Cerebrospinal fluid (CSF) outflow tracked with gadolinium-enhanced MRI in cynomolgus monkeys

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Background: Minimally invasive in vivo measurement of CSF outflow is not possible yet, despite clinical importance of such measurements in many neurological diseases, such as normal-pressure hydrocephalus and Alzheimer's disease.[1] Here, we designed a novel method by tracking MR contrast injected into the CSF space, and applied it to cynomolgus monkeys for proof of the concept and quantitative assessment.

Methods: A 0.5 cc bolus of Gaduvist®, diluted with normal saline to the concentration of 2.5 mmol/L (or 0.25 mmol/L after mixing with 5 cc CSF in the animals), was injected over one minute through a 24-gauge needle placed in the cisterna magna of five cynomolgus monkeys. The concentration was chosen based on human MR arthrography data.[2] A series of T1-weighted MR images were acquired at 0.5, 1, 2, 4, 12, and 24 hours after injections.

The temporal pattern of MRI signal changes were analyzed by visual inspection of the images and by independent component analysis of the 4D data set (3D volume X time) with the constraint of spatial independence. The latter analysis were used to unmix superimposed signal changes in time at different locations across the intra- and extra-cranial spaces.

Results: Expectedly, a rapid spread of T1-enhanced signals were observed across the CSF space, initially through the ambience cistern surrounding the brainstem and then over the cortical convexity. This rapid mixing of the contrast agent with CSF peaked at approximately 3 hours after the injection of the agent into the cisterna magna. Given the volume of CSF, this rate of mixing was consistent with simple diffusion rather than unidirectional circulation of CSF.

More interestingly, a slow increase of T1-weighted signal were detected at the paranasal and paraspinal soft tissue under the basis of cranium. The rate of this presumed lymphatic drainage was at its maximum around 12 hours post-injection and remained significant at 24 hours. The exact routes of lymphatic passage were not determinable at the MR images, yet consistent with those previously reported via perineural sheaths and the cribriform plate and nasal mucosa.

The traditional route of CSF absorption, namely through arachnoid villi to venous sinuses, was examined by measuring T1 signal changes at the venous sinuses, but no significant changes were observed, presumably due to dilution of the contrast agent upon entering the venous compartment.

Discussion: It is a traditional view that CSF is produced by the choroid plexus and drained to the venous sinuses through arachnoid granulations. However, this view has been challenged by recent experimental works demonstrating the importance of extracranial lymphatic drainage, especially at low CSF pressures,[3] and those arguing for filtration from and reabsorption to cerebral blood vessels rather than the separate CSF hydrodynamic routes.[4]

In this study we have demonstrated, first, the possibility of tracking CSF outflow in vivo using minimally invasive techniques. Second, the signal changes could be separated into a rapid component representing diffusion across the CSF space and a slower one due to physiological clearance mechanisms. Third, our results show that the CSF outflow through extracranial lymphatic route is indeed significant in normal primates. This should be compared with pathophysiological conditions, such as the kaolin-induced hydrocephalus model, in future experiments.

References

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