Sequential cerebral MRI of listeria brain stem encephalitis in mice - visualization of sub-clinical lesions

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INTRODUCTION

Brain stem encephalitis may arise during infection with the bacterium *Listeria monocytogenes* (LM) (1, 2). Early diagnosis is of vital importance in this life threatening condition. The aim of this study was to test the ability of sequential cerebral MRI (7T) to visualize early brain stem encephalitis in mice.

METHODS

Experimental brain stem encephalitis may be induced in mice after inoculation of LM into cranial nerves. 32 Female Hsd/ICR mice weighing 20-30g (Harlan, UK) underwent inoculation into the cut left facial nerve before cerebral MRI and parallel histological examination from day 4 of inoculation and onwards. The mice were monitored daily for neurological deficits and killed either at the occurrence of sub-clinical MRI lesions (see below) or brain stem deficits. Surgical anesthesia was applied during the inoculation procedure, MR imaging and sacrifice. National authorities approved the experiments.
MRI was performed at 7T on a Bruker Biospec 70/20 AS with BGA-12 400mT/m gradients. A 72mm volume resonator was used for RF transmit and a dedicated mouse brain surface coil was used for receive only with active decoupling. The MRI protocol consisted of tri-axial and sagittal scout scans, axial T2-w, and axial or 3D T1-w started ~10 min after i.p. injection of Gadodiamide (0.2ml diluted 1:5 ≈ 0.7mmol/kg). Key parameters for MRI:
2D RARE (T2): TE-eff.=45ms, TR=6000ms, FOV=25x25mm, Matrix=256x256, Slice thickness=0.5mm (8 slices, interslice=0), NEX=8, Acq.time=26min.
3D FLASH (T1): TR/TE=15/2.9ms, Flip angle=20º, FOV=20x40x20, Matrix=128x256x128, NEX=4, Acq.time 33min.
2D MDEFT (T1): TR/TE/TI=15/5/1000ms, FOV=25x25mm, Matrix=256x256, Slice thickness=0.5mm (8 slices, interslice=0), NEX=8, Acq.time=33min.
The MR images were visually inspected on the MRI console (PV3.0.2). The brain stems from all 32 mice were fixated after sacrifice and H/E stained serial histological sections prepared as previously described (3). 24 of the 32 mice underwent cerebral MR examination from day 4 after inoculation, while 8 did not; these 8 remained clinically healthy until the end of study. 4 scans were partial since the animals developed respiratory failure at anesthesia during MRI.

RESULTS AND DISCUSSION

7-T MRI can visualize brain stem listeriosis, also at a sub-clinical stage: 10 of the 24 scanned mice exhibited definite radiological brain stem pathology and were killed for parallel histological examination. 5 of these 10 had developed clinical brain stem deficits while 5 were clinically healthy. In animals with brain stem deficits radiological pathology was massive (Fig 1), while it was less extensive in symptom-free mice (sub-clinical brain stem encephalitis) (Figure 2). MRI pathology was absent in the remaining 14 scanned mice. T2-weighted imaging (data not shown) was less sensitive in detecting the pathology compared with T1-weighted post contrast imaging (Figure 1).
Radiological pathology in mice with brain stem deficits: In the clinical stage, MRI revealed edema and contrast enhancement mainly on the side of inoculation in the pons. The contralateral side was also, but less affected (Figure 1A). Histological examination revealed sub-acute inflammation in the corresponding area and necrotizing inflammation in the nucleus of the inoculated facial nerve (Figure 1B).
Radiological pathology in mice without brain stem deficits: Radiologically visible pathology, contrast enhancement on MRI (Figure 2A-D) and acute inflammation at neuropathological examination (not shown) were present as early as on day 4 after inoculation (in some mice as early as three days before onset of clinical brain stem deficits). Early lesions were selectively located along the intracerebral pathway of the facial nerve (Figures 2A-D).

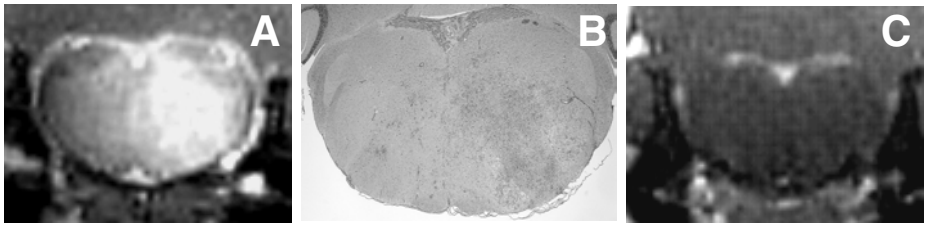

FIGURE 1. *FLASH MRI of (A) a mouse with clinical brain stem deficits developed and scanned on day 7 after inoculation and (C) sham-operated mouse, 7 days after transsection of the left facial nerve. A: Massive contrast enhancement and tissue edema (increased anteroposterior and transversal diameters) mainly at the inoculation side. Representative axial slice reconstructions from 3D post contrast. B: Parallel histological section (H+E) to MRI in A.*

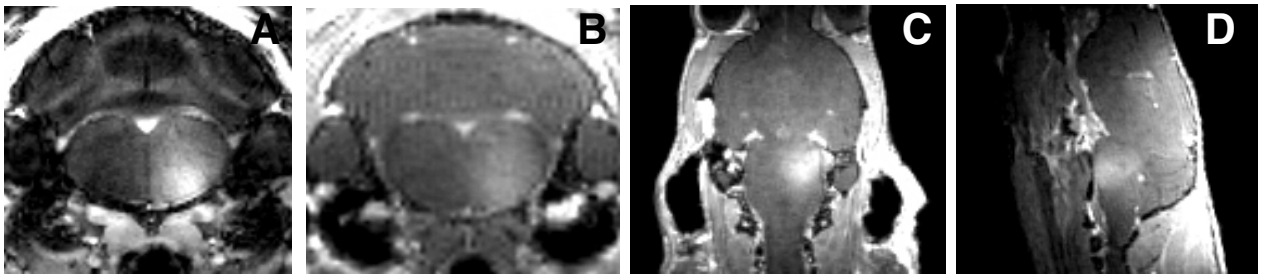

FIGURE 2. *MRI of a clinically healthy mouse on day 5 after LM inoculation. Contrast enhancement locates to the region of the left facial nerve passage, at the side of facial nerve inoculation. 2D axial T1-weighted MDEFT (A) and FLASH reconstructed from 3D volume acquisition (B-D; 2D axial, coronal and sagittal MR images) MRI. The mouse is the same as in Figure 1A.*

Sub-clinical MRI "screening" for brain stem encephalitis in listeriosis is not routine. Nevertheless, our findings demonstrate the potential of MRI in sub-clinical diagnosis. At 7T, the MDEFT sequence is of interest due to its advantageous contrast characteristics. Although a thorough comparison of MDEFT and FLASH was outside the scope of this study, our results suggest that MDEFT should be considered in post-contrast T1-weighted MRI of the brain stem at high field strengths.

CONCLUSIONS

Our study shows that cerebral MRI examination can identify listeria brain stem encephalitis at a sub-clinical stage in mice. The MDEFT images demonstrate the applicability of this sequence in post-contrast T1-weighted MRI at 7T.

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