Development of Experimental Meningitis in Rats Studied using MRI

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Introduction: The aims of this study were to follow the evolution of experimental pneumococcal meningitis in rats using MR imaging and to stage the disease by grading MR images of the brain obtained over a 48 h period. If specific disease stages were defined, MR may then be used to evaluate and optimise the efficacy of adjunctive treatments administered specifically to minimise disease sequelae.

Materials and Methods: Male Wistar rats (n=15) were injected intracisternally with 3.3-3.9 x 10^5 CFU/ml S. pneumoniae serotype 3. Control rats (n=5) were injected with saline. Rats were randomized for MR scanning at 6, 12, 24, 30, 36, 42 and 48 h after infection. Animals imaged at 6 h were allowed to recover and were imaged again at 36 h. A clinical and motor performance score was performed before each scan (1). Anaesthetized animals (Hypnorm/Dormicum/Atropine) were positioned within a stereotactic device placed within a home-built quadrature coil. Images were acquired using a SISCO 4.7T imaging system. T1W, T2W, quantitative diffusion, dynamic MRI and post contrast T1W measurements were performed on each animal. Contrast agent (Magnevist, 0.5 mmol/kg) was administered via a cannulated tail vein. Using post-contrast T1W images and quantitative diffusion maps, inflammation was graded as 0=no inflammation, 1=light, 2=heavy and 3=heavy, diffuse inflammation reaching into the cerebral cortex. The presence of hydrocephalus was given a score of 1. A total image score for each rat was made blinded to all other data. After imaging, samples of cerebrospinal fluid (CSF) were obtained for quantification of bacterial load and white blood cell count (WBC).

Results: Correlations were made using non-parametric Spearman rank with Bonferroni's correction. The score of meningeal inflammation correlated with both clinical and motor score ($P<0.0005$ $\rho=0.84$, $P<0.0005$ $\rho=0.77$). Correlations between inflammation and bacterial load or WBC in the CSF were found to be significant ($P=0.0045$ $\rho=0.7$ and $P=0.002$ $\rho=0.73$). The total image score including damage and hydrocephalus was found to correlate highly significantly to the clinical and motor scores ($P>0.0005$ $\rho=0.81$, $P>0.0005$ $\rho=0.77$). Total image score correlated significantly to the CSF bacterial load and WBC ($P=0.0015$ $\rho=0.74$ and $P=0.002$ $\rho=0.73$). Staging of the meningeal inflammation and enhancement was correlated highly significantly to time after bacterial injection ($P=0.0008$ $\rho=0.83$). Heavy inflammation (score 2) was seen after 24 h. More diffuse inflammation (score 3) with or without hydrocephalus and brain damage were features of disease from 30-48 h. Four rats in the 30-48 h group were diagnosed with hydrocephalus. Two rats were diagnosed as having CNS damage; 1 possible cerebellar infarction and 1 cavity formation close to the corpus callosum (abscess?).

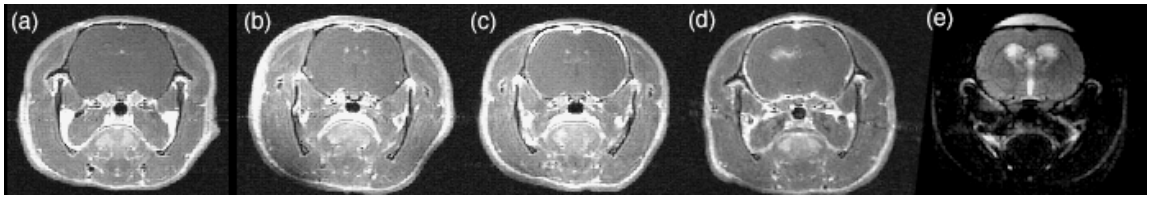

Figure 1: Representative post contrast (Gd-DTPA- 0.5 mmol/kg) T1W spin echo images of meningitis infected rat brains showing differing extents of meningeal enhancement: (a) no significant enhancement; (b) light; (c) heavy, (d) heavy, diffuse enhancement and (e) T2W image showing hydrocephalus.

Discussion: A previous study at 1.5T reported that MR images of meningitis infected rats showed typical characteristics of the human disease (2). This study, performed with higher resolution at 4.7T, shows that MR images of the brain and meninges during experimental pneumococcal meningitis in rats correlate significantly with both paraclinical and clinical assessment of the disease. This work suggests that MR may be used to stage the extent of disease in the experimental model and could be used to assess and optimise the efficacy of adjunctive treatments thereby assisting in the drug development process.

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