

Early MRI-visible lesions in *Plasmodium berghei* ANKA-induced cerebral malaria

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Introduction

Cerebral malaria (CM) is the most lethal complication of *Plasmodium falciparum* infection. We have previously characterized the experimental cerebral syndrome (CBA/J mice infected with *Plasmodium berghei* ANKA) at its ultimate stage using *in vivo* MRI and MRS at 4.7 T, and proved the fatal role of ischemic edema in this disease (1). The purpose of the current study was to provide a detailed anatomical imaging study of the cerebral effects of *Plasmodium berghei* ANKA infection at an early stage to identify clinically-relevant markers of early disease using conventional MRI (T₁- and T₂-weighted MRI) at higher field (11.75 T).

Material and methods

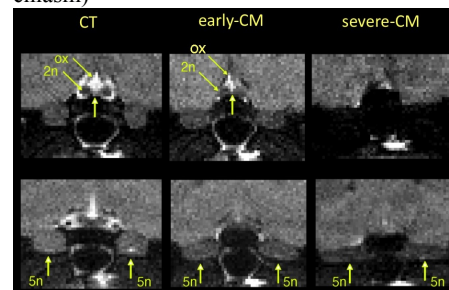
CBA/J mice were infected with *Plasmodium berghei* ANKA and explored at an early stage (day 4 to 5 post-infection, n=14) or at the ultimate stage (day 7 to 8 post-infection, n=3) by *in vivo* brain MRI. The animals were imaged on a 11.75 T vertical Bruker AVANCE 500 WB wide bore MR system (Bruker, Germany) using a transmitting and receiving head resonator of 2.5 mm. T₂-weighted images were acquired in the axial and sagittal planes using a spin-echo sequence (TE, 37.1 ms; TR, 5000 ms; RARE factor 8; 2 averages, 30 contiguous slices of 0.5 mm thickness; matrix, 256²; field of view, 20² mm²). T₁-weighted images were acquired in the axial plane using a 3D gradient echo sequence (GEFC-3D) with strong T₂*-weighting (TE, 5 ms; TR, 30 ms; field of view, 20³ mm³; matrix, 256²x64). MRI data were processed under ImageJ (2).

Results

CM mice at an early stage of the disease did not show any significant brain swelling on the contrary to those explored between day 7 and 8 after parasite injection. They did not present with the typical features of CM at the severest stage (edema of the corpus callosum, T₂-hyperintense focal lesions, crushing of the cerebellum). However, we report on novel MR-visible features detectable at an early stage, including T₂-hypointensity of the internal capsule (in 57 % of CM mice), T₂-hypointensity of the optic nerves and tracts (in 93 % of CM mice), loss of visibility of the optic chiasm, and crushing of the optic and trigeminal nerves. These features were also observed at the latest stage. In addition, discrete hemorrhages (petechiae), characteristic of the disease could be individually identified on T₁/T₂*

images at high field in mice at the severest stage of the disease.

Figure 1: Typical T₂ axial images showing cranial nerve damage. (2n=optic nerve, 5 n= trigeminal nerve, ox=optic chiasm)



Discussion and conclusions

We have demonstrated the detection of early and specific pathological features of experimental CM such as damage to white matter (internal capsule), and to cranial nerves (optic and trigeminal nerve) using conventional MRI at high field. These new findings, previously undetected at 4.7 T in mice explored at the severest stage of the disease (1), may help understand the contribution of cerebral lesions to overt clinical signs at an earlier stage of cerebral malaria.

- (1) Viola A, Penet MF, Confort-Gouny S, Le Fur Y, Duhamel G, Kober F, Ibarrola D, Izquierdo M, Coltel N, Gharib B, Grau GE, Cozzone PJ : Imaging experimental cerebral malaria *in vivo*: significant role of ischemic brain edema. *J Neurosci*, 2005, 25: 7352-7358.
- (2) Rasband WS, ImageJ, U. S. National Institutes of Health, Bethesda, Maryland, USA, <http://rsb.info.nih.gov/ij/>, 1997-2009