Stroke: Vascular and Interventional Neurology

REVIEW

Cerebral Venous Insufficiency as a Contributing Factor in Dementia: An Emerging Hypothesis

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ABSTRACT: Emerging evidence suggests that disturbances in cerebral venous outflow may play a meaningful role in the development and progression of cognitive impairment. The brain's glymphatic system, which facilitates the clearance of metabolic waste, including β-amyloid and tau, relies on stable venous pressure gradients to drive perivascular and interstitial fluid movement. Venous insufficiency, whether from structural narrowing or functional outflow obstruction, can disrupt these gradients, reducing clearance efficiency and promoting protein accumulation, neuroinflammation, and white matter injury. Age-related changes in venous compliance, increased pulsatility, and stenosis of the dural venous sinuses have been observed in patients with mild cognitive impairment and dementia, raising the possibility that such hemodynamic alterations may be a significant part of neurodegenerative pathology. As venous sinus stenosis is a potentially treatable condition, it may represent a future therapeutic target. This review synthesizes current knowledge on the interplay between venous circulation and glymphatic function in brain health, outlines the mechanistic basis for venous contributions to cognitive decline, and highlights the need for systematic investigation of further therapeutic treatments in the context of age-related cognitive impairment.

Key Words: Alzheimer disease ■ brain ■ cognitive dysfunction ■ glymphatic system ■ venous insufficiency

Cognitive decline, whether due to normal aging or underlying pathology, may initially present as mild cognitive impairment (MCI), a condition that does not necessarily preclude independence in activities of daily living.[1] When cognitive deficits begin to interfere with activities of daily living as well as social and occupational functioning, the condition is classified as dementia.[1] Dementia has profound personal, social, and economic consequences,[2–4] placing a substantial burden on healthcare systems through increased hospitalizations, long-term care admissions, and associated macroeconomic losses.[1,5]

A recent global estimate reported that in 2021, ≈56.9 million people were living with dementia, a number projected to rise sharply in the coming decades.[6,7] Alzheimer disease (AD) is the most common cause, accounting for up to 75% of all dementia cases.

Although disease-modifying therapies remain limited, agents such as lecanemab and donanemab[8,9] have recently been approved by the US Food and Drug Administration for the treatment of AD.[10,11] Other interventions, including vitamin E and donepezil,[12] have been used, but current evidence does not support their ability to halt or reverse disease progression.

Despite advances in pharmacological approaches, the underlying mechanisms driving cognitive decline are still incompletely understood. Growing evidence suggests that impaired clearance of metabolic waste from the brain—through dysfunction of the glymphatic system—and abnormalities in cerebral venous outflow may play important roles in the pathophysiology of dementia. This review examines these 2 interrelated hypotheses, exploring how glymphatic impairment and cerebral venous insufficiency could contribute to neurodegeneration and cognitive decline (Figure 1).

GLYMPHATIC SYSTEM AND COGNITIVE DECLINE

Description of the Glymphatic System

In 2012, Iliff et al[13] introduced the term glymphatic system to describe the waste clearance system of

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Nonstandard Abbreviations and Acronyms

AD	Alzheimer disease
ALPS	Analysis Along the Perivascular Space
AQP4	aquaporin-4
CSF	cerebrospinal fluid
ICP	intracranial pressure
IIH	idiopathic intracranial hypertension
ISF	interstitial fluid
MCI	mild cognitive impairment
NAC	N-acetyl-l-cysteine
VSS	venous sinus stenosis

the central nervous system, a glial version of the lymphatic system used in the rest of the body. Interstitial fluid (ISF) is the extracellular fluid of the brain parenchyma, facilitating the exchange of ions, nutrients, and waste.[14] Arteries bring cerebrospinal fluid (CSF) from the subarachnoid space into the periarterial spaces of the parenchyma, where CSF is propelled into the interstitial space via convective flow facilitated by AQP4 (aquaporin-4) water channels found on the end feet of astrocytes and basement membrane, mixing with and contributing to ISF[15] (Figure 2D). Ions, lactate, neurotransmitters, β-amyloid, and tau are washed away in the CSF via perivenous spaces, channels surrounding the dural venous sinuses.[16–18] From the perivenous spaces, CSF is drained into the meningeal lymphatic vessels, and finally the deep cervical lymph nodes, where it enters the peripheral lymphatic system.[19]

Cognitive Impairment and the Glymphatic System

Extracellular plaque deposits of β-amyloid peptide and neurofibrillary tangles of tau protein are found in a majority of patients with AD.[20] β-amyloid (extracellularly) and tau (intracellularly) both misfold and aggregate, disrupting synaptic transmission and axonal integrity.[21] β-amyloid can not only trigger tau pathology, but both proteins can self-propagate, creating a harmful feedback loop.[22] The glymphatic system is crucial in clearing these waste products, and therefore, it is reasonable that dysfunction plays a role in the pathogenesis of AD.[23] Studies have shown that impaired glymphatic clearance occurs before the development of AD,[24–26] with research suggesting that glymphatic failure may predict neurodegeneration and clinical progression.[26] This is further supported by recent findings regarding the significant correlation between the Analysis Along the Perivascular Space (ALPS) index and cognition, which suggest that glymphatic dysfunction may be an early marker of cognitive decline in AD.[24] The ALPS index measures water diffusion along the perivascular spaces, with lower diffusion estimates signifying poorer functioning glymphatics. Lower ALPS values have been shown to be associated with faster neurocognitive decline.[26,27]

A role for the glymphatic system in cognitive decline has also been demonstrated in diseases other than AD. Patients with Parkinson disease have been found to have impaired glymphatic activity when compared with healthy controls.[28] Furthermore, a study that compared patients with Parkinson disease and MCI found that those who progressed to dementia had significantly lower ALPS values compared with those who did not.[29] In addition to Parkinson disease, glymphatic dysfunction has been demonstrated in patients with vascular cognitive impairment due to cerebral small vessel disease or stroke.[30] Studies have also suggested a role for glymphatic impairment in cognitive deficiency in multiple sclerosis,[31] diabetes-induced dementia,[32] and obstructive sleep apnea associated with cognitive dysfunction.[33] It has been further suggested that glymphatic function may have a protective effect against cognitive decline associated with normal aging.[34]

Glymphatic System and the Venous System

The glymphatic system is a separate entity from the venous system, as it does not drain directly into the veins, but uses the scaffold created by the venous system as an area to exchange CSF with ISF. However, arterial and venous flow and pressure influence the efficiency of the glymphatic system. Arterial pulsatility facilitates CSF influx and efflux.[35] Venous pressure modulates this process by creating a pressure boundary—that is, it establishes the level of pressure in the veins against which CSF must drain. If venous pressure is elevated, it raises this boundary, reducing the pressure gradient needed for CSF to flow out of the brain, thereby impairing drainage.

Studies have shown that venous hypertension, impaired venous drainage, or changes in venous compliance can reduce the driving force for glymphatic efflux, leading to stagnation of waste clearance.[36,37] Pardo et al[38] found that the cross-sectional area of cerebral veins (smaller venous drainage system) is significantly reduced in patients with AD and MCI compared with cognitively healthy controls. They suggested that, as the venous and glymphatic systems are closely connected, with CSF waste eventually draining into the venous circulation, dysfunction in either the glymphatic or venous system may intensify β-amyloid deposition.[38] This may imply that venous insufficiency has the potential to create a vicious cycle that contributes to glymphatic dysfunction, drives neurodegenerative processes[38] (Figure 2C).

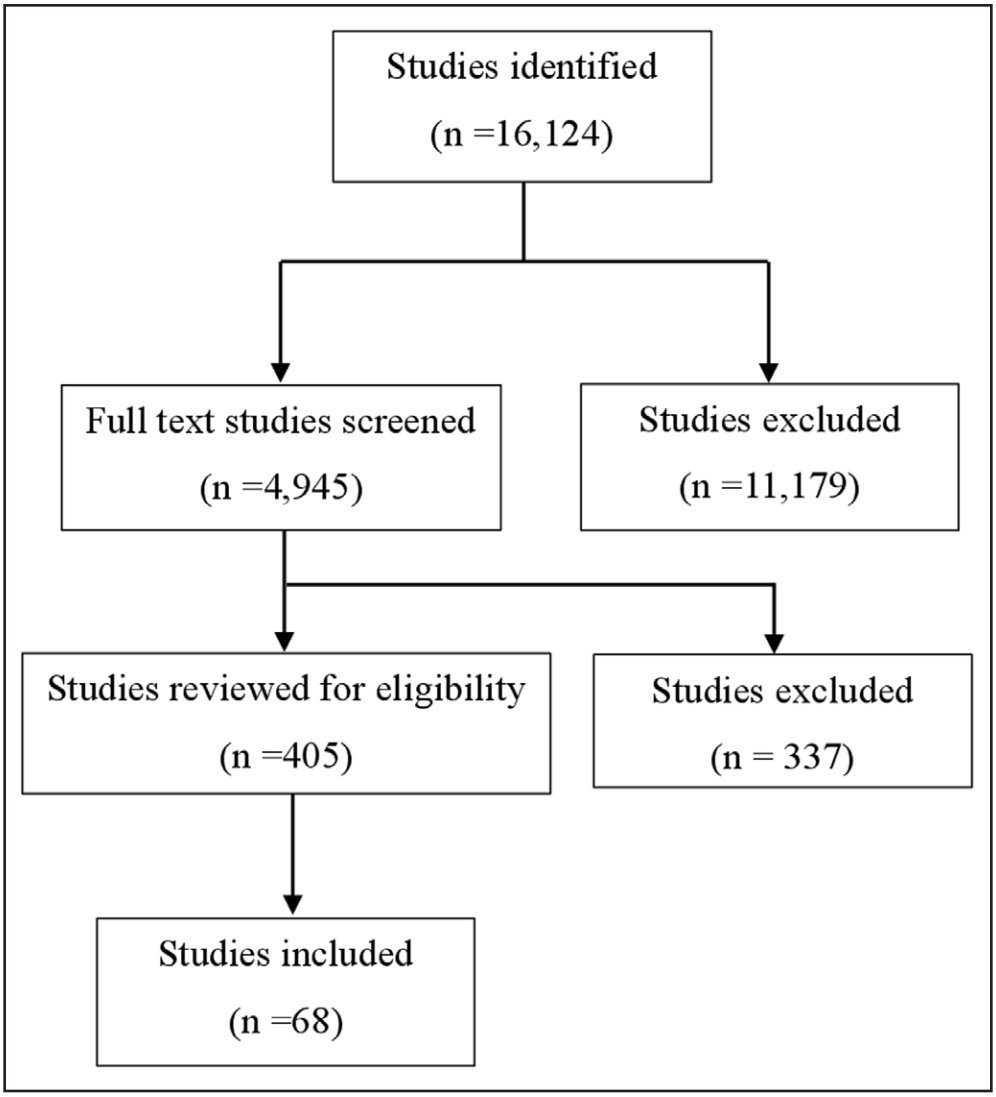

Figure 1. **Flow chart depicting articles reviewed and included.**

Glymphatic and the Venous Drainage During Sleep

Sleep has been found to significantly enhance glymphatic system function. In an animal study, natural sleep or anesthesia led to a 60% increase in cortical interstitial space, boosting convective clearance of β-amyloid.[39] In contrast, sleep deprivation was found to impair glymphatic transport. In a study of 98 cognitively healthy adults, poor sleep was associated with increased β-amyloid accumulation in AD-sensitive brain regions.[40] Even a single night of sleep deprivation can elevate β-amyloid levels in the right hippocampus and thalamus.[41] A systematic review of over 19 000 participants confirmed that sleep problems were associated with altered CSF metabolite concentrations—including β-amyloid and tau—and increased CSF volume and pressure, underscoring sleep's influence on glymphatic exchange.[42] The majority of glymphatic clearance occurs during sleep, particularly during nonrapid eye movement sleep, which is characterized by hemodynamic oscillations that help drive CSF flow.[43,44] In older adults, poor sleep quality has been linked to disrupted glymphatic function and memory decline, with Diffusion Tensor Imaging Along the Perivascular Space index correlating with both sleep and structural-functional brain network integrity.[45] These findings support a model in which the glymphatic system mediates the relationship between sleep and memory, potentially explaining the bidirectional relationship between sleep disturbances and AD pathology.[45,46] Beyond glymphatic flow, venous drainage is also sleep-dependent: in the supine position, the internal jugular veins serve as the primary outflow route for cerebral venous blood, rather than alternative paravertebral pathways.[47] Therefore, stenosis in the draining venous system may further impede glymphatic clearance during sleep, compounding its contribution to neurodegenerative processes and cognitive decline.

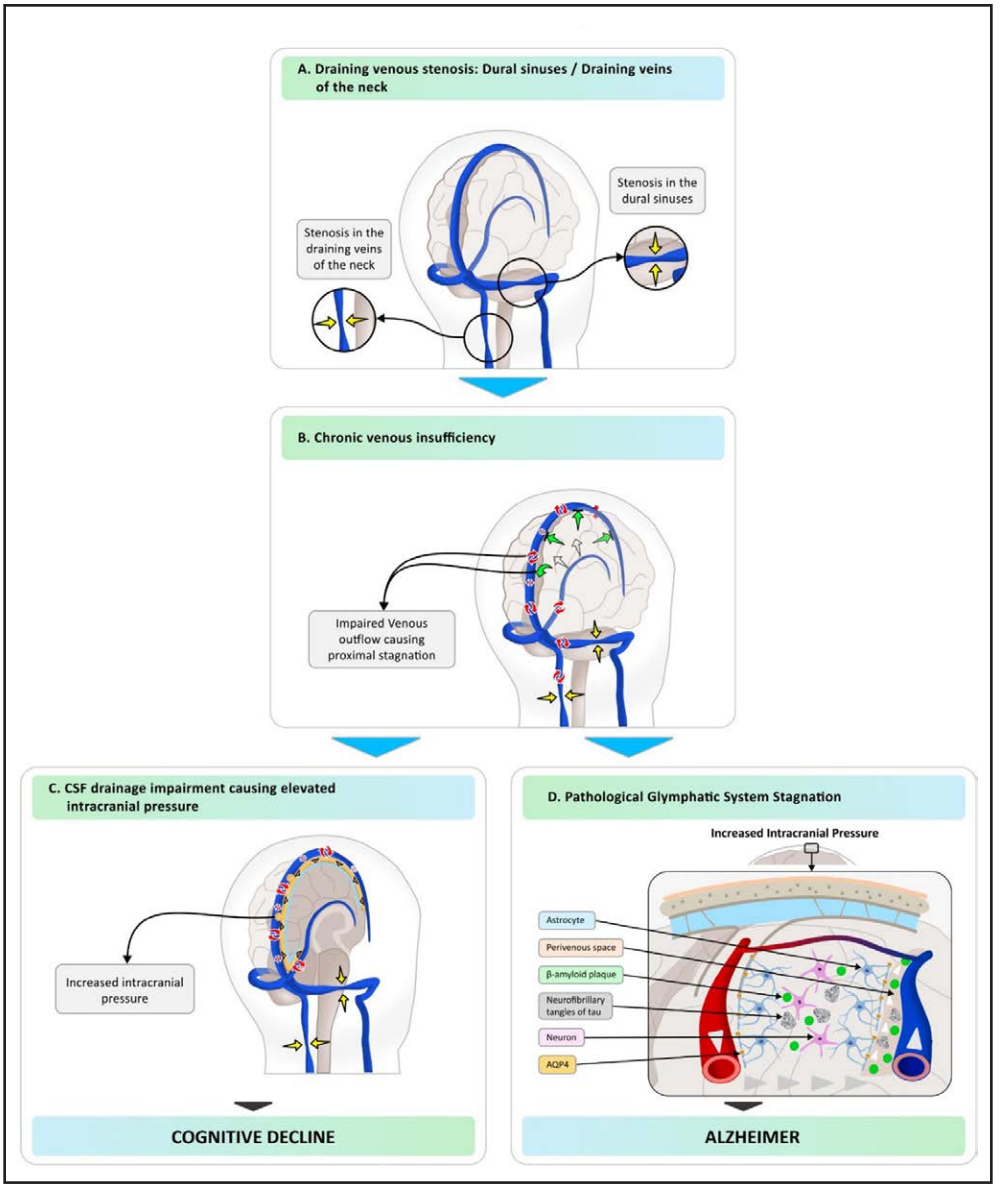

Figure 2. Venous sinus stenosis contributing to cognitive decline.
Stenosis of the draining dural sinuses (**A**) leading to chronic venous insufficiency (**B**), which in turn leads to an increased pressure gradient, inhibiting efficient drainage of cerebrospinal fluid (CSF) through the glymphatic system, in turn causing elevated intracranial pressure (**C**). In specific pathologies, such as Alzheimer disease, β-amyloid plaques and neurofibrillary tangles (tau tangles) are unable to be cleared properly by the glymphatic system, leading to increased intracranial pressure (**D**). AQP4 indicates aquaporin-4.

VENOUS INSUFFICIENCY AND COGNITIVE DECLINE

Venous Sinus Stenosis and Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension (IIH) is a disorder of elevated intracranial pressure (ICP) that most commonly affects women with obesity of childbearing age. It typically presents with chronic headache, diplopia, pulse-synchronous tinnitus, and/or vision loss.[48] Mild-to-moderate IIH is managed medically using ICP-lowering medications and weight loss, but in severe cases, surgical treatments may be necessary.[48] As the name indicates, the cause of IIH was initially poorly understood; however, several studies have demonstrated that venous sinus stenosis (VSS), present in >93% of patients, plays a major role in the disease's pathophysiology[49,50] (Figure 2A). There is now increasing evidence of a positive feedback loop mechanism for the development of extramural VSS in IIH, whereby elevated ICP compresses the sinus at a susceptible site (most commonly the transverse sinus), leading to worsened stenosis and secondary upstream venous congestion, resulting in further elevation of ICP[49] (Figure 2B). High venous pressures, in turn, push back against ICP[49] (Figure 2C). Given the role of VSS in the

pathophysiology of IIH, venous sinus stenting is now recognized as one of the leading surgical approaches to treat severe IIH in patients with VSS that are refractory to medical treatment.[49,51]

Cognitive Impairment in IIH

In addition to the classic symptoms of headache and vision loss, IIH is also associated with cognitive impairment. A retrospective case series of 10 patients diagnosed with IIH showed that these patients had significant cognitive impairment, specifically in memory and learning.[52] This finding was strengthened when a prospective study found that 31 patients with IIH performed significantly worse than healthy age- and sex-matched controls in 4 of 6 cognitive domains, that is, reaction time, processing speed, visuospatial memory, and attention (but not in executive function and working memory).[53] A second prospective study in 30 patients with IIH found that all mean domain index scores (for memory, executive function, visuospatial, attention, information processing speed, and global score) were below average for age and education.[54] These findings were confirmed in a study of 50 patients with IIH with age-matched, sex-matched, and body mass index–matched controls, which showed a multidomain cognitive decline mainly concerning attention and working memory.[55] Similarly, a controlled study in 66 patients with IIH demonstrated multidomain cognitive deficits in IIH, with significant impairment in sustained attention and executive function.[56] Notably, these deficits were reversible, with markers of executive function (sustained attention) improving as ICP was reduced.[56] It is thus evident that IIH impacts cognitive functioning. Given that VSS is found in most patients with IIH and is increasingly acknowledged as a significant factor in the pathophysiology and cause of the condition,[48,50,57] it follows that cerebral venous insufficiency may be an explanation for the cognitive decline observed in patients with IIH.

Pathophysiology of Venous Insufficiency and Cognitive Decline

Several pathophysiological mechanisms have been proposed to explain the relationship between cerebral venous drainage and cognitive decline. Aging leads to structural changes in cerebral veins, such as collagenosis and tortuosity, increasing resistance and impairing venous drainage. This leads to chronic venous hypertension and reduced perfusion pressure, resulting in chronic cerebral hypoperfusion.[58] Periventricular white matter is highly vulnerable to these changes due to its thin medullary veins with poor collateral support. Venous collagenosis in these small vessels can lead to narrowing, impairing ISF and CSF clearance and waste removal, contributing to vasogenic edema. As a result, this region undergoes pathological changes, including axonal loss, oligodendrocyte degeneration, myelin rarefaction, and glial activation. This damage to white matter disrupts neural communication and fluid homeostasis, leading to cognitive deficits, particularly in executive function and processing speed.[59] This is especially disruptive in aging adults who are already at risk for white matter hyperintensities that lead to neuroinflammation and correlate with worse cognitive performance.[58,60]

Venous insufficiency can also contribute to blood-brain barrier dysfunction, primarily through its role in chronic cerebral hypoperfusion. Reduced venous outflow leads to elevated venous pressure and impaired clearance, resulting in decreased cerebral perfusion over time. This hypoperfusion induces oxidative stress and upregulation of matrix metalloproteinases, which degrade tight junction proteins and the basement membrane, key components of the blood-brain barrier.[61] This breakdown of the blood-brain barrier permits infiltration of immune cells and plasma proteins into the brain parenchyma, triggering neuroinflammation, demyelination, and white matter damage.[61] This damage, in turn, can be associated with neurological decline.

Several studies have suggested links between AD or amyloid deposition and venous insufficiency.[38,62–65] They often measure an indirect indicator of venous insufficiency, venous pulsatility index, in the context of neuroimaging to describe blood flow velocity. A low value indicates a decreased speed of blood going through that vessel. In a comparison of patients with AD, MCI, and controls, a significantly higher venous pulsatility index was found in the superior sagittal sinus, straight sinus, and transverse sinus in patients with AD and MCI.[65] This increase is thought to reflect the transmission of excessive arterial pulsatility into the venous system. In healthy individuals, CSF pulsations help absorb the force of arterial blood flow, maintaining stable ICP and protecting brain parenchyma. In AD and MCI, increased arterial stiffness leads to stronger arterial pulsations, while compensatory CSF dynamics may be impaired due to decreased brain compliance, ventricular dilation, or dysfunction of the glymphatic clearance pathways. As a result, more pulsatile force is transmitted to the venous system, increasing the venous pulsatility index. This shift may impair venous drainage and waste clearance, contributing to the progression of neurodegeneration in AD and MCI.

Cerebral microbleeds[66] and superficial siderosis, often caused by venous amyloid angiopathy, may account for another possible mechanism underlying cognitive impairment. These microbleeds are typically located in deep or lobar regions and reflect underlying vascular pathology that compromises neural integrity, particularly in areas responsible for cognition. In addition, impaired venous drainage disrupts the glymphatic system, which normally clears metabolic waste, such as β-amyloid from the brain, leading to its accumulation.[67] Over time, this β-amyloid buildup further damages venous and perivascular structures, worsening drainage and creating a vicious cycle

that promotes cognitive decline. Venous dysfunction not only causes structural damage through microhemorrhages but also exacerbates toxic protein buildup, both of which underlie cognitive deficits.[68] Patients with cerebral venous reflux have also been found to have significantly higher rates of cerebral amyloid angiopathy and lobar hemorrhage, suggesting venous impairment hinders β-amyloid clearance.[63]

Treatment of Cognitive Decline With Venous Stenting

Venous sinus stenting has gained recognition as a primary treatment for severe IIH in patients with confirmed VSS, accompanied by a pathological pressure gradient, and is being performed with increasing frequency,[49,69] and has been found to be relatively safe with a 1-year major adverse event rate of 5.4%.[70] Studies, including meta-analyses, have demonstrated high rates of improvement in neurological outcomes, including headaches and visual function.[49,71] Importantly, improvements in cognition/mental well-being after venous sinus stenting or surgical intervention at a site of jugular vein stenosis have also been reported.[72–74] In a study of patients with Ehlers-Danlos syndrome, 90 venous sinus stenting procedures were performed in 74 patients with a primary venous pressure gradient.[73] After stenting, headaches and cognitive dysfunction, commonly reported as brain fog, significantly improved or resolved in 77% of these patients.[73]

In addition, a 2024 study comparing 37 female patients with IIH who underwent venous sinus stenting with 74 female patients with IIH treated medically found that the group who underwent stenting reported significantly better outcomes in physical well-being, task completion, work/school persistence, and mental well-being.[74] This was replicated in a recent study that retrospectively reviewed 50 patients (47 female) who underwent venous sinus stenting for venopathic intracranial hypertension, a term similarly used to describe intracranial hypertension secondary to VSS or congestion.[69] Patients self-reported scores on cognition, headache, tinnitus, dizziness, and vision before and after stenting, with statistically significant improvements in all domains except dizziness. These studies provide anecdotal evidence that treating venous insufficiency may be an effective approach to managing cognitive decline in patients with IIH.

VENOUS INSUFFICIENCY IN THE CONTEXT OF GLYMPHATIC DYSFUNCTION AND COGNITIVE DECLINE

Although there is increasing evidence for the independent associations of impaired glymphatic clearance and venous insufficiency with cognitive decline, the implications of these associations within a broader systemic context have not been explored. Specifically, the potential role of cerebral venous insufficiency as a contributing factor to cognitive decline warrants greater attention in the context of age-related diseases associated with glymphatic dysfunction.

A possible role for altered cerebral venous circulation in the pathogenesis of cerebral disease and cognitive decline has been suggested,[65] with studies demonstrating impaired venous structure or function, such as narrowing of jugular veins[38] and increased cerebral venous pulsatility,[72] in patients with AD. It is therefore possible that venous drainage in older patients with cognitive decline is similarly impacted, particularly because venous insufficiency increases with age.[46,47] Furthermore, impaired glymphatic clearance in AD has been clearly established.[13,15,75] Studies have demonstrated that the ALPS index, a proxy for glymphatic flow, is reduced in patients with AD, and that the index is correlated with cognitive function,[13,15,76] suggesting impaired perivenous drainage of the glymphatic system and fluid stasis in cases of cognitive decline. This may be secondary to venous insufficiency, leading to stagnation and possible reflux that hinders the influx of glymphatic fluid (CSF/ISF) into the perivenous spaces and brain interstitial compartment.

Furthermore, it is possible that improving venous drainage in locations with significant stenosis may be beneficial in improving both venous and glymphatic drainage. This may allow better drainage of the brain in general, which can improve cognition, as well as possibly prevent further accumulation of β-amyloid in early-stage AD. This assertion is supported by small studies that demonstrate cognitive improvement after venous sinus stenting in younger patients with primary venous pressure gradient or IIH.[73,74] These findings establish a preliminary rationale for further investigating a potential impact of venous sinus stenting on cognitive decline in older adults with VSS.

There is a need to develop more precise cognitive assessment tools tailored for patients with venous congestion. A recent interesting study on rats investigated venous insufficiency and found not only decreased long-term potentiation in the hippocampus, but identified a decreased metabolite, *N*-acetyl-L-cysteine (NAC), that was a key player in cognition.[77] Using jugular venous ligation to artificially induce cerebral venous congestion, Wei et al[77] measured memory with the Y maze test and the novel object recognition test, an open field test to measure locomotion and spontaneous activity, and lastly, a rotarod test for motor coordination. Their ICP was measured, as well as hundreds of hippocampus metabolites, utilizing the untargeted liquid chromatography–mass spectrometry. They found γ-aminobutyric acid, nicotinamide, acetyl-L-carnitine, and NAC levels to be significantly altered, and with targeted assays confirmed that NAC was significantly decreased with decreased cognition, and when supplemented to rats, improved

their cognition. They then investigated 15 patients with cerebral venous congestion and found significantly decreased NAC when compared with healthy controls. Specifically, NAC levels were negatively correlated with subjective cognitive decline scores (high score indicated worse functioning) and positively correlated with Mini-Mental State Examination scores (high score indicated better functioning).

CONCLUSIONS

In conclusion, VSS may be an under-recognized yet potentially reversible cause of cognitive decline. Increasing evidence supports a link between impaired cerebral venous drainage and cognitive dysfunction in conditions such as IIH and AD. Although the anatomic patterns of venous pathology may differ, both localized stenosis and global drainage insufficiency can contribute to cognitive decline through shared mechanisms such as hypoperfusion, neuroinflammation, and impaired glymphatic clearance. Early recognition and targeted intervention may mitigate or even prevent long-term cognitive consequences. Future research should focus on assessing the location of VSS and clinical presentation of older patients with cognitive decline, investigating the association between venous insufficiency and cognitive decline in a context other than IIH, and the potential therapeutic role of venous stenting in managing cognitive decline.

ARTICLE INFORMATION

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Dr Horev contributed to conceptualization and supervision. Dr Eliav contributed to writing—original draft preparation. All authors contributed to methodology, including performing the literature review, writing—review and editing, and have read and agreed to the published version of the manuscript.

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