**Venous Outflow for Brain Arteriovenous Malformations: Overview and Treatment Implications**

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**Abstract**

**Introduction:** Recent evidence has demonstrated a close relationship between the cerebral venous and lymphatic systems. Venous congestion has been implicated in a host of neurologic disorders, with relevance for vascular etiologies.

**Objective:** The authors aim to review the literature as it pertains to brain arteriovenous malformations’ (BAVMs) venous hemodynamics and glymphatic pathways, as well as the implications of BAVM treatment.

**Results:** BAVMs offer a unique challenge, with sudden alteration in flow dynamics leading to increased hemorrhage risk and difficult challenges post-treatment.

**Conclusion:** Recent progress in the understanding of CNS fluid dynamics and glymphatic pathways have revealed important implications for BAVM pathology and treatment. As imaging techniques and treatment modalities advance, there is a need to further investigate this relationship as it relates to therapeutic options and post-treatment sequelae.

**Keywords**

Arteriovenous malformations; Angioarchitecture; Hemodynamics; Glymphatics

**Introduction**

The cerebral venous and lymphatic systems are integral components of a dynamic, complex intracranial system sharing interactions between brain parenchyma, dura, vascular and lymphatic drainage systems, and nearby cerebrospinal compartments. Abnormal venous drainage is a frequent angiographic finding associated with cerebral brain arteriovenous malformations (BAVMs) and has been postulated to contribute to its pathology in utero [55]. Each of the above components contributes towards changes in overall structural organization including venous and cerebrospinal hypertension given limited territory in a fixed cranial
Cerebral venous congestion due to mass effect, as seen with BAVMs, can cause nearby lymphatic blockage and contribute to blood-brain barrier (BBB) disruption and neuroinflammation. Potential downstream sequelae include seizures, intracranial hemorrhage, chronic headaches, or progressive neurologic decline [22]. BAVMs are characterized by an arteriovenous shunt in which one or multiple arterial pedicles feed into a vascular nidus, creating early drainage into a venous outflow channel. Location and flow dynamics have been shown to influence symptomatic presentation [56], and both venous congestion and hypertension appear to correlate closely with risk of hemorrhage in this disorder [66]. However, the contribution of the nearby glymphatic pathways in the pathogenesis of BAVM remains controversial and understudied but is a topic of growing clinical significance [42].

Pre-clinical studies have demonstrated glymphatic involvement in BAVM formation. Yamada et al. utilized a chronic model of cerebral venous hypertension in rats by creation of a cervical arteriovenous fistula with jugular vein occlusion. They found significantly raised intracranial venous sinus pressure [75]. Which likely impedes flow of the nearby glymphatic channels. This may ultimately induce venous congestive encephalopathy, but recent evidence suggests that this may be more dependent upon impaired glymphatic clearance than strictly due to venous congestion.[29] A rat model of cerebrovascular steal with venous hypertension reproduced both hemodynamic and hemorrhagic complications of human BAVMs and emphasized the importance of venous outflow obstruction and venous hypertension in its pathophysiology [13]. Moreover, the restriction of venous drainage presumably causes venous hypertension in the surrounding brain, leading to brain edema and neurological symptoms. In individuals who undergo percutaneous transluminal embolization for BAVMs, there is documentation of active venoconstriction that is likely regulated by specific neurogenic factors [32]. Brain edema can develop in patients with an unruptured BAVM due to venous congestion following spontaneous thrombosis of venous components. In addition, varicosity in the main cortical drainage vein and a small nidus are potential factors that may predispose unruptured BAVMs to brain edema [43]. In one study, brain edema was reported in 3.9% of unruptured BAVMs and frequently associated with venous outflow abnormalities [39]. Furthermore, patients with coexisting BAVMs and developmental venous anomalies (DVAs) tend to have a hemorrhagic presentation [74]. The progressive nonhemorrhagic symptoms are possibly associated with an increased risk of hemorrhage. Palliative embolization arrests the nonhemorrhagic symptoms in select patients, although it may not influence hemorrhagic risk [39].

Observation of vessel wall enhancement, perifocal edema, and luminal thrombosis in all patients with unruptured BAVM points towards a common mechanism. Kortman proposed an interplay between vascular hypoxia, the innate immune system, and thrombosis formation. Current research in the field of immune thrombosis supports this theory. Further elucidation of the involved mechanisms may guide therapy for patients with an unruptured BAVM towards individualized and possibly noninvasive options [40].

Venous Outflow

BAVMs are characterized by high flow arterial feeders into a low resistance tangle of vascular channels (the nidus) in the absence of an intervening capillary bed (Figure
1) [44,45,61]. Compared to mean arterial pressure (MAP), feeding arterial pressure is dramatically reduced in larger BAVMs resulting in a decreased propensity for spontaneous hemorrhage [64]. Higher grade Spetzler-Martin BAVMs are associated with increased venous flow velocities [8]. High flow into the venous system results in non-laminar flow and resultant intimal hyperplasia as well as stenosis at the vein-sinus interface. The resultant venous stenosis increases the likelihood of BAVM rupture [6,14,71].

The presence of a single draining vein and deep or periventricular venous drainage is associated with an increased risk of spontaneous rupture as well [18,36,51]. Elevated pressure within the deep veins is associated with more turbulent flow and a greater likelihood of platelet aggregation and activation. This results in the release of various cytokines stimulating vascular remodeling [67]. Normal vasculature within the vicinity of the BAVM experiences relative hypotension which may lead to a leftward shift of the autoregulatory curve such that cerebral blood flow (CBF) is maintained at lower cerebral perfusion pressure (Figure 2) [73,35]. Hai demonstrated that an end-to-side anastomosis between the distal external jugular vein and common carotid artery can induce a decrease in cerebral perfusion pressure (CPP), whereas a further chronic state of cerebral hypoperfusion may be caused by venous outflow restriction, which is associated with perfusion pressure breakthrough. This animal model conforms to the basic hemodynamic characteristics of human BAVM [27].

It is proposed that angiographic features suggesting unbalanced inflow and outflow might be helpful in identifying BAVMs at higher risk for future hemorrhage [48]. Fukaya reported a case showing only a venous thrombus preceding intracranial hemorrhage from BAVM. This was the first evidence showing an association between venous thrombosis and BAVM rupture [21]. In addition, three cases are reported of delayed intracranial hemorrhage in patients with BAVMs treated with radiosurgery in which no residual BAVM was found on catheter angiography at the time of delayed post-treatment hemorrhage. It is speculated that the pathophysiology of these hemorrhages involves progressive venous outflow restriction, and the possible mechanistic link to subsequent vascular rupture is discussed in the case series [5]. In the case described by Higgins treatment was focused purely on relieving venous hypertension with no attempt to reduce arteriovenous shunting. This suggests there is no attempt to reduce any arterial steal. In fact, the reverse, the measures used to lower venous pressures, would have been almost certain to increase arteriovenous shunting and, therefore, to increase any supposed arterial steal. The clinical result of this approach, in which there was a significant amelioration of symptoms, testifies to the relative importance of venous hypertension in this situation [28]. Fierstra demonstrated a strong association between impaired perinidal cerebrovascular reserve and epileptic seizure presentation in patients with BAVM [20]. This impaired cerebrovascular reserve may be associated with venous congestion. Quantitative measurements of cerebrovascular reactivity using blood oxygen level-dependent MRI appear to correlate with seizure susceptibility in patients with BAVM [20].
Current and Future Neuroimaging for BAVMs

Computerized Tomography Angiography (CTA) has been frequently utilized in the imaging of BAVMs, as it allows for identification of essential anatomy and angioarchitecture subsequently used to plan further management. CTA is also particularly sensitive in identifying arterial pathology such as hemorrhage, a potentially life-threatening complication seen in individuals with BAVM [34]. This is especially useful in identifying cases that require emergent endovascular or surgical intervention due to complications such as hemorrhagic stroke. Additionally, CTA is useful in identifying vital features affecting the ultimate surgical approach, such as enlarged or calcified vessels that may course along the margins of hemorrhagic regions [68]. However, in the absence of hemorrhage, this form of neuroimaging has lower sensitivity for detection of existing BAVMs, as it fails to adequately detect decreased cerebral perfusion and may overlook a thrombosed BAVM [69]. This may lead to delayed treatment, the need for emergent care, and a greater risk of complications. Like CTA, computed tomography (CT) has utility in identifying areas of BAVM rupture leading to acute hemorrhage but has decreased ability to visualize angioarchitecture and surrounding vasculature. This creates intra-operative challenges when surgical management is indicated. CT is most useful in the urgent setting of assessing for active extravasation of arterial blood into the brain parenchyma or the ventricles [17].

Alternatively, magnetic resonance angiography (MRA) and magnetic resonance imaging (MRI) of the brain are comparatively more sensitive in identifying the location of a BAVM nidus, the vessels, and the adjacent parenchyma due to their improved temporal and spatial resolution when compared to CT and CTA [17]. MRA and MRI also demonstrate superiority in their ability to identify thrombosed vessels as well as areas of acute and chronic hemorrhage, allowing quicker surgical intervention before potential hemorrhage. However, like CTA and CT, MRA and MRI have decreased ability to detect areas of cerebral hypoperfusion, and therefore, ischemic tissue may be overlooked in the absence of symptoms [69]. However, 4D flow MRI, a novel technique combining ECG-synchronized 3D phase-contrast MRI with advanced post-processing strategies, can quantitatively evaluate 3D blood flow of vascular territories. Currently, its primary utility is in research protocols, although, it has been validated in extracranial arteries [61,49,50]. Given the complex angioarchitecture of BAVMs, 4D flow MRI can assist in the characterization of BAVM hemodynamics. However, expansion to clinical use will require optimization of acquisition time, spatiotemporal resolution, velocity range, and post-processing time [61].

Digital Subtraction Angiography (DSA) is currently deemed to be the gold standard for imaging BAVMs and assessing the risk of rupture preoperatively as well as for surveillance postoperatively. DSA is a more invasive method of imaging when compared to CT, CTA, MRI, and MRA. This method utilizes fluoroscopy, allowing for visualization of blood flow through the BAVM as well as the surrounding vasculature feeding into the BAVM nidus without the interference of bone or soft tissue. As a result, DSA has the greatest temporal and spatial resolution of all the methods used to image BAVMs [17]. Preoperatively, it is more sensitive at detecting angioarchitecture, the presence of perinidal aneurysms, and arterial supply. Post-operatively, DSA has demonstrated superiority in surveillance of new and recurrent hemorrhage that were missed by MRA [52].
Open and Endovascular Implications

Following the surgical obliteration of BAVMs, a phenomenon of cerebral edema or hemorrhage of the surrounding parenchyma is well described [7,12,56,70]. The theory of “normal perfusion pressure breakthrough (NPPB)” suggests that peri-AVM vasculature maintains CBF by exhibiting a chronically vasodilatory phenotype (Figure 3) [65]. This theory was initially described in a case illustration of a large BAVM experiencing ischemic attacks owing to arterial “steal” by the BAVM. Obliteration of the BAVM results in the normalization of blood pressure to surrounding vasculature in the setting of dysautoregulation, resulting in edema and hemorrhage. To test this idea, the authors created an experimental feline model of arterial venous fistula by anastomosing the rostral carotid artery with the distal jugular vein. Five cats developed a large fistula. Iatrogenic hypertension in the form of a dopamine challenge resulted in a commensurate increase in CBF following occlusion of the large fistula (impaired autoregulatory response). Dopamine challenge following occlusion of the arteriovenous shunt in cats that did not develop large fistula resulted in no change in CBF, suggesting preserved autoregulation. The authors suggested that NPPB is a function of impaired autoregulation. Strict lowering of blood pressure following BAVM resection may reduce the likelihood of NPPB in the setting of a leftward shift of the autoregulatory curve [65].

The “occlusive hyperemia theory (OHT)” postulates that following BAVM resection, there is stagnation of flow in arterial feeders and venous outflow obstruction in peri-AVM veins. The combination of ischemia and venous outflow obstruction leads to edema and/or hemorrhage [2]. Vascular stasis of arterial feeders may result in retrograde thrombosis and compromise nearby vessels perfusing normal brain [2,50]. Meyer et al. urge caution at the adoption of OHT, as cortical oxygen saturation measured using microspectrophotometry is greatest in brain tissue with angiographic evidence of arterial stagnation following AVM resection [49]. Staged deconstruction of arterial feeders can gradually decrease BAVM flow and decrease the likelihood of complications related to normal perfusion pressure breakthrough [62,63,7]. However, compounded risk for repeat intervention, inaccessibility of deep arterial feeders, and incomplete understanding of BAVM autoregulatory physiology may favor shorter interval for attempted BAVM cure. During treatment, obliteration of venous outflow prior to nidus obliteration can precipitate catastrophic rupture [2]. Partial embolization serves to decrease flow without increasing resistance [61]. Endovascular embolization of arterial feeders decreases BAVM flow rate and luminal diameter. Quantitative MRA demonstrates that the total number of arterial pedicles embolized and obliteration of an intranidal fistula results in the greatest decrease in BAVM flow following endovascular treatment [3]. Obliteration of arterial feeders and an absence of penetration of embolic material into the nidus may result in preserved flow rates due to redistribution of flow through pial collaterals [3,38,61]. Following surgical resection, ipsilateral cerebral flow was observed to be significantly less than the contralateral hemisphere, though the authors do not compare baseline BAVM characteristics for size and steal phenomenon [3].
Radiosurgery Implications

Radiosurgical treatment of BAVMs is an efficacious and safe treatment modality that may offer a complete obliteration (CO) rate of up to 85% at 2 years [15, 55, 65]. Given the wide availability and safety of the procedure, it is a viable alternative or adjuvant to microsurgery and embolization for AVMs. With the advancement of imaging and radiosurgical techniques, there is an increased focus regarding hemodynamic flow patterns and angioarchitectural changes following radiosurgery to assist with therapeutic decisions. Currently, it is proposed that radiosurgery induces intraluminal proliferation and thrombus formation leading to vaso-occlusion of BAVM vessels. Kashba et al. demonstrated these changes in an AVM animal model through histologic evidence of concentric subendothelial cell growth, vessel wall thickening, and luminal narrowing following gamma knife surgery (GKS) [37].

Furthermore, at the molecular level Tu found expression of inflammatory and thrombotic molecules soluble E, P-selectin, ICAM-1, VCAM-1, and tissue factor were upregulated in irradiated rat AVMs and human cerebral microvascular endothelial cells [71]. These inducible changes are not rapid. Compared to microsurgical dissection and embolization, the risk of AVM hemorrhage is not immediately eliminated following treatment. Rather, the time to complete obliteration is delayed and can occur as early as four months or as long as three years or greater following radiosurgery [55, 47]. Moreover, animal studies have shown angiographic evidence of vessel narrowing and reduced blood flow as early as 6-weeks [37].

Due to the complex angioarchitecture of BAVMs, there is a multitude of factors that may influence their flow patterns including size, feeding arteries, and venous outflow [59, 65, 30, 15]. The network of tangled vessels results in arteriovenous shunting without interposed capillaries creating a low-resistance, high-flow intra-nidal environment [19]. As a result, perinidal angiogenesis develops secondary to the steal effect that occurs from the high flow shunting to the BAVM [65]. Assumed from Poiseuille’s formula \(Q=(P_2-P_1)/R\), as the resistance (R) in the nidus decreases the flow (Q) in the feeding and parent arteries would increase [59, 54, 35]. In a dynamic MRA study, Schuster [59]. Observed a direct relationship between mean arterial blood flow in the ipsilateral internal carotid artery (ICA) and BAVM volume. They found medium (>3.5 ≤10 cm³) and large-sized (>10 cm³) BAVMs to have a significant increase in ICA blood flow. In the same study, a significant reduction of ipsilateral ICA blood flow was observed in patients with CO (25/34) that followed up 2–4 years after radiosurgery. In support, Takeda [66] observed a correlation coefficient of 0.83 between nidus volume and apparent BAVM inflow and outflow.

Given the increased blood flow of BAVMs via diversion of blood from surrounding brain parenchyma, there is a relative increase in cerebral blood volume (CBV) and CBF. Subsequently, there is increased venous perfusion. Following BAVM treatment with radiosurgery, there is promotion of draining vein occlusion leading to a low-flow state and subsequent thrombosis. In a hemodynamic study of 19 AVMs treated with radiosurgery, authors observed a decrease (return to normal) in CBV, CBF, and mean transit time [26]. There was a change toward normal perfusion at 6 months. In addition, post-treatment edema was noted in 15 patients. Given the initial imbalance of inflow and outflow after radiosurgery, the venous drainage may become overwhelmed, possibly
altering cerebrospinal fluid (CSF) and glymphatic drainage. Ultimately, this may lead to post-surgical radiologic changes and symptoms (Figure 4).

**Meningeal Lymphatics and Glymphatic System: Implications for AVM Treatment**

The discovery of dural meningeal lymphatic vessels and the glymphatic system present a new avenue of inquiry into the fluid dynamics of BAVMs (Table 1). The presence of lymphatic vessels within the cranium was long debated and often discounted until 2015 when multiple groups documented lymphatic vessels adjacent to dural venous sinuses in mice [11,46]. These vessels expressed all classical markers of lymphatic endothelial cells including Lyve-1, Prox1, VEGFR3, and CD31. Further, tracer experiments demonstrated that meningeal lymphatic vessels collect fluid from the intraventricular space and drain into deep cervical lymph nodes [46]. The study of meningeal lymphatics in humans is more challenging, but radiographic studies have shown that structurally similar vessels and histologic analysis in non-human primates demonstrated lymphatic cell markers including Prox1, CD31, and podoplanin [1,4]. These exciting discoveries are now laying the foundation for investigation into meningeal lymphatic impairment as a mediator in neurological and neurovascular disease.

The unique location of meningeal lymphatics within the dural folds of the venous sinuses suggests lymphatic flow may be affected by perturbations in venous flow. In the context of BAVMs, this correlates with high venous pressure and wall stress due to loss of the capillary resistance network. It is unknown if venous outflow directly affects meningeal lymphatic flow, but advances in imaging techniques now allow this hypothesis to be investigated in human BAVM patients. The first studies of meningeal lymphatic flow in humans used contrast media to follow CSF into the lymphatic vessels; however, recent MRI techniques allow visualization of these vessels without the use of contrast media [1,4]. Animal studies have demonstrated methods for increasing lymphatic vessel flow and can also modulate immune response to central nervous system (CNS) disease [60]. Utilizing these techniques and methods in future studies may further elucidate the mechanism in which meningeal lymphatic flow is affected by BAVMs and which, if any, pathways can be targeted to improve lymphatic function.

The glymphatic system, named as a portmanteau of glia and lymphatic, is an interface for fluid exchange between CSF and the interstitial space first characterized in 2012 [31,57]. This exchange occurs as CSF moves through the subarachnoid space, to the Virchow-Robin space ensheathing penetrating arteries, and eventually to the basal lamina of astrocyte process end feet that surround the vascular capillaries and the neurovascular unit [33]. The basal lamina is a complex extracellular matrix comprised of laminins, collagens, and many other glycoproteins. The organization of proteins within the basal lamina, as well as the presence of highly charged molecules, offer little resistance to fluid flow from the Virchow-Robin space. Another critical element of the glymphatic system is the polarized expression of aquaporin-4 (AQP4) on astrocytic endfeet. Genetic deletion of AQP4 in mice reduces interstitial solute clearance by approximately 70%, demonstrating that astrocytes are crucial...
mediators of fluid influx from the CSF to the interstitial space [25,31]. The forces governing fluid flow in the interstitium are still unclear, but most evidence suggests that a combination of osmotic forces, hydrostatic pressure gradients, and arterial pulsatility is likely involved [67]. Ultimately, the molecular content of interstitial fluid flows towards perivenous and perineuronal spaces where it reenters the CSF and either recirculates or egresses through one of the four known CSF outlets: dural meningeal lymphatic vessels, perineural sheaths of cranial nerves, the choroid plexus, or arachnoid granulations [11,24,31,46,57,75]. The novelty of the glymphatic system presents an important opportunity to reassess hypotheses of neurological and neurovascular diseases in light of how they could be affected by glymphatic disruption.

BAVMs interfere with the formation of local glymphatic channels due to absent capillaries and malformed surrounding tissue. BAVMs often have decreased pericyte coverage, as they are often large and unstable [72]. Pericytes, in addition to secreting extracellular matrix proteins to the basal lamina, are also critical mediators of astrocyte AQP4 expression [25]. Mice lacking functional PDGF-B have reduced pericyte coverage and AQP4 expression [9]. Dysregulated AQP4 expression is likely to impair CSF influx to the interstitial space near BAVMs, although this remains to be tested experimentally in a BAVM model. Pericytes are also the primary source of platelet-derived growth factor receptor β (PDGFRβ) [16]. Histological analysis has demonstrated that PDGFRβ is downregulated in BAVMs, consistent with decreased pericyte coverage. Lack of PDGFRβ signaling can disrupt glymphatic flow. Mice lacking the ligand for PDGFRβ exhibit impaired development of the glymphatic system, which persists throughout adulthood [53]. The functional consequences of glymphatic disruption within BAVMs are unknown, in part, due to the novelty of the glymphatic system. Hydrocephalus is a known feature of BAVM pathology due to inhibited CSF flow [23]. However, what has predominantly been attributed to mass effect could also be affected by glymphatic flow [41,58]. Inflammatory and metabolic waste products are cleared through the glymphatic system, including amyloid β proteins [31]. Future studies are warranted to investigate glymphatic involvement in the accumulation of pro-inflammatory and angiogenic factors mediating BAVM pathology.

Conclusion

Recent progress in the understanding of CNS fluid dynamics and glymphatic pathways have revealed important implications for BAVM pathology and treatment. Advances in imaging and research protocols allow for more sensitive, non-invasive methods of studying BAVM hemodynamics. This may allow for further understanding of patient-specific flow patterns. In addition, key advancements in understanding angioarchitectural and hemodynamic changes of BAVMs after obliteration warrant further investigation of the relationship between BAVMs and the glymphatic system to potentially decrease risk for treatment complications.

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Figure 1:
BAVM are characterized by a low resistance nidus resulting in more flow across the arteriovenous shunt (Flow=Pressure/Resistance). Arrows represent magnitude of flow.
Figure 2:
Normal peri BAVM cerebral vasculature exhibit a dilated phenotype and exhibit a leftward shift in the autoregulatory curve. The dotted line represents vascular hemodynamics of normal vessels in the setting of BAVM. The solid black line represents vascular hemodynamics under normal circumstances. This compensatory response allows for the maintenance of blood flow in the setting of diminished pressures due to steal phenomenon in the presence of large BAVM.
Figure 3:
Following BAVM obliteration, the normal capillary beds will receive greater flow at stable pressure due to the loss of a low resistance parallel circuit represented by the BAVM, which may result in the phenomenon of normal pressure perfusion breakthrough.
Figure 4:
Hemodynamic and angioarchitectural changes following radiosurgical treatment.
Table 1:
Significant studies of meningeal lymphatics and glymphatic system.

| Study                                                                 | Authors and Year of Publication | Key Findings and context                                                                                                                                                                                                                           |
|----------------------------------------------------------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRL. | Absinta [1].                      | First evidence of meningeal lymphatic vessels in humans. Meningeal lymphatic vessels of non-human primates express same cell markers as rodent tissue.                                                                                                               |
| Non-invasive MR imaging of human brain lymphatic networks with connections to cervical lymph nodes. | Albayram [4].                    | New radiographic technique for visualization of meningeal lymphatics without use of contrast media. This technique could promote investigation in humans, especially those with cerebrovascular disease, by minimizing invasiveness. |
| VEGF-C-driven lymphatic drainage enables immunosurveillance of brain tumours. | Song [30].                       | VEGF-C signaling promotes meningeal lymphatic vessel remodeling and enhances immune surveillance. This pathway could be targeted in future therapeutic applications.                                                                              |
| Photobiomodulation of lymphatic drainage and clearance: perspective strategy for augmentation of meningeal lymphatic functions. | Semyachkina-Glushkovskaya[60]. | Photostimulation dilates meningeal lymphatic vessels and can enhance clearance of waste products.                                                                                                                                             |
| Reductions in brain pericytes are associated with arteriovenous malformation vascular instability. | Winkler [72].                    | AVMs have lower pericyte abundance along endothelium compared to control tissue. Ruptured AVMs have reduced pericyte coverage compared to unruptured AVMs.                                                                                                |
| Pericytes regulate the blood–brain barrier.                          | Armulik [9].                      | Mice with mutant PDGF-B have impaired pericyte development in addition to reduced perivascular AQP4 expression. Highlights the importance of pericytes and PDGF-B in regulating AQP4 expression.                                                   |
| PDGF-B Is Required for Development of the Glymphatic System.         | Munk [53].                       | PDGF-B, known to be highly expressed by pericytes, is required for proper development of glymphatic system.                                                                                                                                     |
| Evidence that pericytes regulate aquaporin-4 polarization in mouse cortical astrocytes. | Gunderson [25].                  | AQP4 expression in astrocyte endfeet is polarized towards endfeet adjacent to pericytes, suggesting pericytes may promote AQP4 expression. AQP4 is required for CSF influx into the interstitial space.                                                   |