DIFFERENCES IN IRON PARTICLE ENHANCED MRI OF BRAIN AND SPINAL CORD LESIONS IN MOG-INDUCED EAE MICE

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Introduction: EAE is an animal model for multiple sclerosis. Ongoing pathogenesis in EAE is due to an active inflammatory process and a diverse accumulation of lymphocytes and macrophages, primarily in white matter regions of optic nerves, brainstem and spinal cord. Contrast agents based on small particles of iron oxide have been employed to visualize macrophage infiltration in EAE, providing a tool to increase sensitivity for the detection of EAE lesions (1, 2). Iron-enhanced MRI depends upon activated macrophages engulfing the iron particles *in vivo* within the vascular space and the MRI hallmarks of the lesions were apparent as a signal loss on T2*-weighted images. EAE lesions are associated with a variety of pathological processes and MRI does not measure such pathological changes (3). In this study, we examined the MRI detection of brain and spinal cord lesions using a clinically approved iron particle in the MOG-induced EAE mice.

Material and Method: EAE was induced in C57BL/6J mice (female, 10 weeks old) with MOG_{35-55} by standard procedures and clinical scores recorded daily. MRI was performed in an 11.7T Bruker AVANCE scanner with a microimaging gradient insert and 20mm birdcage RF coil for brain imaging and 30mm birdcage RF coil for lumbar spinal cord (LSP). MR images were acquired before EAE induction and pre- and 24h post-injection of Feraheme via tail vein at a dose of 30mg/kg beginning at the relapse phase (clinical score=3). Two in vivo imaging protocols were used for each animal: 1) T2* weighted 3D FLASH (TR/TE: 25ms/5ms; flip angle: 15°) with matrix size 220x128x88 and FOV 22x12.8x8.8 mm^3; 2) T2* weighted 2D FLASH pulse sequence (TR/TE: 285ms/5ms; flip angle: 25°) with matrix size 256x256, FOV 18x18 mm^2 and slice thickness 0.5mm for lumbar spinal cord imaging. Feraheme administration and MR imaging was repeated every 6 days. After in vivo scan, the mice were sacrificed via cardiac perfusion and the brain and spinal cord were scanned ex vivo with T2* weighted 3D FLASH pulse sequence (TR/TE, 50ms/6.4ms; flip angle, $35^{0)}$; image matrix 512x256x256; FOV 25x12.5x12.5mm^3).

Results and discussion: In the EAE mice at the relapse phase (score=3), brain and lumbar spinal cord lesions could be identified by high-resolution T2*-weighted MRI without Feraheme. The lesions were observed as hypo-intense regions typically in the brainstem, the cerebellum and the peripheral spinal cord in comparison with pre-disease images of the same mice (Fig.1). MR images 24 h after iron particle injection showed particle clearance from vascular circulation, while iron particles (hypointense areas) were still evident in muscle & kidney. Increased hypointensity was observed in the periphery of the lumbar spinal cord, but MRI lesion detection was not obviously improved in the brainstem and cerebellum (Fig.1).

Conclusion: Acute EAE lesions could be readily identified in mouse brain and spinal cord by T2* weighted imaging. Administration of Feraheme provided limited improvement in lesion identification. Further histological analysis is required to determine pathological processes giving rise to MRI discrepancy between the brainstem and spinal cord.

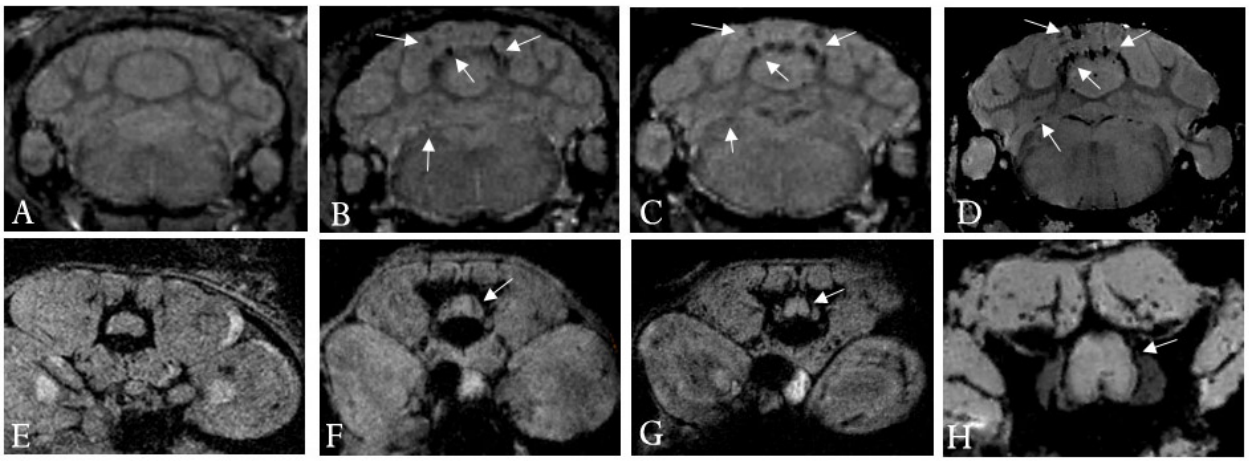

Fig.1. Representative MR images obtained from a mouse before EAE induction (A & E); at stage 3 pre- Feraheme (B & F); 24 h post-injection of Feraheme (C & G); and ex vivo (D & H). Hypointense lesions were observed in the brainstem, the cerebellum and the peripheral spinal cord at Stage 3 EAE in vivo and ex vivo (arrows). In 24h post Feraheme images, the periphery of the lumbar spinal cord increased hypointensity (F & G), but MRI lesion detection was not improved in the brainstem or cerebellum (B & C).

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