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Glymphatic System and Post-hemorrhagic Hydrocephalus

Fenghui Ye, MD,

Richard F. Keep, PhD,

Ya Hua, MD,

Hugh J. L. Garton, MD,

Guohua Xi, MD

Department of Neurosurgery, University of Michigan, Ann Arbor, MI, USA

Abstract

The glymphatic system is a recently identified route for exchanging parenchyma interstitial fluid and cerebrospinal fluid along perivascular space, facilitating brain waste clearance. Glymphatic system dysfunction has been reported in many neurological diseases. Here we discussed the possible role of glymphatic system in posthemorrhagic brain injury, especially posthemorrhagic hydrocephalus.

Keywords

Glymphatic System; Hydrocephalus; Hemorrhagic Stroke

Introduction

Hydrocephalus, characterized as the excessive accumulation of cerebrospinal fluid (CSF) within the cranium, is one of the most common neurological disorders worldwide. With poor long-term outcomes, including impaired overall intelligence, epilepsy, gait disturbance, urinary incontinence, and chronic severe headaches, hydrocephalus brings a huge global health expenditure burden[1]. Post-hemorrhagic hydrocephalus (PHH) of prematurity is the most common cause of pediatric hydrocephalus. Preterm neonates and very low birth weight infants are at the highest risk to develop germinal matrix hemorrhage (GMH) and subsequent hydrocephalus. Adult-onset hydrocephalus can result from intraventricular hemorrhage (IVH) and subarachnoid hemorrhage (SAH). Yet, the pathophysiology of PHH remains largely unknown, and little has progressed in the treatment approaches for decades with a reliance on neurosurgery (shunt placement and endoscopic third ventriculostomy). The classic hypothesis of CSF hydrodynamics was first established a century ago, which indicated hydrocephalus was a result of the imbalance of CSF production (primarily at the

Correspondence: Fenghui Ye, M.D., R5018 Biomedical Science Research Building, University of Michigan, 109 Zina Pitcher Place, Ann Arbor, Michigan 48109-2200, Telephone: (734) 764-1207, Fax: (734) 764-7322, fenghuiy@umich.edu Or Guohua Xi, M.D., R5018 Biomedical Science Research Building, University of Michigan, 109 Zina Pitcher Place, Ann Arbor, Michigan 48109-2200, Telephone: (734) 764-1207, Fax: (734) 764-7322, guohuaxi@umich.edu.

Declaration of Competing Interest

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choroid plexuses) and absorption (at the arachnoid villi/granulations and other CSF outflow sites). However, the description of a brain 'glymphatic system' by Iliff et al[2] a decade ago and the impact of different disease states on that system[3] presents another potential contributor to brain fluid imbalances.

Glymphatic System and Brain Fluid

Apart from CSF, the brain also has interstitial fluid (ISF) between all parenchymal cells (e.g., neurons and glia) and fluid within the perivascular space (PVS) around the arterioles and venules that penetrate the brain parenchyma[3]. Anatomically, the PVS occurs between the blood vessel (endothelium and surrounding smooth muscle) and an enclosing sheath of astrocyte endfeet. Iliff et al.[2] described a link between CSF and ISF whereby CSF in the subarachnoid space enters the brain along the periarterial space, fluid then moves into brain parenchyma across the astrocyte endfeet and exits the brain along the PVS along venules. Since the system has similarities in function to the lymphatic system in other body organs and largely depends on glial cells, it was termed "glymphatic system"[2,3]. The glymphatic system and the exchange of fluid from PVS to ISF was found to be facilitated by the polarized distribution of the water channel aquaporin-4 (AQP4) in astrocytes.

Glymphatic system dysfunction has been reported in many neurological diseases. For example, aging and Alzheimer's disease are associated with impaired glymphatic clearance and accumulation of amyloid β protein, which will further aggravate glymphatic dysfunction. In animal models, glymphatic function appears to decrease after SAH, acute ischemia, multiple microinfarctions, and traumatic brain injury in animal models[4]. Glymphatic impairment has also been observed in patients with idiopathic normal pressure hydrocephalus, along with astrogliosis (upregulation of glial fibrillary acidic protein, GFAP, expression) and AQP4 overexpression[5].

Glymphatic System and Post-ischemic Brain Edema

Most attention has focused on the role of the glymphatic system in clearing waste products and neurotoxic agents such as amyloid β from the brain[3]. However, recently, Mestre et al.[6] presented evidence on a role in brain fluid imbalance. They presented evidence that the CSF influx entering brain parenchyma along the glymphatic system drives hyperacute post-ischemic brain edema, a hitherto unsuspected source of edema. The researchers also demonstrated that the CSF driven brain edema was largely dependent on AQP4. In AQP4 knockout mice, the increased glymphatic CSF flow and acute brain edema was decreased after ischemia. Moreover, the glymphatic influx of CSF was possibly triggered by the sudden waves of spreading depolarization which caused the vasoconstriction of arterioles, thus extending the PVS creating a pressure gradient for the CSF flow into the brain. This study introduces a new theory of CSF-induced brain edema through the glymphatic system, suggesting that the glymphatic system or AQP4 could be a therapeutic target. Furthermore, it would be interesting to know if this CSF-induced brain edema is important longer term; whether it occurs in other kinds of acute brain disease, such as IVH and SAH; and if changes in the glymphatic system are involved in PHH development.

Glymphatic System and SAH

Glymphatic function was severely impaired after 24 hours in a mouse SAH model, reducing brain clearance of low-molecular-weight compounds[7]. An impairment in glymphatic circulation after SAH also occurs in nonhuman primates[8]. Moreover, lymphatic perfusion, vasospasm, and microcirculation impairment following SAH could be ameliorated by intracisternal administration of tissue-type plasminogen activator (tPA)[9]. Another study[10] demonstrated that blood components rapidly enter the PVS after SAH, which induces neuroinflammation and neurological deficits on day 7. AQP4 knockout mice showed reduced blood in the brain parenchyma after SAH, but no improvement in neurological deficits at day 7; with an impaired glymphatic system, AQP4 knockout mice had increased brain water content and worse brain injury after SAH[11]. Impaired glymphatic function after SAH might lead to more intense secondary damage caused by accumulation of neurotoxic blood components and metabolites within the parenchyma. Blood components in CSF/ISF impaired the function of glymphatic system which resulted in disturbance of CSF flow and eventual development of hydrocephalus[12]. An ongoing clinical trial is investigating the effect of intracerebroventricular tPA administration after aneurysmal SAH (NCT03187405). This evidence suggests the glymphatic pathway plays a role in blood removal and CSF drainage after SAH and might be related to PHH development. Further investigations are warranted into how glymphatic function may influence long-term neurofunctional outcomes after SAH and the role of the glymphatic system in SAH-induced hydrocephalus.

Glymphatic System and IVH

Recent research indicated impairment of the exchange between CSF and ISF, and the development of hydrocephalus on day 28 in a neonatal rat GMH model, effects which were partially reversed by astrogliosis inhibition[13]. The authors suggested that glymphatic system dysfunction might be associated with AQP4 redistribution. This is the first study to characterize the role of the glymphatic system in neonatal PHH, implying the glymphatic system along with the gliosis might be a potential therapeutic approach for PHH.

Perspective and Prospective

Evidence of how brain glymphatic system changes and how brain fluid is transferred through the brain after cerebral hemorrhage is still limited. The glymphatic hypothesis after hemorrhage includes the blood components entering PVS, glial end foot damage, AQP4 disfunction causing glymphatic circulation impairment, which might be related to PHH. Future research is needed to understand the glymphatic system's role in posthemorrhagic brain injury with two-photon fluorescence and MRI which have been utilized to show the periarterial fluid movement in real-time in vivo. Moreover, glymphatic function could be a therapeutic target for PHH; developing agents that can enhance glymphatic function or prevent dysfunction is an important goal.

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Abbreviations:

CSF	Cerebrospinal Fluid
PHH	Post-hemorrhagic Hydrocephalus
GMH	Germinal Matrix Hemorrhage
IVH	Intraventricular Hemorrhage
SAH	Subarachnoid Hemorrhage
ISF	Interstitial Fluid
PVS	Perivascular Space
AQP4	Aquaporin-4
GFAP	Glial Fibrillary Acidic Protein
tPA	Tissue-type Plasminogen Activator

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