The peri-olfactory pathway: An "e-scent-ial" route for cerebrospinal fluid clearance?

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The circulation of cerebrospinal fluid (CSF) plays a key role in maintaining the homeostasis of the central nervous system (CNS). Production of CSF occurs primarily at the choroid plexuses within the ventricles of the brain. The fluid and its solutes then flow within the subarachnoid spaces of the cranial and spinal compartments, where a tightly controlled exchange with the interstitial fluid of the CNS parenchyma occurs. Remarkably, the mechanisms of clearance for this important fluid are still incompletely understood. An intense debate about the main routes of CSF outflow that originated in the late 19th century has continued to the present day with some favouring a direct efflux through arachnoid villi to the dural venous sinuses or others proposing routes to lymphatic vessels located in proximity to exiting cranial nerves or within the dura mater layer of the meninges surrounding the CNS.[1]

Indeed, dozens of physiological studies in rodents and larger mammals have provided strong evidence for a lymphatic, rather than venous, outflow of CSF.[1,2] Much of this research has indicated the existence of an egress pathway to lymphatics along olfactory nerve bundles through the cribriform plate of the ethmoid bone. On the other hand, in vivo studies in humans have been much more challenging to carry out as these experiments typically require the introduction of an exogenous tracer, usually into the intrathecal space of the spine by lumbar puncture. In pioneering studies from Norway, Ringstad and Eide have performed a series of MRI investigations involving intrathecal administration of a gadolinium contrast agent that is often used in patients with suspected disturbances of CSF flow. In these studies, a significant signal enhancement from the contrast agent was found within the dura mater near the parasagittal sinus, near the basal skull foramina and within draining cervical lymph nodes.[3,4] However, these authors could not detect a significant enhancement of contrast agent within the nasal turbinates in their cohort of patients,[5] in opposition to an earlier clinical report using PET imaging.[6]

In the December 2022 issue of *eBiomedicine*, Zhou et al. have recruited an impressive cohort of 92 patients, with a majority suffering from peripheral neuropathies that would likely have limited effect on CSF circulation.[7] The patients were injected with gadodiamide contrast agent and were given MRI scans before injection and at 4.5, 15 and 39 h after injection. In an unbiased approach, the authors assessed three potential CSF outflow pathways simultaneously: to the parasagittal dura, through the cribriform plate to the nasal turbinates and along the perineural space of the optic nerve, as well as accumulation of the contrast agent at the draining deep cervical lymph nodes. Significant contrast enhancement was found at each of these evaluated areas providing clinical evidence for multiple active sites of CSF outflow to the lymphatic system. Taking advantage of the large range of subjects, the authors performed correlation analysis between measurements of efflux and patient age and assessments of quality of sleep and cognitive decline (which were both determined by telephone survey). Interestingly, significant negative correlations were found between increasing age and clearance function at the peri-olfactory nerve and parasagittal dura regions. The authors also determined that impairments in sleep quality and cognitive function were most closely associated with a reduced clearance of contrast agent to the nasal turbinate regions, indicating that the peri-olfactory nerve pathway may be of particular importance.

One limitation of the study is that the resolution of the MRI technique does not allow direct visualization of contrast agent drainage within lymphatic vessels at the three assessed regions, thus the authors are correct to describe these routes as "putative" clearance pathways at this point. In addition, small molecular weight contrast agents are not ideal for the assessment of CSF clearance as significant diffusion into the CNS parenchyma or extracranial interstitial tissue may occur. However, clinically-approved macromolecular contrast agents are lacking at this time. Finally, other potential efflux routes from the basal skull or spine[8,9] would need to be evaluated. This may require the development of whole-body scanning techniques, ideally with multiple timepoints in the hours immediately following injection.

These intriguing findings have provided more evidence for a concept of a decline in CSF turnover during physiological ageing,[2,10] which may play a role in the accumulation of toxic metabolites such as amyloid beta.

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More research would be necessary to determine at which stage a functional decline may occur in patients suffering from cognitive decline or if the frequent loss of olfactory function seen in early-stage Alzheimer's disease may be related to a reduction of CSF clearance along olfactory nerves.

Contributors

S.T.P. is the sole author.

Declaration of interests

The author has no conflicts of interest to disclose.

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