 22]. This integrated hydrodynamic system not only maintains CNS homeostasis but also bridges the CNS with the peripheral immune system [4, 15]. However, aging severely compromises this system (Fig. 1) [23–28]. Diminished arterial pulsatility, AQP4 depolarization, and mLV atrophy reduce cerebrospinal fluid (CSF)-interstitial fluid (ISF) exchange efficiency by 40-90% [29–31].

We hypothesize that this systemic drainage failure may act as an upstream driver of meningioma pathogenesis in the elderly. The resulting accumulation of toxins could construct a proinflammatory niche, facilitate immune escape, and induce hydrodynamic edema [32–34]. This review explores meningioma from a "neuroimmune-hydrodynamic" perspective, detailing how glymphatic aging may remodel the tumor microenvironment and discussing implications for imaging markers, such as diffusion tensor image analysis along the perivascular space (DTI-ALPS) and therapy.

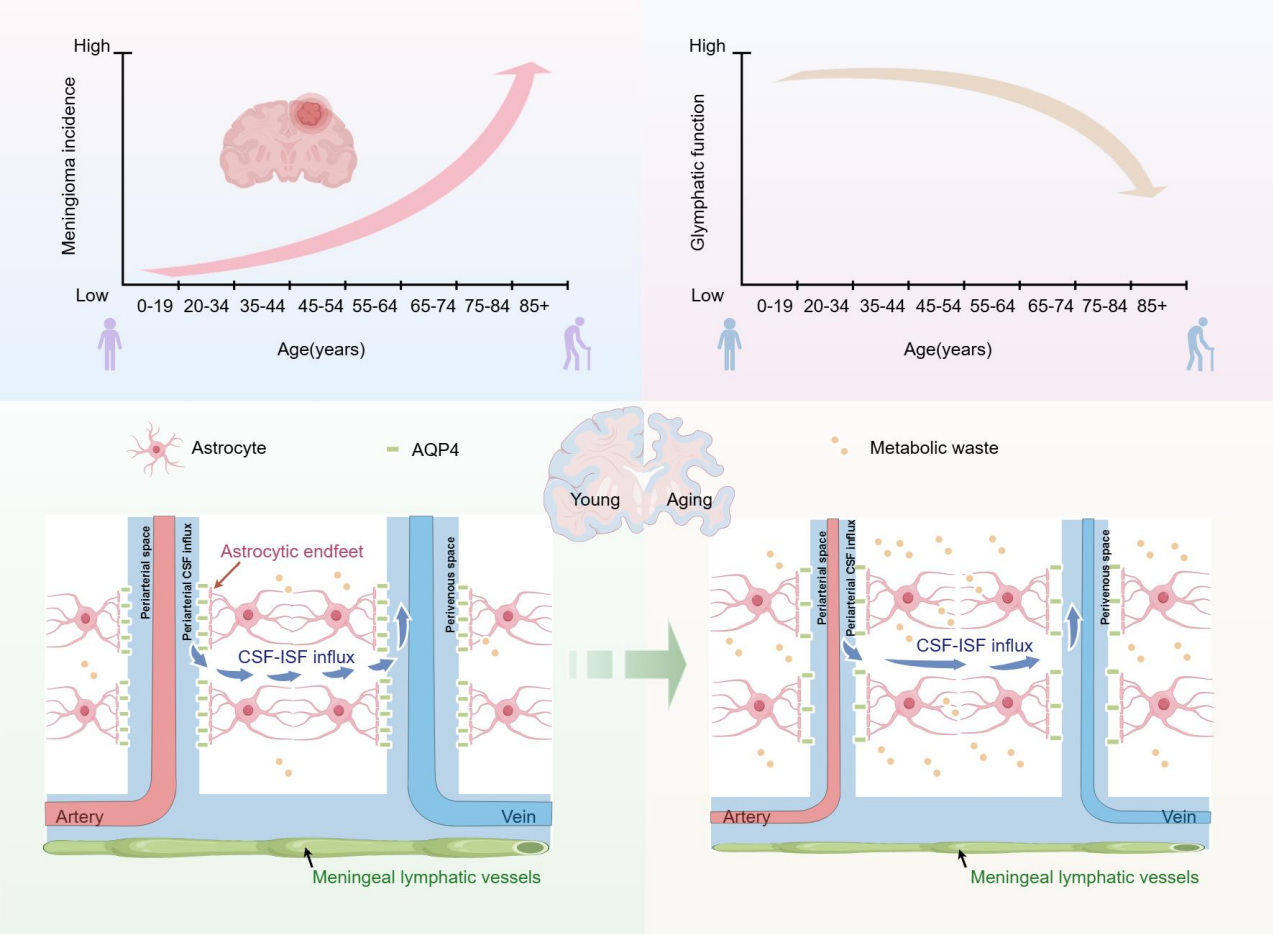

Figure 1. **Schematic representation of the relationship between aging, meningioma incidence, and the glymphatic system.** This diagram illustrates that meningioma incidence increases with age, peaking in individuals over 85 years, whereas glymphatic function deteriorates with advancing age. In the healthy brain, aquaporin-4 (AQP4) at astrocytic endfeet is highly polarized. Cerebrospinal fluid (CSF) flows into the brain parenchyma through AQP4 via periarterial spaces, facilitating CSF-interstitial fluid (ISF) exchange to clear metabolic waste, including neurotoxic proteins. Subsequently, the waste-laden fluid moves towards perivenous spaces, ultimately draining into meningeal lymphatic vessels and deep cervical lymph nodes. In the aging brain, arterial stiffening and loss of smooth muscle tone lead to a reduction in CSF inflow velocity. AQP4 loses its specific localization at astrocytic endfeet—termed "depolarization," and meningeal lymphatic vessels undergo atrophy.

2. Aging-Related Glymphatic System Dysfunction

The efficiency of the glymphatic system is not static; it is a dynamic physiological process that deteriorates progressively with age (Fig. 1). This decline is not merely a slowing down of metabolism but a structural and molecular collapse of the brain's clearance infrastructure.

2.1 Parenchymal Transport Failure

The functional operation of the glymphatic system depends on two critical elements: the hydrostatic driving force generated by arterial pulsations and the molecular polarity of water channels [35]. Aging systematically dismantles both of these pillars. First, the "pumping" force is compromised. The influx of CSF into the brain parenchyma flows along the periarteriolar spaces, driven by the pulsatile movement of the arterial wall. In the healthy young brain, compliant arteries effectively transmit the cardiac cycle's energy into the CSF, creating a convective mixing force [36]. However, the aging brain is invariably accompanied by arteriosclerosis, vascular stiffening, and a loss of smooth muscle tone. This reduction in cerebrovascular compliance dampens the pulsatility transmission, effectively causing a "power failure" in the glymphatic pump. Recent particle tracking studies in murine models have quantified this deficit, revealing that the speed of CSF influx along periarteriolar spaces decreases by over 40% in aged mice compared to young controls [25, 37]. This stagnation means that metabolic waste products, which should be flushed out rapidly, instead linger in the interstitial space.

Second, and perhaps more nuanced, is the molecular disruption of AQP4. In the healthy CNS, AQP4 water channels are not randomly distributed; they are highly polarized, concentrating at the astrocytic endfeet that wrap around blood vessels. This "perivascular polarization" is thought to be essential for facilitating low-resistance water flow across the blood-brain barrier (BBB) interface [38]. The maintenance of this polarity relies on a complex scaffolding machinery known as the dystrophin-associated Protein complex (DAPC). Specifically, the C-terminal tail of AQP4 contains a PDZ-binding domain that interacts with the cytoplasmic adapter protein α-syntrophin, which anchors the channel to the basement membrane via dystroglycan and laminin [39].

In the aging brain, this anchoring complex disintegrates. Proteolytic activity increases, and the expression of α-syntrophin declines, leading to the detachment of AQP4 from the endfeet. Consequently, AQP4 diffuses laterally across the astrocyte soma—a phenomenon termed "depolarization" [40]. Although the total levels of AQP4 protein may remain unchanged or even increase (reactive astrogliosis), its chaotic distribution renders it functionally incompetent to direct convective flow. This molecular disarray uncouples the water transport machinery from the vascular interface, creating a "short circuit" that halts interstitial solute clearance [24].

2.2 Meningeal Lymphatic Atrophy

If the glymphatic system represents the plumbing within the house, the mLVs are the sewer lines leading out to the street. Located within the dura mater, precisely the tissue of origin for meningiomas, these vessels undergo profound anatomical regression with age [27]. This degeneration is characterized by a significant reduction in vessel diameter, a decrease in branching complexity, and a sparseness of lymphatic endothelial cells (LECs). The underlying mechanism involves the attenuation of the vascular endothelial growth factor-C (VEGF-C) signaling pathway. VEGF-C is the primary trophic factor for lymphatic maintenance, binding to vascular endothelial growth factor receptor 3 (VEGFR3) on LECs to promote survival [32, 41]. In the aging dura, the bioavailability of VEGF-C plummets. This is exacerbated by the downregulation of Ccbe1 (collagen and calcium binding EGF domains 1) and the protease ADAMTS3 (a disintegrin and metalloproteinase with thrombospondin motifs 3), which are required to cleave pro-VEGF-C into its active, receptor-binding form [41, 42]. Without this trophic support, mLVs undergo apoptosis and atrophy.

Crucially, this lymphatic regression exhibits regional heterogeneity. Studies utilizing whole-mount immunofluorescence of the dura have shown that dorsal mLVs (located along the superior sagittal sinus) atrophy earlier and more severely than basal mLVs (located at the skull base) [43]. This finding is clinically relevant for meningiomas. Dorsal meningiomas in the elderly may develop in a region of "lymphatic desert," where the capacity to clear local edema and immune cells is virtually non-existent. In contrast, skull base tumors might benefit from the residual function of basal lymphatics, potentially explaining differences in edema profiles between these anatomical locations.

2.3 Biomechanical Constraints

Beyond the vessels themselves, the stromal environment of the dura mater deteriorates. Aging is synonymous with fibrosis; dural fibroblasts increase collagen production and cross-linking, leading to a significant increase in dural stiffness [44]. This "physical rigidification" has hydrodynamic consequences. A stiff extracellular matrix (ECM) is less compliant, leading to higher interstitial fluid pressures for a given volume of fluid.

According to the starling resistor model, lymphatic vessels are thin-walled and highly susceptible to external compression. As the dural stroma stiffens and interstitial pressure rises, the "transmural pressure" gradient collapses, effectively pinching the lymphatic vessels shut [45, 46]. This biomechanical obstruction acts as a third barrier, compounding the effects of reduced arterial pumping and biochemical signaling deficits. For an elderly patient with a growing meningioma, the dural

"soil" is thus physically hostile to fluid drainage, predisposing the brain to fluid retention and high intracranial pressure.

3. Glymphatic Dysfunction and Meningioma Microenvironment Remodeling

Before detailing the proposed mechanisms, it is important to clarify the level of evidence supporting each link. Where possible, we distinguish between established findings (e.g., age-related AQP4 depolarization and meningeal lymphatic atrophy), emerging evidence (e.g., accumulation of HMGB1 and S100A4 in the peritumoral microenvironment), and hypothetical or speculative mechanisms (e.g., the precise contribution of RAGE signaling to meningioma progression). The following sections are intended to generate hypotheses for future testing rather than to assert definitive causality.

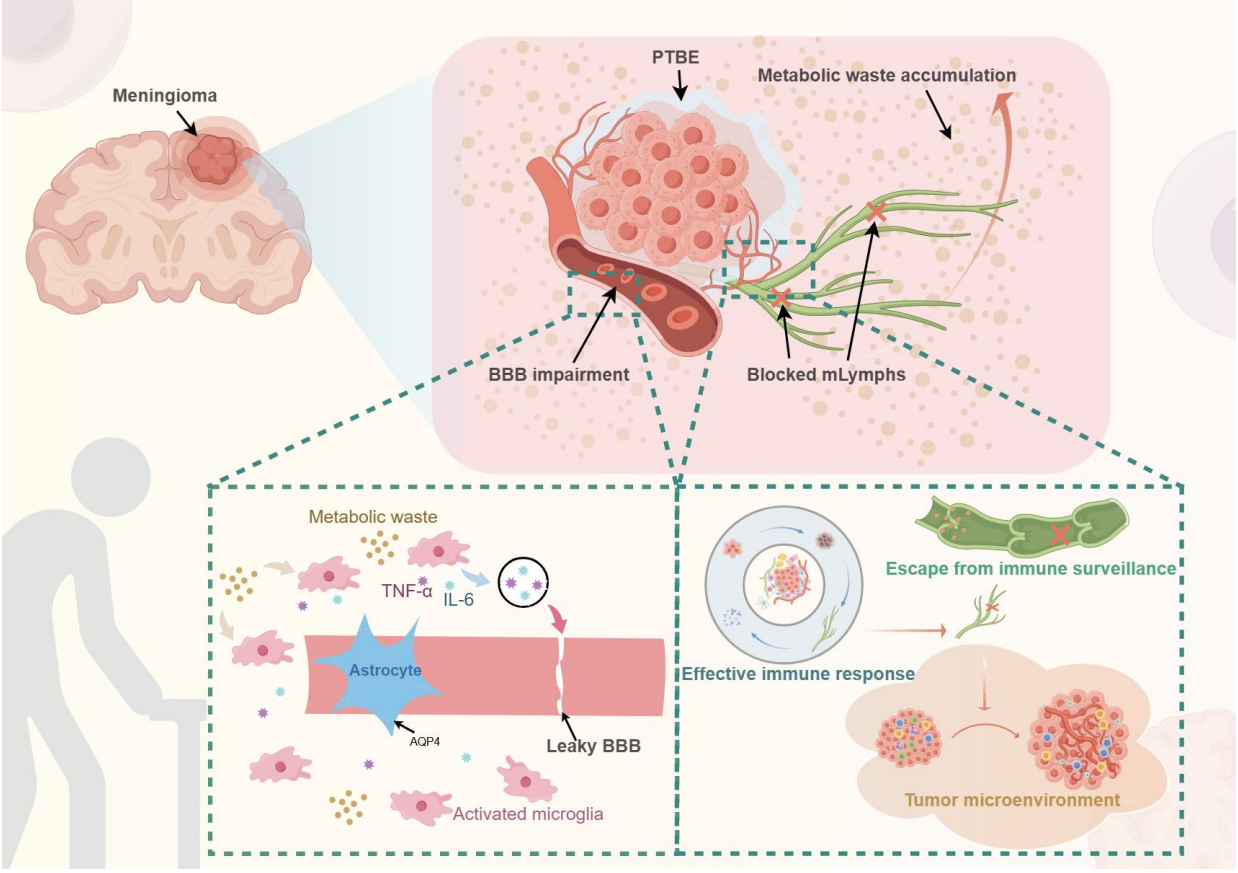

Figure 2. **Schematic diagram of lymphatic dysfunction and meningioma progression.** In the context of aging, the failure of the lymphatic system leads to the accumulation of metabolic waste within the brain parenchyma. This waste induces a cascade release of proinflammatory cytokines (e.g., IL-6, TNF-α), which act on vascular endothelial cells to disrupt tight junctions, resulting in a leaky blood-brain barrier (BBB) and exacerbating peritumoral brain edema (PTBE). Under physiological conditions, the central nervous system relies on meningeal lymphatic vessels (mLVs) to present antigens to the peripheral immune system, a process crucial for generating anti-tumor immunity. However, during aging, the atrophy of lymphatic vessels physically interrupts this intelligence gathering, resulting in immune evasion. The persistent inflammatory state and "immunological ignorance" caused by lymphatic failure provide a fertile ground for the development of meningiomas.

3.1 Metabolic Toxicity

The primary consequence of glymphatic failure is the parenchymal accumulation of neurotoxic proteins (Fig. 2). While Alzheimer's research focuses on Aβ and Tau, in the context of meningioma, the accumulation of damage-associated molecular patterns (DAMPs) such as high mobility group box 1 (HMGB1) and S100 calcium binding protein A4 (S100A4) is likely more pathogenic [47–49]. HMGB1 is a nuclear protein that, when released into extracellular space (e.g., due to cell stress or uncleared turnover), acts as a potent proinflammatory cytokine. In the stagnant ISF of the aging brain, HMGB1 accumulates to pathological levels and binds to the receptor for advanced glycation end products (RAGE). RAGE is constitutively overexpressed on arachnoid cap cells (the precursors of meningioma) and reactive astrocytes in the peritumoral zone [50]. The engagement

of the HMGB1-RAGE axis is hypothesized to trigger a sustained, low-grade inflammatory response, although direct evidence in human meningiomas remains limited. Upon ligand binding, the cytoplasmic tail of RAGE recruits adaptor proteins like diaphanous-related formin-1 (DIAPH1) to activate downstream signaling cascades, principally the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathways [48, 51–53]. The nuclear translocation of NF-κB drives the transcription of prosurvival genes (e.g., B-cell lymphoma 2 [Bcl-2]), cell-cycle promoters (e.g., cyclin D1), and proinflammatory cytokines, such as Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). This could create a feed-forward loop: inflammation may induce more HMGB1 release, which in turn could further activate RAGE, a possibility that warrants investigation in meningioma models.

Moreover, recent evidence links this pathway to metabolic reprogramming. Activation of RAGE has been shown to enhance mitochondrial bioenergetics via the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway, increasing ATP production to fuel the high metabolic demands of proliferating tumor cells [54]. Similarly, S100A4, an established metastasis-associated protein and RAGE ligand, has been identified as a prognostic biomarker for higher-grade meningiomas. Unlike S100 calcium binding protein B (S100B), which is often expressed in benign meningiomas, elevated S100A4 correlates with an aggressive phenotype and recurrence, potentially by driving epithelial-mesenchymal transition (EMT) via RAGE signaling activation [55]. Thus, it is plausible that the "trash" left behind by a failing glymphatic system serves as "fuel" for tumor growth, though this remains a hypothetical model requiring experimental validation.

3.2 Immunological Ignorance

The CNS was long considered "immune privileged," but we now know it is "immune distinct," relying on mLVs to present antigens to the peripheral immune system. This process is critical for the generation of anti-tumor immunity. Dendritic cells (DCs) capture tumor antigens in the CNS and migrate via mLVs to the dCLNs, where they prime CD8+ cytotoxic T cells [56, 57].

In the elderly, lymphatic atrophy physically interrupts this intelligence gathering. Recent landmark studies have demonstrated that experimentally ligating dural lymphatics completely abolishes the ability of the immune system to mount a T-cell response against brain tumors [32, 58]. This state has been termed "Immunological Ignorance" in experimental models. In the context of aging, the immune system may not be suppressed but rather unaware of the tumor because the "messenger"—the meningeal lymphatic vessel—is atrophic. This concept, while supported by animal studies, requires direct confirmation in elderly meningioma patients (Fig. 2).

This blockade may have profound implications for the tumor microenvironment. In the absence of effective T-cell priming, the tumor bed could become infiltrated by immunosuppressive cells that do not require lymphatic transport to arrive, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). The stagnant fluid environment, rich in transforming growth factor-β (TGF-β) and Interleukin-10 (IL-10) that cannot be flushed out, may further polarize tumor-associated macrophages (TAMs) towards the protumoral M2 phenotype [32, 59]. This offers a potential explanation for why elderly meningioma patients often exhibit a "cold" immune microenvironment that is resistant to checkpoint inhibitors: the problem is not just checkpoint expression, but a fundamental failure of antigen presentation.

3.3 Hypoxia and Mechanotransduction

The decline in CSF dynamics physically reshapes the niche. As fluid retention elevates the tumor interstitial fluid pressure (TIFP) [60–62], two physical forces come into play: mechanical stress and hypoxia.

First, the tumor mass effect superimposed on a stiff, fluid-filled brain may activate mechanosensitive pathways [63]. The Hippo pathway effectors Yes-associated protein (YAP) and Transcriptional co-activator with PDZ-binding motif (TAZ) are known to translocate to the nucleus in cells exposed to high stiffness or fluid pressure [64]. In meningiomas, YAP/TAZ activation has been shown to upregulate genes associated with "stemness," invasion, and resistance to contact inhibition, potentially driving the tumor towards a higher grade [65]. Second, high TIFP compresses the delicate microvasculature within and around the tumor. This compression reduces blood flow, creating zones of perfusion-diffusion mismatch and pathological hypoxia. Hypoxia stabilizes Hypoxia-Inducible Factor-1α (HIF-1α), the master transcriptional regulator of angiogenesis [66–69]. HIF-1α drives the overexpression of Vascular Endothelial Growth Factor (VEGF), promoting the formation of chaotic, leaky blood vessels. Unlike normal angiogenesis, these tumor vessels lack proper pericyte coverage and are hyper-permeable. This could establish a vicious cycle wherein drainage obstruction elevates TIFP, potentially inducing hypoxia and subsequent VEGF upregulation, a sequence that has been observed in other tumor types but needs specific investigation in meningiomas [7].

4. Pathophysiology of Peritumoral Brain Edema

PTBE is the hallmark complication of meningiomas in the elderly. The traditional "Vasogenic Edema" theory, which attributes PTBE solely to VEGF-induced BBB breakdown [70], is insufficient. It fails to explain why small meningiomas in the elderly can cause massive edema, while large tumors in younger patients may have none. We propose a "Hydrodynamic Mismatch" theory as a working model.

4.1 The Inflow-Clearance Imbalance

Edema is a dynamic equilibrium between fluid formation (inflow) and fluid resorption (clearance). In healthy individuals, the glymphatic system possesses a significant "functional reserve." Even if a tumor secretes VEGF and causes localized leakage, the AQP4-mediated bulk flow can rapidly clear the excess fluid and proteins, preventing edema accumulation.

In elderly patients, this equilibrium is shattered. On the "inflow" side, the tumor vasculature is fragile, and the aged BBB is leakier. On the "clearance" side, the glymphatic system and mLVs are atrophied and operating at near-maximum capacity just to maintain baseline homeostasis. They lack the reserve to handle the surge of edema fluid. This creates a severe hydrodynamic mismatch, wherein the combination of high fluid inflow and exhausted functional reserve may predispose to intractable edema [71–73]. Furthermore, the relationship between glymphatic failure and meningioma progression is not unidirectional; rather, it constitutes a self-amplifying feedback loop. While age-related clearance deficits create a protumorigenic niche, the emerging tumor may actively exacerbate the collapse of the surrounding hydrodynamic infrastructure. Specifically, meningioma cells secrete high levels of VEGF and proinflammatory cytokines (e.g., IL-6), which could trigger the loss of AQP4 polarization in peritumoral astrocytes, potentially dismantling the glymphatic pump at the lesion site [74]. Mechanically, the expanding tumor mass increases interstitial fluid pressure, which physically compresses the adjacent perivascular spaces and mLVs. This 'mass effect' creates a localized 'hydrodynamic bottleneck,' trapping metabolic byproducts and fibrinogen, which further stiffens the extracellular matrix and may promote tumor invasion [60]. Consequently, the 'Neuro-Glymphatic-Tumor Axis' could function as a vicious cycle where tumor-induced structural disruption and age-related functional decline synergistically drive the clinical malignancy observed in elderly patients. This model offers a potential explanation for the clinical observation that edema severity often correlates more with age and biomarkers of glymphatic dysfunction, such as enlarged perivascular spaces (EPVS), than with tumor size itself [2].

4.2 The "Fibrinogen Gel" and PVS Blockade

The breakdown of the BBB allows plasma proteins, particularly fibrinogen, to enter the brain parenchyma. In the absence of efficient clearance, fibrinogen is not flushed out but deposits in the perivascular spaces. It can polymerize into fibrin, forming a gel-like matrix that physically occludes the PVS [36, 75]. This "clogs the plumbing" at the microscopic level.

This blockade has catastrophic consequences. It transforms the PVS from a low-resistance conduit into a high-resistance barrier. Fluid that extravasates from the tumor cannot drain and is forced into the white matter tracts, expanding the edema [76]. Furthermore, fibrin deposition triggers distinct inflammatory pathways via the integrin CD11b/CD18 on microglia, exacerbating neuroinflammation and causing further astrocytic damage [77]. This explains the "irreversible" nature of edema in some elderly patients, where edema persists for months even after the tumor is removed; the drainage pathways remain physically obstructed by proteinaceous debris.

4.3 The AQP4 Dichotomy

A critical, often overlooked aspect is the dual and opposing role of AQP4 in meningioma pathology. On the tumor side, meningioma cells themselves often overexpress AQP4. This upregulation facilitates the transmembrane entry of water from the bloodstream into the tumor tissue, effectively acting as a "water pump" that actively draws fluid into the cranium [74, 78]. On the host side (the peritumoral brain), the astrocytes suffer from the loss of polarity described in Section 2.1. The AQP4 channels are present but misplaced, meaning they cannot effectively pump the edema fluid back into the venous circulation [38]. This creates a deadly synergy: the tumor actively pumps water in, while the host brain has lost the ability to pump water out. This molecular dichotomy is the fundamental basis for the intractable edema observed in geriatric patients and represents a specific therapeutic target.

5. Preoperative Assessment

In the era of precision medicine, assessing the glymphatic status of an elderly patient is as important as assessing their cardiac reserve. Since we cannot directly visualize molecular channels in the clinic, we rely on neuroimaging surrogates.

5.1 Enlarged Perivascular Spaces (EPVS)

Enlarged Perivascular Spaces (EPVS), visible on T2-weighted magnetic resonance imaging (MRI), were once dismissed as benign incidental findings of aging. We now understand them as scars of chronic drainage failure. An EPVS represents a PVS that has become congested with stagnant fluid and cellular debris, forcing the space to dilate [2]. In meningioma patients, the distribution of EPVS is telling. Studies have shown that the EPVS burden is often asymmetric, being significantly higher in the hemisphere containing the tumor [79]. This suggests that the tumor places a locoregional load on the drainage system. A high EPVS score should be interpreted by the neurosurgeon as a sign of "Lymphatic Decompensation" — a warning that the patient has zero fluid reserve and is at high risk for postoperative edema fulmination. Nevertheless, EPVS are a non-specific sign of parenchymal injury. Their correlation with glymphatic function is indirect, and distinguishing dilated PVS from other pathologies like lacunar infarcts or Virchow-Robin spaces can be challenging on standard MRI sequences.

5.2 DTI-ALPS

DTI-ALPS is a novel, non-invasive MRI technique that estimates glymphatic function. It works by measuring the diffusivity of water molecules specifically in the direction of the PVS surrounding the medullary veins, thereby isolating glymphatic flow from general tissue diffusion [80]. Recent clinical cohorts have established DTI-ALPS as a robust biomarker. Meningioma patients consistently show lower ALPS indices than healthy controls, and crucially, the index correlates negatively with edema volume: the worse the drainage, the worse the edema [72]. More importantly for the geriatric population, the ALPS index correlates with cognitive reserve. A low preoperative ALPS index is a strong predictor of postoperative delirium and long-term cognitive decline [81, 82]. It serves as a measure of "Neuro-Glymphatic Frailty," helping surgeons weigh the risks of aggressive resection versus conservative management. Despite their clinical promise, it is critical to acknowledge that DTI-ALPS and EPVS remain indirect imaging surrogates rather than direct measures of glymphatic flow. The ALPS index, while sensitive to changes in water diffusivity along the perivascular space, can be influenced by inherent tissue anisotropy and the overwhelming presence of vasogenic edema in the peritumoral zone. Furthermore, the morphological enlargement of PVS (EPVS) may represent stagnant fluid or proteinaceous debris, but it does not provide real-time kinetic data on clearance velocity. Therefore, while these markers are invaluable for 'glymphatic frailty' screening in a clinical setting, their interpretation must be integrated with traditional hemodynamic and volumetric assessments to avoid overestimating the degree of functional impairment.

5.3 Radiomics and Occult Invasion

Beyond the human eye, radiomics (high-throughput extraction of quantitative features from medical images) is uncovering microenvironmental secrets. Machine learning models trained on MRI texture features can now predict brain invasion and World Health Organization (WHO) grade with high accuracy [83]. Interestingly, the texture features that are most predictive often relate to tissue heterogeneity and fluid distribution in the peritumoral zone. This suggests that radiomics may serve as a proxy for detecting the microscopic consequences of glymphatic failure—micro-edema, protein deposition, and tissue disorganization—long before they become macroscopically visible.

6. Microenvironment-Targeted Therapeutic Strategies

The following therapeutic strategies are discussed as investigational concepts based on preclinical models and theoretical reasoning. None of these approaches is currently ready for clinical application in meningioma patients, and they should be interpreted as future research directions rather than near-term clinical recommendations. The "neuro-glymphatic-tumor" axis may necessitate a shift from purely cytoreductive surgery to microenvironment-targeted therapies [84].

6.1 Pharmacological Modulation

Current anti-edema therapies rely on corticosteroids (dexamethasone), which have severe side effects in the elderly and do not address the drainage failure. One potential future direction is AQP4 modulation. Preclinical studies have shown that drugs such as the specific AQP4 inhibitor TGN-020 or trifluoperazine can inhibit AQP4 or modulate its subcellular localization in animal models [85]. While AQP4 inhibition might seem counterintuitive, in the acute phase of cytotoxic edema, it prevents water entry. However, for vasogenic edema clearance, agents that promote AQP4 repolarization to the endfeet would be needed. This is an active area of drug discovery.

Another investigational frontier is lymphatic regeneration. In mouse models of glioblastoma, VEGF-C treatment enhanced antigen drainage and synergized with checkpoint inhibitors to eradicate tumors [32, 86]. Whether this strategy can be safely applied in elderly meningioma patients remains unknown and would require extensive preclinical safety studies. In the context of

elderly meningioma, adjuvant VEGF-C therapy could theoretically restore the drainage necessary to resolve edema and prevent recurrence, although the risk of inducing tumor angiogenesis must be carefully balanced and has not been evaluated.

6.2. Physical and Chronobiological Interventions

The glymphatic system is highly dependent on circadian rhythms, being most active during Non-Rapid Eye Movement (NREM) sleep [87]. Sleep fragmentation, common in hospitals, is detrimental to brain clearance. "Sleep as Medicine" could be considered a core component of perioperative care. Avoiding nighttime interruptions, managing pain to ensure deep sleep, and perhaps using pharmacological agents that enhance NREM sleep (e.g., dexmedetomidine) could be simple, low-cost ways to boost edema clearance [88].

Patient positioning also matters. Animal studies suggest that the lateral decubitus position maximizes glymphatic flow compared to supine or prone positions [87]. While clinical evidence is emerging, encouraging elderly patients to sleep on their side (if not contraindicated by the craniotomy site) is a low-risk intervention worth considering.

Table 1. Comparison of glymphatic and meningeal lymphatic features between rodent models and humans.

Feature	Rodent Models	Human Anatomy/Physiology	Translational Implication	Key Refs
Arachnoid Barrier	Thin, permeable; allows significant direct CSF-ISF exchange.	Thick, collagenous; may restrict paravascular entry; arachnoid granulations (AGs) are major CSF efflux routes.	Paravascular transport may be less efficient in humans; AGs may compensate for meningeal lymphatic dysfunction.	[94]
Meningeal Lymphatics	Abundant, well-mapped; dorsal vessels dominate drainage.	Present but regional distribution and density are debated; may be sparser in some dural regions.	Location of meningioma (e.g., dorsal vs. skull base) may have a more profound impact on drainage capacity in humans.	[95]
CSF Dynamics	Flow heavily driven by arterial pulsations; studied in anesthetized, prone position.	Influenced by both arterial pulsation and posture (upright vs. supine); gravity creates hydrostatic gradients.	Posture (sleep position) may be a more critical modifiable factor in humans for optimizing clearance.	[25, 96, 97]
Lymphatic Atrophy	VEGF-C/VEGFR3 pathway regression well characterized.	Evidence supports similar age-related regression, but the rate and regional heterogeneity require further validation with advanced imaging.	Therapeutic strategies for lymphatic regeneration (e.g., VEGF-C) must be carefully evaluated for off-target effects in complex human CNS vasculature.	[26, 27]

6.3. Surgical Innovation

Finally, the surgeon's hand may need to adapt. We now know that the parasagittal region and the skull base are rich in lymphatic vessels. Traditional aggressive coagulation of the dura in these areas may inadvertently destroy the major drainage highways of the brain, leading to iatrogenic venous/lymphatic congestion. We suggest that "lymphatic-sparing" techniques, such as minimizing dural coagulation near the superior sagittal sinus and preserving dural integrity where possible, could be considered as a principle for future surgical protocol development, although their benefit remains to be demonstrated.

For patients with devastating, permanent lymphatic destruction (e.g., after radiation or repeated surgeries), the future may hold reconstructive options. Lymphatic-Venous Anastomosis (LVA), a standard procedure for limb lymphedema, has been proposed as a theoretical approach for intractable intracranial hypertension, but this concept is highly speculative and faces substantial anatomical and physiological hurdles before any clinical consideration [84, 89, 90].

7. Current Limitations, Challenges, and Controversies

Terminological note: In this review, "glymphatic frailty" and "Neuro-Glymphatic Frailty" are used interchangeably to describe the age-related deterioration of both the glymphatic system (parenchymal clearance) and the meningeal lymphatic drainage. The term "lymphatic frailty" alone, which does not appear in this manuscript, would refer exclusively to meningeal lymphatic dysfunction and is not equivalent to the broader concept of glymphatic frailty.

While the glymphatic hypothesis is compelling, it is important to acknowledge the "translational gap." First, while rodent models have been instrumental in elucidating the core principles of glymphatic flow, significant anatomical and physiological differences between species must be considered when translating

these findings to human pathology (Table 1). As summarized in Table 1, these anatomical and physiological divergences underscore the "translational gap". While rodent data provide a mechanistic blueprint, the clinical manifestation of glymphatic failure in elderly meningioma patients may be more heterogeneous due to the complex interplay of posture, gravity, and human-specific outflow structures. For instance, the human brain is characterized by a thick, collagenous arachnoid barrier and well-developed arachnoid granulations (AGs)—structures that are rudimentary or absent in mice. The functional role of AGs in CSF efflux, potentially acting as low-resistance pressure-relief valves, is distinct from the dural lymphatic-dominated outflow in rodents. Furthermore, the hydrostatic pressure gradients in upright, bipedal humans fundamentally differ from those in quadripedal rodents, potentially altering the relative contribution of postural changes and arterial pulsations as driving forces for glymphatic transport. Recent critical appraisals suggest that these human-specific features may confer a greater reliance on positional drainage pathways, complicating the direct extrapolation of data derived from anesthetized, prone rodents [91].

Second, the causality dilemma remains: does glymphatic failure cause the aggressive tumor phenotype, or does the tumor cause glymphatic failure? It is likely a bidirectional relationship, but current cross-sectional studies cannot definitively tease this apart. Pre-existing glymphatic frailty may create a permissive niche for aggressive tumor behavior, while the tumor itself may actively disrupt local and regional clearance mechanisms. The high levels of VEGF secreted by meningiomas may not only promote aberrant angiogenesis and BBB breakdown but could also directly destabilize the integrity of nearby mLVs by altering pericyte-endothelial cell interactions. The tumor mass and associated PTBE physically compress the surrounding parenchyma, potentially collapsing PVS and impeding local CSF-ISF exchange. This self-perpetuating cycle suggests that even a small, indolent tumor may trigger a cascade of fluid retention and inflammation in an already compromised drainage system, accelerating both its own progression and the host's neurological decline. Longitudinal studies tracking ALPS indices years before tumor diagnosis would be the gold standard but are logistically difficult [92].

Third, imaging biomarkers like DTI-ALPS are indirect. They measure water diffusion, which is a proxy for flow, not flow itself. They are sensitive to acquisition parameters, such as repetition time (TR) and echo time (TE), as well as head positioning and the confounding influence of the tumor itself on tissue microarchitecture [93]. While studies show promising correlations, the field lacks a non-invasive gold standard for validation. There is an urgent need for direct, non-invasive flow tracers—perhaps utilizing Oxygen-17 magnetic resonance imaging (17O-MRI) or intrathecal tracers in safe, low doses—to validate these findings in clinical trials.

8. Conclusion

The discovery of the glymphatic system has provided the missing piece of the puzzle in geriatric neuro-oncology. It challenges the simplistic, hormone-centric view of meningiomas and forces us to confront the reality of the aging brain microenvironment. We propose that the age-related collapse of brain-wide clearance—mediated by the molecular depolarization of AQP4 and the structural atrophy of meningeal lymphatics—may act as a permissive upstream driver that contributes to disease progression.

This "Neuro-Glymphatic-Tumor Axis" provides a plausible framework for understanding the unique clinical features of elderly meningioma: the toxic accumulation of RAGE ligands may drive tumorigenesis; the blockade of antigen drainage could lead to immunological ignorance; and the hydrodynamic mismatch may result in intractable edema. Recognizing this axis may have profound translational implications. It suggests that functional imaging such as DTI-ALPS could be used to assess "physiological reserve" rather than just chronological age. It also suggests that a shift from purely cytoreductive surgery to a comprehensive management strategy that includes sleep optimization, lymphatic-sparing techniques, and the development of microenvironment-targeted molecular therapies may be warranted as evidence accumulates. By restoring the brain's ability to cleanse itself, we may eventually offer new therapeutic avenues to the vulnerable geriatric population that extend beyond the scalpel.

Author contributions:

Wenfei Zhou and Naili Wei jointly conceived and wrote this manuscript. Feng Xu completed the article illustrations. Hailiang Tang and Xiaoyu Ji reviewed and edited the manuscript. Jian Chen is a guarantor of the article. All authors read and approved the final manuscript.

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Competing interests

The authors declare that there are no potential competing interests.

Ethical Statement

As this manuscript is a review article and does not involve the collection of original data from human participants or animals by the authors, specific ethical approval and informed consent were not required for its preparation. All clinical data and imaging cases cited in this review are sourced from previously published studies. The authors have verified that the original studies cited herein were conducted in accordance with the Declaration of Helsinki and received appropriate approval from their respective institutional review boards (IRBs) or ethics committees. No unpublished personal data from human subjects were used in this manuscript.

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