Neurofluid as assessed by Diffusion-weighted Imaging

Toshiaki Taoka

Department of Innovative Biomedical Visualization (iBMV), Department of Radiology,

Nagoya University Graduate School of Medicine

Corresponding author:
Toshiaki Taoka, MD. PhD.
Professor, Department of Innovative Biomedical Visualization (iBMV),
Nagoya University Graduate School of Medicine,
65 Tsurumai-cho, Showa-ku, Nagoya,
Aichi, 466-8550 Japan
Tel: +81-52-744-2328
Fax: +81-52-744-2335
e-mail: ttaoka@med.nagoya-u.ac.jp

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Synopsis.

The glymphatic system hypothesis is associated with the circulation of cerebrospinal fluid (CSF) in the skull and interstitial fluid (ISF) in the brain. There are several imaging techniques to visualize the dynamics of CSF and ISF. Magnetic resonance imaging (MRI) is one of the promising modalities for glymphatic imaging and diffusion MRI is expected imaging tool. Several disorders are associated with glymphatic dysfunction or impairment in the dynamics of CSF or ISF. The Central Nervous System interstitial fluidopathy concept has been proposed to encompass diseases with pathologies that are predominantly associated with abnormal ISF/CSF dynamics.

Key words: interstitial fluid dynamics, magnetic resonance image, diffusion image, glymphatic system

Key Points

1. The glymphatic system facilitates clearance of neurofluids clearance and waste removal via glia-supported perivascular channels.

2. SeveralThere are many attempts have been made to visualize the glymphatic function by magnetic resonance imagingMRI including the diffusion technique.

3. “Central Nervous System (CNS) interstitial fluidopathy” is a new concept proposed to encompass diseases withwhose pathologies that are predominantlymajorly associated with abnormal neurofluidneurofluids dynamics.

1. Introduction

1-1 Glymphatic system hypothesis

The glymphatic system hypothesis is associated with the circulation of cerebrospinal fluid (CSF) in the skull and interstitial fluid (ISF) in the brain. This term was coined based on combination of the words glia and lymphatic system. The concept has garnered attention in several fields since its proposition by Iliff et al. in 2012 (1), following which several reports have been published. This hypothesis does not represent discovery of a previously unknown anatomical structure. Instead, it appears to be based on observation of an already known structure from the perspective of waste product clearance from the brain. The hypothesis is outlined as follows. The perivascular space functions as a conduit that drains CSF into the brain parenchyma. The driving force of this system is arterial pulsation. CSF guided to the perivascular space around the arteries enters the interstitium of brain tissue via water channels controlled by aquaporin 4 (AQP4), which are distributed in the foot processes of astrocytes that constitute the outer wall of the perivascular space. CSF that enters the interstitium washes waste proteins in tissues. Following clearance of the intercellular spaces in this manner, the CSF flows into the perivascular space around the veins and is drained from the brain (Figure 1a).

The glymphatic system theory has attracted attention due to its association with sleep, among other reasons. Drainage by the glymphatic system is suppressed during awakening and markedly increases during sleep. This is because the volume of the glial cells decreases during sleep and the interstitial space expands more than during awakening, facilitating mass transport of tissues (2). Studies have shown that a similar effect can be obtained by anesthesia. A study reported that the volume ratio of interstitial space of tissues is 13-15% when a person is awake, as opposed to 22-24% when sleeping (3). Furthermore, a continuous scanning 3D electron microscope study reported that the axon-spine interface was reduced during sleep and the interstitial space was relatively enlarged at most synapses in the motor and sensory cortices of mice (4).

1-2 Neurofluids concept

In 2018, the International Society for Magnetic Resonance in Medicine used the term “Neurofluids” as the title of a session on the glymphatic system. The term was first used by Professor E. F. Toro, an Italian applied mathematician (University of Trento), as the project title of a series of studies simulating the entire fluid dynamics of the central nervous system (CNS) using a mathematical model.

The model was used to apply for a grant supported by the European Research Council. Neurofluids is the collective term for the fluids in which the CNS is immersed, which includes blood, CSF, and ISF. This term helps to understand the dynamics of the aforementioned fluids (Figure 1b). In this review, we aimed to introduce the glymphatic system hypothesis and its association with neurofluid dynamics, as well as with sleep and disease.

2 Neurofluid dynamics

2-1 Classical understanding of CSF dynamics

The concept established by Cushing and Weed in the early 20th century regarding the production, circulation, and absorption of CSF was supported by several studies (5-7). Accordingly, CSF was thought to be produced by the choroid plexus in the ventricle and to flow out of the ventricular system from the foramens of Luschka and Magendie. CSF was then thought to flow up into the subarachnoid space on the surface of the brain and be absorbed by the arachnoid granules distributed in the parasagittal area. However, this concept has been questioned since the end of the 20th century, and various studies have disproved it.

2-2 Modern understanding of neurofluid dynamics: Production of CSF/ISF

In the classical concept, CSF was suggested to be produced mainly by the choroid plexus in the ventricles; however, this assumption has been challenged in recent years. The currently accepted idea is that production of CSF is mainly due to hydrostatic pressure exerted by capillaries in the brain. It is known that 70%-90% of water molecules in the arteries are transferred to the brain parenchyma in one passage (8, 9). Oreskovic et al. stated that both production and absorption of CSF occur in capillaries (Oreskovic and Klarica hypothesis) (10). According to their hypothesis, the difference in hydrostatic pressure causes movement of water from the capillaries to tissues producing ISF. Conversely, there is a bidirectional movement of water molecules, wherein ISF is absorbed by capillaries due to the difference in osmotic pressure. Part of the ISF passes through the surface of the brain and the perivascular space to fill the ventricles and subarachnoid space as CSF. In contrast, there is a bidirectional movement of water, wherein a part of the CSF is indirectly discharged into the capillaries. Cerebral ISF, together with CSF, is considered a source of CSF to the ventricles (10, 11). In addition to the production of ISF/CSF from capillaries of the brain parenchyma, migration of water also occurs from the ependymal tissue of the ventricle, pia matter of the brain surface, and perivascular space (12).

2-3 Modern understanding of neurofluid dynamics: Absorption of CSF/IS

Multiple pathways have been identified pertaining to the absorption of CSF in addition to the classical pathway via the arachnoid granules. Absorption in the brain parenchyma, spinal arachnoid granules, dural lymphatic system, nasal cavity, and other lymphatic systems are the other known absorption routes of CSF. It is considered that multiple pathways function in parallel in a complementary or compensatory manner. The drainage of CSF is broadly divided into the venous and lymphatic systems. In the venous system, as the passage of water is bidirectional in the wall of the ventricle and pia matter, which results in a rapid transfer of ISF and CSF, it is believed that an indirect drainage route exists through the ISF and the capillary wall (11). In addition, CSF drains into the venous system via the classical arachnoid granule pathway. The arachnoid granules are covered with an endothelial structure and project into the sinus, and are believed to drain CSF into the venous system. Arachnoid granules are present in the intracranial sinuses as well as in the spinal epidural venous plexus, which is also associated with drainage of CSF (13).

3 Imaging evaluation of neurofluid dynamics in humans using tracers

3-1. Intrathecal gadolinium-based contrast media

Evaluations using intrathecally injected gadolinium-based contrast media (GBCA) as tracers have been reported in humans. For example, a study reported accidental intrathecal injection of relatively high doses of GBCA in a clinical setting (14). Other studies have reported systematic injection of small doses of GBCA into the intrathecal space for diagnostic purposes (15, 16). All reports have shown that gadolinium penetrates from the surface to the cortex and further into deep tissues of the brain in humans. These findings confirm that CSF flows from the surface of the brain into the parenchyma in humans, as stated by the glymphatic system hypothesis, and suggest that GBCA could be used to evaluate the activity of the system. A study reported intrathecal injection of GBCA to evaluate decreased activity of the glymphatic system in normal pressure hydrocephalus (17). However, intrathecal injection of GBCA is not approved, making its clinical application practically impossible. Evaluation using radio-isotope cisternography may be a possible technique to observe tracers that are injected intrathecally over time. However, presently, there are no systematic reports on the glymphatic system.

3-2. Intravenous GBCA

Intravenous injection of gadolinium has also been reported to evaluate the glymphatic system. A study assessed the permeation of intravenously injected gadolinium into normal brain tissue using permeability imaging to evaluate the brain parenchyma. This study reported that the transfer coefficient of the blood-brain barrier was elevated in patients with Alzheimer's disease (18). Furthermore, transfer of intravenously injected gadolinium into the CSF has also been confirmed in humans. It has been reported that intravenously administered gadolinium-based contrast agents leak into the CSF even in healthy subjects (19). Transfer of the contrast agent into the CSF and the perivascular space at the base of the brain could be observed at approximately 4 hours after intravenous injection of gadolinium on heavily T2-weighted fluid-attenuated inversion recovery images (20, 21). Another study reported an interesting aspect that intravenously administrated gadolinium-based contrast agents demonstrated leakage from the cortical veins with delayed imaging after injection, and the leakiness of the cortical veins significantly correlated with age (21).

4 Evaluation of neurofluid dynamics on diffusion images

4-1 Diffusion tensor image analysis along the perivascular space (DTI-ALPS)

Attempts have been made to evaluate the activity of the glymphatic system on diffusion images. In tracer studies, the behaviors of tracers after injection are assessed using integral evaluation. Meanwhile, assessment of diffusion images uses differential evaluation because the behavior of water molecules in the tissue at the time of imaging is evaluated. The latter may enable evaluation of the activity of the glymphatic system at any given point in time. While hypothesizing that diffusivity limited to the running direction of the perivascular space correlates with the activity of the glymphatic system. An evaluation technique called diffusion tensor image analysis along the perivascular space (DTI-ALPS) has been proposed. In this technique, the behavior of water molecules in the deep white matter is evaluated using diffusion tensor images (22). During evaluation of the diffusivity of water molecules in the brain, the effects of diffusion along large white matter fibers are substantial; therefore, evaluation of diffusion along the perivascular space is difficult. However, if the large white matter fibers and perivascular space intersect at a right angle, the effects of the former should be separable. In the human brain, the medullary arteries and veins intersect with the ventricular wall at a right angle in the white matter, on the outer side of the body of the lateral ventricle. In the DTI-ALPS technique, the diffusivity along the perivascular space in the white matter, on the outer side of the body of the lateral ventricle,

is evaluated as a ratio of the diffusivity along the perivascular space to that perpendicular to the running direction of the main white matter fibers (ALPS index). Evaluations performed in healthy volunteers, patients with mild cognitive decline, and patients with Alzheimer's disease showed that the ALPS index significantly inversely correlated with the Mini-Mental State Examination score and significantly correlated with age (Figure 2). As several animal experiments have demonstrated impaired ISF dynamics in Alzheimer's disease (1, 23, 24), the aforementioned result suggests that the ALPS index might be an indicator of the function of the glymphatic system.

4-2 Advanced diffusion methods

Several studies, including animal experiments and human studies, have evaluated the glymphatic system by diffusion imaging. TGN-020 is a compound that blocks AQP4 channels in vivo in the mouse brain (25). An animal study used TGN-020 for diffusion imaging (26). This study determined the shifted ADC (sADC) and S-index, which are diffusion markers of tissue microstructure. The sADC and S-index are derived from diffusion MR signals acquired at two key b values (low and high) indicating the degree of diffusion hindrance to discriminate malignant from benign tissue (27). Following inhibition of the AQP4 channel with a TGN-020 solution, a decrease in the S-index and increase in sADC were readily observed in the cortex, more in the hippocampus, but not in the striatum, reflecting local differences in astrocyte and vascular density. The decrease and increase in the S-index and sADC, respectively, jointly indicated a decrease in the degree of hindrance to water diffusion in astrocyte rich areas (cortex and hippocampus) under acute AQP4 channel inhibition induced by TGN-020 (26).

A human study utilized multi-shell diffusion tensor imaging (b-values= 0, 50, 300, and 1000 s/mm2) to measure slow and fast components of the apparent diffusion coefficient of water in the brain. The findings of the study revealed both increase in slow ADC as well as decrease in fast ADC in relation to sleep, which reflected the distinct biological significance of fast- and slow-ADC values and sleep-induced changes on the volume of CSF (28). One study utilized the intravoxel incoherent motion method to investigate the intermediate diffusion component by the non-negative least-squares method to evaluate functions of the glymphatic system. The values of both the parenchymal diffusivity and microvascular perfusion could be detected and the perivascular fluid motion in relation to the glymphatic system could be evaluated by this method (29).

4-3 CSF dynamics on diffusion MRI

Diffusion-weighted imaging (DWI) enables visualization of the motion of water molecules as a decrease in signal due to phase shift created by the motion. When the phase shift becomes larger than $\pm\pi$ or when various velocities exist in a single voxel, signal decrease on the diffusion-weighted image becomes prominent depending on the b-values (motion related signal dephasing: Figure 1). CSF has been reported to cause prominent decrease in the signal due to its substantial and/or non-uniform motion (30). A study reported that a diffusion-weighted image of b=500 s/mm2 reflected changes in the dynamics of CSF (31). The study reported that CSF within the lateral ventricle at b=500 s/mm2 on DWI showed higher signal in the ventricle dilatation group compared to the control group. However, a single b-value such as b=500 s/mm2 cannot detailed distribution of the CSF dynamics. DWI based on different b-values would enable visualization of the degree of CSF motion. As explained previously, DWI with lower b-value will demonstrate signal dephasing only in areas with substantial CSF motion. In contrast, DWI with higher b-value will show signal dephasing of the CSF in a wide area with minimal to substantial CSF motion. The multi b-value diffusion-weighted image diphase map indicated that the motion of the CSF was prominent in areas such as the ventral portion of the posterior fossa, suprasellar cistern, and Sylvian fissure. However, the motion was limited in the lateral ventricles and parietal subarachnoid space, thereby creating uncertainty regarding the classical model of CSF dynamics. A study also indicated that the motion of the CSF correlated with age in the third ventricle and interhemispheric fissure (32). (Figure 3)

5. Disorders in the dynamics of neurofluids: CNS interstitial fluidopathy

The glymphatic system hypothesis has provided new insights into the physiology and pathophysiology of the CNS, including the concept of neurofluids. An increasing number of studies are reporting on the dynamics of ISF and CSF within the brain. Many diseases are known to develop due to abnormality of the glymphatic system. As previously explained, several reports have reported impaired dynamics of the ISF in Alzheimer's disease (1, 23, 24). Moreover, glymphatic influx of the CSF tracer was reduced in a Parkinson's disease mouse model, causing severe accumulation of α-synuclein, glial activation, inflammation, dopaminergic neuronal loss, and motor deficits (33). An experimental model of moderate to severe trauma demonstrated that migration of the tracer injected into the perivascular cortex of mice after injury was significantly reduced compared to the region ipsilateral to the trauma,

suggesting reduced activity of the glymphatic system (34). Another study reported severe impairment of the glymphatic system after SAH and in the acute phase of ischemic stroke (35). Arteriolosclerosis is the most common small vessel alteration in aged brains. An animal experiment, wherein MRI was performed following intrathecal administration of GBCA on spontaneously hypertensive rats reported that ventricular reflux of the agent was observed only in the hypertensive rats, indicating abnormal ISF dynamics (36). Glaucoma has also been hypothesized to occur due to alterations in fluid dynamics in the intraocular and intracranial spaces. These alterations might result in impaired entry of the CSF into the subarachnoid and perivascular spaces of the optic nerve, thereby inhibiting glymphatic clearance of waste products from the retrobulbar or retrolaminar portion of the optic nerve (37). Meniere's disease is a complex, heterogeneous disorder associated with many underlying factors including endolymphatic hydrops. The disorder occurs due to excessive accumulation of endolymph in the inner ear, which damages the ganglion cells. Endolymphatic hydrops share the characteristics of dysfunction of ISF dynamics in the inner ear (38, 39). Several reports have indicated altered dynamics of the ISF of the CNS in idiopathic normal pressure hydrocephalus (17). One study employed the DTI-ALPS method and evaluated the aforementioned diffusivity limited to the direction of the perivascular space (40).

Table presents the list of the disorders that are reported to demonstrate altered glymphatic function or neurofluid dynamics. The listed disorders including Alzheimer's disease, traumatic brain injury, stroke, and other disorders share the characteristics of glymphatic system dysfunction or other mechanisms related to dynamics of the ISF. In this context, CNS interstitial fluidopathy has been proposed as a new concept encompassing diseases with pathologies that are predominantly associated with abnormal dynamics of the ISF or CSF (41).

6 Conclusion

Currently, the glymphatic system hypothesis is not established, and there are several reports to point out the problem of the hypothesis (42, 43). However, no study has opposed that CSF and ISF play important roles in the maintenance of brain function and homeostasis. Therefore, visualizing the dynamics of neurofluids using various methods, including diffusion MR technique, will provide significant information on the maintenance of healthy brain function in humans.

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Table

List of the disease or disorders categorized as "CNS interstitial fluidopathy"

Alzheimer's disease (1, 23, 24)
Parkinson's disease (33)
Traumatic brain injury (34)
Stroke
Subarachnoid hemorrhage (35)
Ischemic stroke (35)
Small vessel diseases of CNS
Arteriolosclerosis (36)
Cerebral amyloid angiopathy (44)
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (45)
COL4A1 mutation related disorders (46)
Glaucoma (37)
Meniere's disease (47)
Idiopathic normal pressure hydrocephalus (17)
Mucopolysaccharidoses (48)

Figure 1: Outline of the glymphatic system and concept of neurofluids in the brain.

Figure 1A illustrates that perivascular clearance comprises perivascular drainage and glymphatic pathways. Cerebrospinal fluid (CSF) flows into the brain parenchyma via the periarterial space and enters the interstitial space of the brain tissue via aquaporin 4 (AQP4)-controlled water channels, which are distributed in the end feet of astrocytes that constitute the outer wall of the perivascular space. CSF entering the interstitial space removes waste proteins in the tissue. Following this, CSF flows into the perivenous space and is discharged outside the brain.

Figure 1B illustrates the concept of neurofluids. Interstitial space or CSF space of the brain tissue is considered a common space, which not only acts as a supportive structure, but also functions as a space for mass transportation, immune function, or inter-cellular signal transmission. This space is filled with "neurofluids," a term that is used to indicate all fluids that fill the central nervous system, including CSF, interstitial fluid, and blood. Exchanges occur among the compartments of neurofluids.

Adapted from Taoka et al. J Magn Reson Imaging 2020;51:11-24

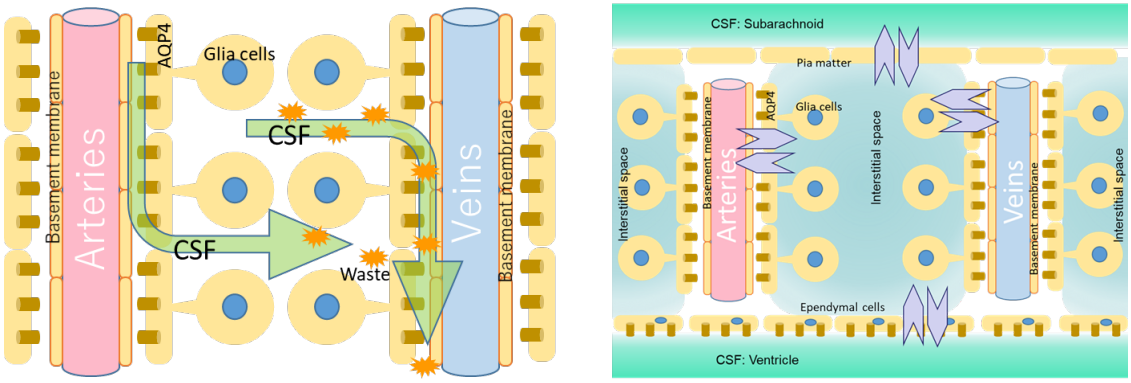

Figure 2: Concept for the diffusion tensor image analysis along the perivascular space (DTI-ALPS) method and its result for Alzheimer's disease cases

a: Superimposed color display of DTI on SWI indicating the distribution of projection fibers (z-axis: blue), association fibers (y-axis: green), and the subcortical fibers (x-axis: red). Three ROIs are placed in the area with projection fibers (projection area), association fibers (association area), and subcortical fibers (subcortical area) to measure diffusivities of the three directions (x, y, z).

b: Schematic indicating the relationship between the direction of the perivascular space (gray cylinders) and directions of the fibers. Note that the direction of the perivascular space is perpendicular to both the projection and association fibers.

c-e: Correlation between directional diffusivity and Mini-Mental State Examination (MMSE) scores.

Correlation between MMSE and diffusivities of the three directions of the three areas (projection: c, association: d, subcortical: e). Diffusivity of the x-axis is plotted as red, y-axis as green, and z-axis as blue. In the projection area (e), a significant positive correlation was found between the diffusivity along the perivascular space (x-axis) and the MMSE scores. Similarly, in the association area (d), a significant positive correlation was found between the diffusivity along the perivascular space (x-axis) and the MMSE scores.

f: Correlation between ALPS index and MMSE

Correlations between MMSE and ALPS index are shown, which was assessed based on the following ratio:

ALPS index = mean (Dxproj, Dxassoc)/mean (Dyproj, Dzassoc)

There was a significant positive correlation (r = 0.46, p = 0.0084) between the ALPS index and the MMSE scores

Adapted from Taoka et al. Jpn J Radiol 2017;35:172-178, with permission.

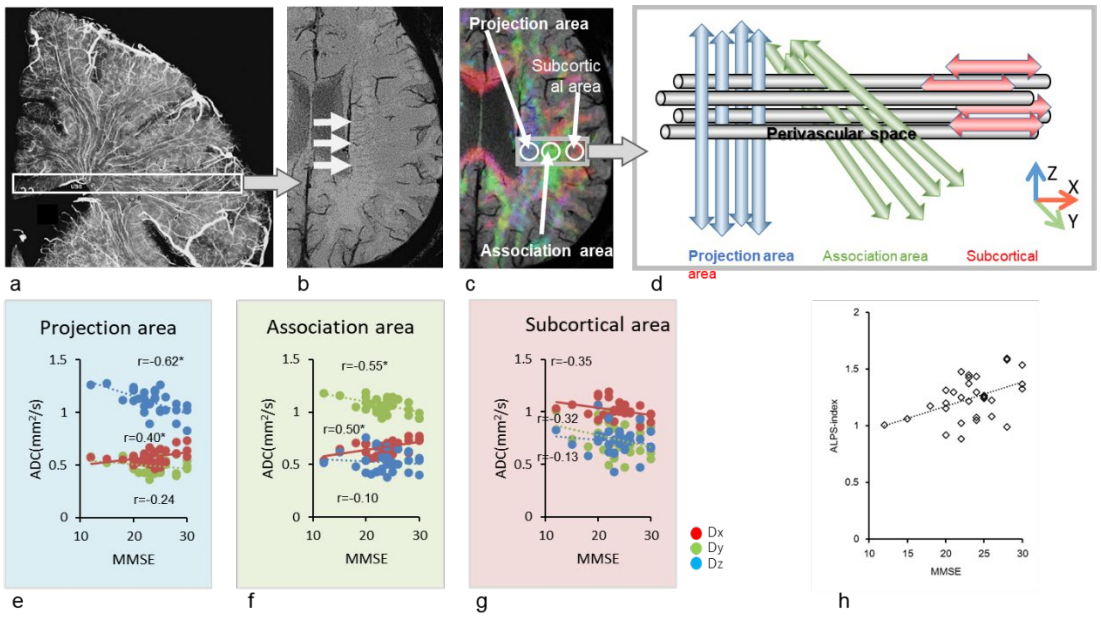

Figure 3. Multi b-value diffusion weighted image diphase map (MbDDM)

Color composite images with different b-values in the areas of signal drop due to motion-related signal dephasing

Orange: b=50 s/mm2, Yellow: b=100 s/mm2, Light green: b=200 s/mm2, Green: b=300 s/mm2, Blue: b=500 s/mm2, Indigo: b=700 s/mm2, Purple: b=1000 s/mm2

Note that the signal drops occurred in instances of lower b-value in the ventral portion of the posterior fossa, suprasellar cistern, and Sylvian fissure indicating substantial motion of the CSF. In contrast, a signal drop in the lateral ventricle and the subarachnoid space of the parietal region occurred only with a higher b-value indicating limited motion of the CSF.