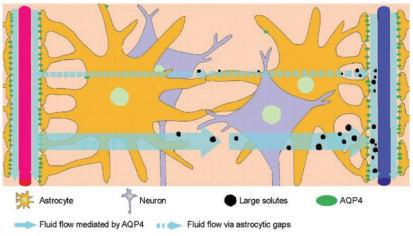
Radiology Science

Original Research

Magnetic resonance imaging-based progress in human glymphatic system research

Graphical abstract



Key points

- This review summarized the contributions of MRI to the research advances involving the human glymphatic system, followed by a consideration of prospective applications in the future.
- DTI, CEST, ASL, and intravenously- or intrathecally-administrated macrocyclic GBCAs as MR methods can be used in human glymphatic system research.

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Magnetic resonance imaging-based progress in human glymphatic system research

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Abstract

The recently discovered glymphatic system is considered a prominent breakthrough in neuroscience. The glymphatic system serves as a cerebrospinal fluid-interstitial fluid exchange system involving polarization of the water channel protein, aquaporin-4, in astrocyte endfeet. In this review we summarize the MRI findings that have contributed to the research advances of the human glymphatic system and propose prospective future applications.

Keywords: human glymphatic system, MRI

1. CONCEPT AND FUNCTION OF THE GLYMPHATIC SYSTEM

Iliff et al. [1] first described a rapid exchange system involving cerebrospinal fluid (CSF) and interstitial fluid (ISF) in 2012, which serves as one of the mechanisms by which metabolites and waste are removed from the brain. Because of the functional similarity to the peripheral lymphatic system and the functional dependence on gliocytes, it is designated as the glymphatic system or glymphatics. A schematic of glymphatics is depicted in **Figure 1**. [1, 2]

CSF enters the brain parenchyma from the subarachnoid space (SAS) along para-arterial spaces (glymphatic influx) to drive the bulk flow of ISF toward the paravenous spaces, from which solutes and fluid will flow into the SAS or drain out of the brain tissue toward the cervical lymphatic tissue (glymphatic outflow). In addition to moving through the astrocytic clefts, the CSF-ISF exchange around the para-vascular spaces is facilitated by aquaporin-4 (AQP4) water channels, which are highly expressed in the astrocytic endfeet. Glymphatic efflux primarily functions to facilitate the removal of metabolites and waste solutes, such as lactate and soluble amyloid beta in the ISF, thus having a role in draining waste from the brain. In contrast, due to its critical role in the delivery of CSF solutes into the brain parenchyma, glymphatic influx may serve as a brain-wide distribution system for choroid plexus/CSF-derived nutrients and neuroactive substances. Recent studies have demonstrated that the glymphatic system also contributes to the transport of neural active substances and nutrients (such as glucose, lipids, and apolipoprotein E) from the CSF to the brain, in addition to the removal of intracerebral metabolites (such as lactic acid), soluble proteins (such as amyloid beta and tau), and foreign materials [1, 3-8].

Therefore, glymphatics can be divided into two parts (glymphatic influx and efflux). The glymphatic system clears metabolic wastes from the brain, and transports and distributes neural active substances and nutrients from the CSF to the ISF [1-8].

Glymphatic system activity is significantly higher during sleep compared to the awake state, illustrating that sleep serves as a considerable condition for removing metabolic wastes from the brain [9]. Moreover, the glymphatic system will sustain damage in line with aging [10], which may also be a common factor in the pathophysiology of several neurodegenerative diseases. Numerous studies have demonstrated that the glymphatic system is attenuated in conditions, such as small vessel disease [11,12], Alzheimer's disease [13-15], traumatic brain injury [4, 8, 16-20], stroke [21-23], diabetes [24], migraine [25], and others that are associated with changes in the perivascular space, and abnormal expression and distribution of AQP4.

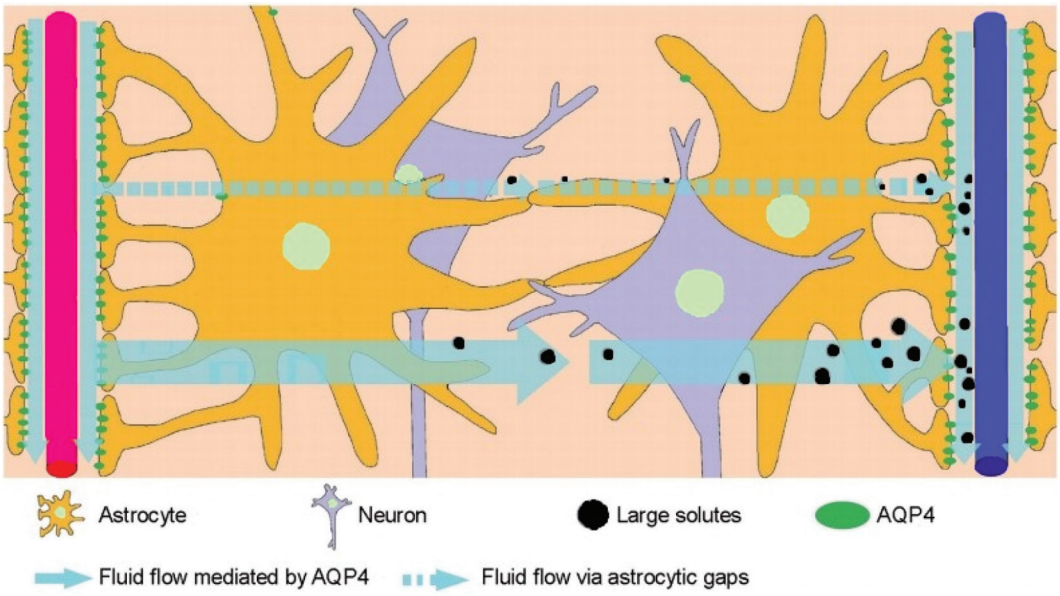

Figure 1 | Schematic drawing of glymphatics.

2. MAGNETIC RESONANCE IMAGING IN HUMAN GLYMPHATIC SYSTEM RESEARCH

Nearly all of the studies on glymphatics have been conducted using experimental animals, with few studies involving humans. Thus, there are few safe and effective methods to monitor the flow of CSF-ISF exchange *in vivo* at present; however, popularization of MRI will help fill our gaps in knowledge.

At present, only macrocyclic gadolinium-based contrast agents (GBCAs) are used as a tracer in glymphatics *in vivo*. Long-term persistence of GBCAs in brain tissue has been demonstrated for less stable and linear GBCAs, but not for macrocyclic GBCAs [26, 27]. Macrocyclic GBCAs are generally administered intravenously at a dose of 0.1 mmol/kg [28]. In the first 90 min after intravenous administration of macrocyclic GBCAs, the plasma concentrations are followed by three phases: distribution; rapid elimination; and long-lasting residual elimination from a third compartment [29]. In the last phase, tiny amounts of macrocyclic GBCAs cross the blood-brain barrier into the CSF and glymphatics. Macrocyclic GBCAs undergo a slow, gradual process, then peak 4-24 h after intravenous administration, thus serving as a tracer of glymphatics *in vivo* [30].

2.1 Intrathecal administration of macrocyclic GBCAs

In November 2015 Eide et al. [31] first reported a young woman undergoing MRI with an intrathecal injection of gadobutrol, which was distributed throughout the entire brain in 60 min and the glymphatic system in 270 min. Therefore, MRI with an intrathecal administration of macrocyclic GBCAs may become a useful method for glymphatics research of the human brain.

Subsequently, on February 2018, Eide et al. [32] carried out a study involving 30 patients with idiopathic normal pressure hydrocephalus (iNPH) and 8 patients with suspected CSF leaks as a reference. Multiple MRI acquisitions with the intrathecal administration of gadobutrol were obtained over a 24-48 h time span in the cognitively-affected iNPH patients and unaffected reference patients. CSF tracer enrichment was confirmed by alterations in normalized MRI T1WI signal units. Compared to the reference patients, the iNPH patients exhibited an increased Evan's index, medial temporal lobe atrophy score, and inferior entorhinal cortex thickness. The delayed clearance of intrathecal gadobutrol from the CSF, entorhinal cortex, and adjacent white matter suggested dysfunction of the glymphatic system. The reduced clearance and accumulation of metabolites and toxic waste materials may serve as a mechanism underlying dementia in patients with iNPH, and glymphatic MRI may be tool contributing to the early evaluation of dementia.

On May 2018 Eide et al. [33] highlighted the evidence which showed that the central nervous system had functional lymphatic tissues, and included data on central lymphatic drainage to cervical lymph tissues in humans with enhanced MRI and intrathecal administration of gadobutrol. MRI scans in 19 people were performed before and 2-4, 4-6, 6-9, 24, and 48 h following intrathecal administration of 0.5 ml of 1.0 mmol/ml of gadobutrol. The enhancement was determined according to the signal variations in the inferior frontal gyrus and the adjacent CSF, pons and thalamus, parahippocampal gyrus, and cervical lymph nodes, with the sagittal sinus and neck muscles used as the reference tissues for the cranial and neck MRI acquisitions, respectively. The time course of the lymph tissue contrast

enhancement was shown to coincide with the brain glymphatic contrast enhancement that peaked at 24 h rather than CSF enhancement that peaked at 4-6 h.

The advantages of the human glymphatic MRI intrathecal injection of macrocyclic GBCA technique can be summarized as follows: (1) The technique continuously reflects the clearance performance of the glymphatic system for a long time. (2) The distribution of tracers in the brain is not affected by the blood-brain barrier and blood circulation. The disadvantages of the human glymphatic MRI intrathecal injection of macrocyclic GBCA technique are as follows: (1) The technique is invasive. (2) Multiple imaging studies are required at regular intervals. (3) GBCAs are deposited in the brain.

2.2 Diffusion-weighted images (DTIs)

On February 2017 Taoka et al. [34] conducted a study involving 31 patients, 9 of whom had mild cognitive impairment, 16 had Alzheimer's disease, and 6 had subjective cognitive dysfunction (mini-mental state examination [MMSE] score ranging from 12-30). DTI scanning was performed for calculating diffusivities in the x, y, and z axes of the lateral ventricle body plane. The diffusivity along perivascular spaces, as well as the association and projection fibers, were assessed separately to obtain the analysis along the perivascular space (ALPS) index that was correlated with the MMSE score. The ALPS index is calculated as follows: mean (Dxassoc, Dxproj)/mean (Dzassoc, Dyproj). Taoka et al. [34] reported that in the projection areas of the b = 1000 s/mm^2 datasets the MMSE score and x-axis diffusivity along the perivascular spaces exhibited a positive and statistically significant correlation, and a statistically significantly negative correlation between the MMSE score and z-axis diffusivity along the projection fibers, while no significant correlation existed with the y-axis diffusivity in the anterior-posterior direction. In the association areas of the b = 1000 s/mm^2 datasets, the MMSE score had a positive correlation with x-axis diffusivity along the perivascular spaces and a negative correlation with y-axis diffusivity along the association fibers, while no statistically significant correlation with z-axis diffusivity in the head-to-feet direction. No statistically significant correlation existed between the MMSE score and the diffusivity of the three directions in the subcortical area. When evaluating the ALPS index, a positive correlation was detected between the MMSE score and the ALPS index in the b = 1000 s/mm^2 datasets. The lower diffusivity along perivascular spaces on DTI-APLS represented impairment of the glymphatics, thus assessing glymphatics function.

The advantages of the human glymphatic MRI DTI technique can be summarized as follows: (1) Contrast medium can be omitted to perform a non-invasive examination. (2) The safety of the technique in human research has been widely confirmed. The downside of the human glymphatic MRI DTI technique is that the technique can only reveal transient glymphatic system function during scanning.

2.3 Intravenous administration of macrocyclic GBCAs

On October 2017 Absinta et al. [35] proposed the existence of meningeal lymphatics in humans and common marmosets, accompanied by the feasibility of non-invasively mapping *in vivo* and imaging with clinical MRI. On T1-weighted black-blood imaging and T2-fluid-attenuated inversion recovery (FLAIR), lymphatic vessels coursing alongside dual venous sinuses were enhanced by gadobutrol, which has a high propensity to extravasate across a permeable capillary endothelial barrier, but not with gadofosveset, a blood-pool contrast medium. Immunohistochemically, meningeal lymphatic vessels exhibit a typical panel of lymphatic endothelial markers in common marmosets.

On November 2018, Naganawa et al. [36] conducted an evaluation on GBCA leakage from cortical veins of patients with delayed imaging and intravenous GBCA (IV-GBCA). Six patients, 37-58 years of age, with suspected endolymphatic hydrops (EH) were assessed. The patients accepted a single dose of IV-GBCA in the first part of the study. Three-dimensional real inversion recovery images were obtained before administration of the contrast agent, as well as 5 min and 4 h after IV-GBCA. If contrast enhancement around cortical veins was observed 5 min after IV-GBCA with further spread into the CSF 4 h after IV-GBCA, leakage from cortical veins to the CSF was graded as positive. Twenty-one patients, 17-69 years of age, with suspected EH were evaluated in the second part of the study. Only the images 4 h after IV-GBCA were obtained. The slices with positive GBCA leakage from the veins were counted, and the correlation between the number of slices with gender, age, and degree of EH were assessed according to Spearman's rank correlation coefficient. In the first part of the study the GBCA leakage from cortical veins was shown to be positive in all patients. In the second part of the study GBCA leakage was observed in patients > 37 years of age, but not in patients < 37 years. The number of slices significantly correlated only with age, but not the degree of EH or gender.

On November 2018 Ohashi et al. [37] utilized magnetic resonance cisternography (MRC) and heavily T2-weighted three-dimensional fluid attenuated inversion recovery (hT2W-3D-FLAIR) imaging in 25 patients with suspected EH 4 h after IV administration of a single dose of a GBCA. CSF space segmentation in the ambient cistern, the perivascular space (PVS) in the basal ganglia, the CSF surrounding the vein of Labbe, and the CSF surrounding the superficial middle cerebral vein was carried out on MRC. The former two segments were then co-registered onto the hT2W-3D-FLAIR and the signal intensities were measured. The signal intensity ratio of post-contrast hT2W-3D-FLAIR to pre-contrast hT2W-3D-FLAIR was calculated. Ohashi et al. [37] found a significantly stronger enhancement of the CSF space around the vein of Labbe determined on hT2W-3D-FLAIR 4 h after IV-GBCA compared to the other CSF spaces and the PVS, and concluded that the vein of Labbe might play a role in GBCA leakage into the CSF.

In April 2019 Deike-Hofmann et al. [38] demonstrated that the glymphatic system could be visualized *in vivo* by observing the GBCA pathway into and through heavily T2-weighted FLAIR (hT2W-FLAIR) MRI obtained after IV-GBCA. hT2W-FLAIR was acquired in 33 neurologically-normal control subjects and 7 patients with an impaired blood-brain barrier resulting from cerebral metastases before, and 3 and 24 h after IV-GBCA. The signal intensity was determined in various kinds of cerebral fluid spaces. In addition, white matter hyperintensities were quantified using the Fazekas scoring system. The delayed hT2W-FLAIR showed that GBCAs entered the CNS through the ciliary body and choroid plexus with drainage along perivascular spaces of penetrating cortical arteries and perineural sheaths of cranial nerves. Furthermore, a statistically significantly positive correlation was demonstrated by a Fazekas score with signal intensity elevation in the perivascular spaces 3 h after IV-GBCA. The correlation between glymphatic system functioning and deep white matter hyperintensities, an imaging sign of vascular dementia, illustrated the feasibility of exploiting the GBCA pathway through the glymphatic system for diagnostic purposes.

Sleep is acknowledged to promote glymphatic activity [3, 9, 39, 40]. In September 2021 Lee et al. [41] examined the feasibility of applying multiple intravenous enhanced T1-mapping in the quantitative evaluation of glymphatic clearance in different brain regions, demonstrating the effect of sleep on glymphatic clearance in humans. Lee et al. [41] confirmed greater clearance of contrast agents after sleep, as well as a connection between sleep and glymphatic activity.

In 2020 Mijnders et al. [42] evaluated the most promising MRI sequence for glymphatic MRI 4-24 h after administration of a GBCA, thus identifying long TE 3D-FLAIR as the most promising MRI sequence for detecting low-dose GBCAs in the glymphatic system.

An advantage of the human glymphatic MRI IV-GBCA technique is the higher safety compared to an intrathecal injection. The disadvantages of the human glymphatic MRI IV- GBCA technique are as follows: (1) The technique is invasive. (2) Multiple scans are required at regular intervals. (3) The distribution of tracers in the brain will be affected by the blood-brain barrier and the blood circulation.

3. PROSPECTS OF MRI FOR HUMAN GLYMPHATIC SYSTEM RESEARCH

3.1 Chemical exchange saturation transfer (CEST)

On June 2020 Chen et al. [43] reported visualization of the glymphatic system by CEST MRI. The MRI effect was measured *in vitro* at 7.0 Tesla using lymph, blood, and CSF from a pig. In the *in vitro* study the CEST effect of the lymph fluid was evident at 1.0 ppm and was distinguishable from CSF and blood. Unilateral deep cervical lymph nodes of 20 adult male rats were ligated, then CEST MRI was used to observe the CEST signal changes in rat brain followed by correlation analysis with behavior. The CEST signal intensity was significantly higher in the ipsilateral than the contralateral hippocampus, with a statistically significant correlation of the behavioral score with the signal abnormality. These results supported the notion that CEST MRI might serve as a tool for evaluation of the glymphatics *in vivo* and for prediction of glymphatic function impairment.

The advantages of the glymphatic CEST technique can be listed as follows: (1) Molecular information, such as protein, can be captured. (2) Metabolic function is determined.

3.2 Arterial spin labelling (ASL)

On April 2020 Evans et al. [44] proposed a technique for measuring blood-CSF barrier function non-invasively using a tracer-free MRI to quantify rates of water delivery from the arterial blood to the ventricular CSF. Evans et al. [44] reported a 36% decrease in blood-CSF barrier function in old mice compared to a 13% decrease in the parenchymal blood flow; however, this usage was preliminary and the analysis was confined to the CSF near the choroid plexus.

The advantages of ASL are as follows: (1) ASL is non-invasive. (2) ASL is closely related to AQP4. The disadvantages of ASL are as follows: (1) The calculation process and the establishment of the model are relatively tedious. (2) The evaluation can only be performed to assess glymphatic system inflow function.

At present, CEST and ASL techniques are only used in glymphatic studies involving mice; studies involving humans have not been conducted. It can be expected that in the near future, however, CEST and ASL technology studies will be conducted on the human glymphatic system.

The authors are of the opinion that DTI, CEST, ASL, and the intravenous administration or intrathecal administration of macrocyclic GBCAs as MR methods can be used in human glymphatic system research. DTI, CEST, and ASL do not require a contrast agent, which can illustrate transient glymphatic system function during scanning in a safe and non-invasive manner, as well as capture molecular information. The intravenous or intrathecal administration of macrocyclic GBCAs reflect the clearance performance of glymphatic system for a long time.

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CONFLICTS OF INTEREST

The authors have no potential conflicts of interest.

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