This scientific commentary refers to ‘Impaired glymphatic function in idiopathic intracranial hypertension’, by Eide et al. (https://doi.org/10.1093/braincomms/fcab043).

Beginning in 2015, 3 years following its initial characterization in rodents,1–3 Eide, Ringstad and colleagues4,5 have published a series of seminal studies defining the function and dysfunction of the ‘glymphatic’ system in the human brain and in the setting of human neurological disease. Utilizing repeated MRI following intrathecal injection of the gadolinium-based contrast agent (GBCA) gadobutrol, this group has demonstrated that the same manner of perivascular CSF influx and interstitial solute efflux that characterizes the glymphatic exchange observed in rodents also occurs in the human brain. In the present study in Brain Communications,6 Eide and colleagues compare GBCA influx into and efflux from the ventricular CSF and brain tissue of patients with idiopathic intracranial hypertension (IIH) and a matched group of reference subjects. Observing abnormal CSF tracer reflux into the ventricular system and slowed GBCA clearance from various brain regions, the authors demonstrate for the first time that impaired glymphatic function is present in the setting of clinical IIH. While this finding is in itself novel, the study provides a clear view into the present-day glymphatic research field, illuminating arising obstacles and opportunities in defining the role that this biology and its dysfunction plays in human neurological disease.

**A role for glymphatic dysfunction in idiopathic intracranial hypertension**

The recently defined glymphatic system is a network of perivascular pathways that facilitates the exchange of CSF through the brain interstitium that is dependent on the perivascular astroglial water channel aquaporin-4 (Fig. 1A).1,2 Importantly, glymphatic function is most rapid during sleep compared to waking, but reduced with age, following ischaemic or traumatic brain injury.3,7 The current understanding of glymphatic function is that CSF moves along perivascular spaces surrounding leptomeningeal vessels within cisternal CSF compartments, entering the brain along perivascular spaces surrounding penetrating arteries (Virchow-Robin spaces), and exchanging throughout the entire brain interstitial compartment. Interstitial solutes and wastes not able to directly efflux across the blood–brain barrier or undergo local cellular degradation are cleared along perivascular spaces and white matter tracks to cisternal compartments associated with dural sinuses, such as the quadrigeminal cistern, which houses the origin of the straight sinus. These solutes are then cleared through uptake into meningeal lymphatic vessels, or by CSF reabsorption via arachnoid villi, cranial or spinal nerve sheaths.7,7

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Glymphatic function is most directly assessed by introducing a tracer into the subarachnoid CSF compartment and measuring the kinetics of its movement into and clearance from brain tissue. Although in rodent models, this has commonly involved dynamic imaging of fluorescent CSF tracer by in vivo 2-photon microscopy, dynamic contrast-enhanced MRI following intrathecal GBCA injection has increasingly been used to define glymphatic CSF influx and interstitial solute efflux throughout the entire brain volume in rodents, and more recently in human subjects.

The present study builds upon this work, using serial MRI following intrathecal GBCA injection to characterize glymphatic function in the setting of clinical IIH. This condition presents clinically as a constellation of
symptoms associated with increased intracranial pressure (ICP) including headache, nausea, dizziness, papilledema and vision loss believed to result from disruption of physiological routes of CSF resorption. Measuring GBCA enhancement in CSF compartments and the brain parenchyma hours (0–7 h), days (1–2 days) and weeks (4 weeks) following GBCA injection, Eide and colleagues report two key findings. First, the authors report early GBCA enhancement of ventricular CSF compartments, suggesting the retrograde reflux of CSF from the cisternal through the ventricular CSF pathway. This retrograde movement of CSF in IIH is similar to that reported previously by the authors in the setting of idiopathic normal-pressure hydrocephalus (iNPH) and is consistent with a global derangement of CSF flow. Second, the authors note higher peak levels of parenchymal GBCA enhancement, with slowed clearance suggesting impaired interstitial solute clearance in the presence of IIH. These findings provide a clear demonstration of reduced lymphatic function in the setting of clinical IIH (Fig. 1B).

In a sub-analysis, Eide and colleagues report that among the subjects that underwent overnight ICP monitoring, those with increased ICP mean wave amplitude (MWA, 14 IIH patients) exhibited impaired lymphatic function compared to those with normal ICP MWA (8 reference patients). Yet these data cannot resolve whether this impairment of lymphatic exchange is the cause or consequence of altered ICP dynamics in IIH. It is possible that in IIH, reduced CSF resorption and the resulting intracranial hypertension disrupt the physiological cranial pressure gradients that support perivascular CSF influx and efflux. Alternatively, impairment of lymphatic function may itself contribute to changes in ICP dynamics. A third possibility is that changes in ICP dynamics and lymphatic exchange in IIH are not causally related to one another, but rather result from a common upstream trigger, such as obstruction of CSF resorption pathways. Future studies, including potentially those in experimental model systems, will be required to define the causal relationships between these features.

In rodent models, impairment of lymphatic function promotes the development of Alzheimer’s disease-associated amyloid β and tau pathology and accelerates cognitive decline. Glymphatic dysfunction has also been suggested to underlie the development of headache, including migraine. Yet whether the clinical symptoms associated with IIH, including cognitive impairment and headache, result from this observed slowing of lymphatic exchange remains an important question to address in future studies.

**Glymphatic dysfunction in neurological disease: beyond neurodegeneration**

Early studies into the biology of the lymphatic have focused its role in ‘waste clearance’, particularly the clearance of interstitial peptides and proteins including amyloid β and tau. As a result, translational studies involving lymphatic system dysfunction have most often centred on neurodegenerative conditions or neurovascular disorders such as ischaemic and traumatic injury that are risk factors of these age-related diseases. In these settings, age- or injury-associated slowing of lymphatic exchange is proposed to underlie the mis-aggregation of amyloid β, tau and α synuclein in proteinopathies such as Alzheimer’s disease, Parkinson’s disease and chronic traumatic encephalopathy.

It is important to note, however, that the same perivascular network and processes of fluid exchange that support waste clearance likely contribute to the distribution of growth factors and nutrients, the clearance of inflammatory molecules such as cytokines, and the dynamics of neuromodulators such as norepinephrine, serotonin, dopamine and acetylcholine released by volume neurotransmission within the CNS. Although little data yet links them to lymphatic dysfunction, it is possible that a range of neurological disorders, including neurodevelopmental, neuroinflammatory and neuropsychiatric conditions that are connected to these processes may feature alterations in perivascular lymphatic exchange or meningeal lymphatic drainage. Indeed, in one such example, Shen has reported that increased extra-axial CSF volumes, speculated to reflect impaired perivascular CSF exchange, prospectively predict diagnosis with autism spectrum disorder in paediatric populations.

The studies conducted by Eide, Ringstad and colleagues, which reflect the most extensive descriptions of lymphatic function and dysfunction in human subjects to date, have demonstrated a clear role for slowed perivascular exchange in iNPH and IIH, conditions associated with alterations in CSF flow and ICP dynamics. These studies will likely pave the way for the evaluation of lymphatic function in conditions beyond neurodegenerative diseases (Fig. 1C).

### The need for non-invasive measures of lymphatic pathway function

The current gold-standard approach to measuring lymphatic function is the assessment of contrast or tracer movement from the CSF compartment into and through brain tissue following intrathecal administration. While these approaches have been widely adopted in rodent studies of lymphatic function, the off-label use of GBCAs for intrathecal administration, clinical concern surrounding the potential consequences of long-term CNS retention of gadolinium and popular anxiety surrounding intrathecal injections have restricted these types of studies of lymphatic function to populations undergoing clinical workup for neurosurgical intervention, including iNPH and IIH, for which these approaches may be clinically justified.
Eide, Ringstad and colleagues have provided important data regarding the safety of intrathecal gadobutrol injection for the MRI-based assessment of glymphatic function in human subjects, validated approaches for the non-invasive assessment of the glymphatic system in human populations are clearly needed.

Several proposed non-invasive MRI-based approaches have been developed to capture distinct elements of glymphatic biology. These include, among others, an arterial spin-labeling-based approach to capture glial-vascular water exchange and the measurement of perivascular fluid movement by diffusion tensor imaging. While individually promising, none of these non-invasive techniques have yet been validated against gold-standard contrast-based imaging either in rodent models or in humans. Moreover, few have been tested across physiological interventions or pathological states known to alter perivascular glymphatic exchange. Once validated, imaging and fluid-based biomarkers that reflect glymphatic function may provide a critical view into this biology and its dysfunction that may impact understanding, prevention and treatment of a wide range of neurological conditions.

Conclusion

Since its initial characterization in 2012, the glymphatic system has garnered much interest and debate, particularly regarding the proposed role of its dysfunction in the development of neurodegenerative diseases. The series of studies conducted by Eide, Ringstad and colleagues extending these findings into human clinical populations has been pivotal in confirming the presence of glymphatic exchange in the human brain and in describing its impairment in the setting of clinical iNPH and IIH (present study). Although the initial studies of the glymphatic system focused on the relevance of this biology to neurodegenerative conditions (such as Alzheimer’s disease) and neurovascular injury (such as traumatic and ischaemic brain injury), these and other emerging studies suggest that impairment of glymphatic function may contribute to a wide range of neurological conditions, ranging from disorders of CSF circulation and intracranial pressure to CNS tumours, to headache, to neurodevelopmental conditions. The restriction to date of contrast-based studies of human glymphatic function primarily to neurosurgical settings highlights the importance of the development and validation of non-invasive measures of glymphatic function to evaluate the role of glymphatic impairment in larger clinical populations.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed.

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Competing interests

The authors report no competing interests.

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