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A Brief Review of the Glymphatic System - Introduction & Clinical Implications

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Relevant Anatomy & Physiology: The cerebrospinal fluid (CSF) circulation is widely regarded as a major sink for the clearance of interstitial fluid (ISF) and its solutes from the brain. As CSF is reabsorbed across arachnoid granulations, along cranial and spinal nerve sheaths, or along the brain microvasculature, solutes are cleared from the cranial cavity (1–5). In a recent study we reported that a large proportion of sub-arachnoid cerebrospinal fluid (CSF) recirculates through the brain parenchyma along perivascular spaces, exchanging with brain interstitial fluid (ISF) before being cleared via peri-venous pathways (6,7). The continuous circulation of CSF along this pathway facilitates the clearance of extracellular solutes, including soluble Aβ, from the brain. We termed this brain-wide pathway the 'glymphatic system', based upon the critical role that astroglial water transport through the astrocytic aquaporin-4 water channel plays in facilitating CSF-ISF exchange and solute clearance (7).

The researchers propose that the glymphatic system could be the first step of the brain drainage system, in which ISF is drained into the CSF, and as a second step ISF could then enter the newly identified lymphatic vessels in the dura. In mice, a tracer study has already demonstrated that these lymphatic vessels are the major outflow pathway of drainage from the brain (8). Another possibility is that CSF containing waste products circulates in the arachnoid space and flows through the arachnoid villi to the dural venous sinuses, thereby entering the blood circulation (9,10). Either through the lymphatic or blood circulation, eventually solutes reach the liver where they are degraded.

CNS, however, is the only organ of the body that lacks anatomically defined lymphoid tissues (11), and as a result, has developed unique adaptations for achieving fluid balance and interstitial waste removal. In addition to its traditionally identified role providing buoyancy to the brain and thus protecting it from the rigid surrounding skull, the CSF has also been suggested to function as a pseudo-lymphatic system, acting as a sink for brain interstitial solute, particularly high molecular weight substances such as proteins (12, 13). Consequently, this review will focus on the efforts that have been made to identify the anatomical pathways and physiologic regulation governing the interaction between the CSF and ISF, the role of CSF-ISF exchange in neurophysiology and the promotion of extracellular homeostasis, and how the breakdown of this exchange may result from and contribute to diseases of the CNS, as well as have implications for the diagnosis and treatment of these diseases.

Clinical Implications: Impaired glymphatic transport with accumulation of cellular waste products such as amyloid-b and tau aggregation has been proposed as instrumental in conditions such as normal ageing (14), brain trauma (15) and Alzheimer's disease (7). Glymphatic transport of solutes is highly dependent on sleep (16) and body posture (17).

Imaging findings: In the recent study by Ringstad et al. (18), MR contrast in CSF was observed to penetrate along arteries as well as into brain parenchyma; however, the superior sagittal venous sinus was not enhancing at any time point, suggesting that dural sinuses (and arachnoid villi) are not major drainage pathways for interstitial solute waste, or that the rate of drainage in to the venous sinuses was too slow to show up as an increase in the blood signal. A recent study addressed clearance of the MR contrast agent from human entorhinal cortex. MR contrast enhancement peaked at 6–9 h and disappeared from the entorhinal cortex of normal subjects at 24 h and was slower in iNPH patients (19). However, this study did not quantify clearance rates, and specific anatomical drainage pathways were not identified. Thus, there appears to be no direct documentation in human brain of waste clearance in relation to large central veins as described in rodent brain (7). On the contrary, based on data from patients with sporadic cerebral amyloid angiopathy where Aβ is observed to accumulate in the wall of cortical cerebral arteries and arterioles as well as in leptomeningeal arteries (20,21,22), it has been suggested that waste clearance in human brain does not follow a glymphatic transport pattern (22,23) as originally described (7).

Currently, only a few clinical research studies support the existence of a sleep-dependent CSF-ISF metabolic waste removal system in the human brain, including (1) evidence of circadian variation in the CSF concentration of Aβ and tau (24); (2) evidence that chronic sleep deprivation increases CSF Aβ (25); (3) evidence that among older adults, shorter sleep duration and poorer sleep quality are associated with greater Aβ

burden (26); and (4) neuroimaging studies find that the human brain is slightly larger in the morning compared with the evening hours (27). A major step toward understanding the implication of AQP4 for AD pathology was recently shown in post-mortem human brain where significant loss of peri-vascular expression of AQP4 was demonstrated in AD human brain tissue in comparison with normal aging brain (28).

As of now there are no diagnostic tests to measure the function of the glymphatic system in the human brain. Glymphatic pathway function is mediated by astrocytic AQP4 water channels, while genetic deletion of the Aqp4 gene in mice dramatically slows paravascular CSF–ISF exchange and impairs the clearance of intra-striate interstitial solutes such as amyloid. These findings were confirmed in a new set of experiments where the interaction between Aqp4 gene deletion and TBI on interstitial solute clearance was evaluated. In agreement with our prior study, among sham-treated animals Aqp4 gene deletion significantly reduced the amount of both intracortically injected 3 H-mannitol and 14 C-inulin cleared within the first hour post injection. When Aqp4 ?/? mice were subjected to TBI, 7 d after injury the impairment of interstitial solute clearance was dramatically exacerbated compared with the effect observed for TBI alone, two-way ANOVA with Tukey's post hoc test for multiple comparisons. Because Aqp4 ?/? mice subjected to TBI exhibited a profound impairment in glymphatic pathway function, we next used this approach to evaluate whether impairment of glymphatic pathway function contributes to aberrant accumulation of phosphorylated tau after TBI. There are radiological scintigraphy procedures that can measure the transport of radiotracers in the CSF of humans these are used to diagnose CSF leaks, normal pressure hydrocephalus, or intraventricular shunt malfunction. Analyses of CSF through lumbar punctures is being proposed as a biomarker for monitoring reduced clearance of beta amyloid in patients with early AD that is interpreted to reflect reduce clearance rates (29).

The glymphatic system starts with CSF flowing through the peri-vascular space. Future attempts to measure activity in the glymphatic system could focus on imaging the CSF flow within the perivascular space. Recently, Naganawa et al. detected contrast agent in the human brain with an imaging technique (heavily T 2 -weighted FLAIR) that is highly sensitive to low gadolinium concentrations in the CSF. With this technique, researchers were for the first time able to detect signal enhancement in the perivascular space of the human brain, several hours after gadolinium administration (30). The perivascular space is an entrance point to the glymphatic system (31). This new imaging technique to visualize gadolinium in the CSF and perivascular space offers a new way to image the clearance pathway through the glymphatic system in humans (30). The same research group also introduced a method to measure water diffusivity along the perivascular space in the human brain, called 'diffusion tensor image analysis along the perivascular space' (DTI-ALPS) (32). Lower diffusivity along the perivascular space indicates less activity in the glymphatic system and thus less CSF influx and glymphatic dysfunction. DTI-ALPS in 16 AD, nine mild cognitive impairment and six subjective cognitive impairment patients demonstrated a positive correlation between water diffusivity along the perivascular space and Mini-Mental State Examination (MMSE) score.

With lower MMSE score and thus more cognitive decline, less activity in the glymphatic system was found. Imaging brain fluid dynamics may help in understanding the pathogenesis of glymphatic dysfunction and early detection of neurodegeneration.

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