Gadofluorine M enhanced MRI reveals circumventricular organ involvement in CNS inflammation and facilitates occult lesion detection

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Background: The central nervous system (CNS) may no longer be considered immune privileged but rather a site of selective immune activity. Although the blood-brain barrier (BBB) covers most parts of the CNS, certain brain regions are devoid of it and are, therefore, in permanent contact to blood-born molecules and cells. These “exposed” areas include the choroid plexus and other small structures, which line the cavity of the third and of the fourth ventricle, and are known as circumventricular organs (CVO). CVO are characterized by a very dense capillary network with wide perivascular areas and provide an access route for immune cells into the brain parenchyma. Thus CVO might guide CNS immune surveillance. However, until recently no reliable method had been available to survey CVO in vivo. Assuming a crucial function as CNS “gate” for immune cells, the visualization of alterations in CVO might become of additional diagnostic and therapeutic value for the assessment of neuroinflammatory conditions.

Methods: After induction of adoptive transfer EAE as previously described, 21 mice underwent cerebral Gadopentate dimeglumine (Gd; 0.2 mmol/kg) and Gadofluorine M (Gf; 0.1 mmol/kg bodyweight) enhanced MRI daily between day five and 16 post T cell transfer on a 7 Tesla rodent scanner (Pharmascan 70/16AS, Bruker BioSpin, Germany), applying a 20 mm RF-Quadrature-Volume head coil. Axial and coronal T1-weighted images (MSME; TE 10.5 ms, TR 322 ms, 0.5 mm slice thickness, matrix 256x256, FOV 2.8 cm, 8 av.) were acquired.

Results: Inflammatory plaques were widely distributed throughout the brain, with predominance to the brainstem and the periventricular region. In 15 mice that received both, Gd and Gf, a total number of 61 contrast enhancing lesions (CEL) could be visualized. Among these, 26 were exclusively detected after Gf administration, but not on Gd enhanced MRI. Gf signal intensity of the choroid plexus, the subfornicular organ and the area postrema increased significantly during EAE (A, B), correlating with disease severity and delay of disease onset after immunization (C). Furthermore, Gf improved the detection of EAE lesions, being particularly sensitive to optic nerve inflammation (D). Correlated histological slices, Gf initially accumulated in the extracellular matrix surrounding inflammatory foci, and was subsequently incorporated by macrophages/microglia (E).

Interpretation: Gf enhanced MRI provides a novel highly sensitive technique to study cerebral BBB alterations. We demonstrate for the first time in vivo the involvement of CVO in the development of neuroinflammation.