Quantitative relaxometry reveals the early involvement of rostral white matter tracts in a murine model of cerebral malaria

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Target audience: basic scientists, physicians and pharmaceutical companies

Purpose:

Cerebral malaria (CM) is an often fatal encephalopathy caused by Plasmodium infection. A number of MRI detectable anatomical lesions have been described in murine models of CM such as hypointensities in the internal capsule and the optic nerve tracts as well as hyperintensities in the corpus callosum and the external capsule on T_2 weighted images. [1,2] However, their relation to brain metabolism and microstructure and therefore their involvement in neurological impairment is not completely elucidated. Since quantitative relaxation parameters have a less indirect link to the pathological mechanism we explored their sensitivity along the time course of CM development in an effort to contribute to a better characterization of murine CM.

Methods:

This study was conducted on six 8-week-old female C57BL/6J mice (Janvier Labs, Le Genest St Isle, France) four of which were induced for CM by intraperitoneal injection of 10^6 P. berghei ANKA infected erythrocytes. They were monitored daily for general signs of disease (weight loss, reduced locomotion, curved posture, parasitemia) and specific symptoms of CM (hypothermia, ataxia, paralysis, convulsions and coma). Starting day 5 post infection, imaging was performed at 11.75T in a vertical AVANCE 500 WB system (Bruker, Germany) with a transmit and receive birdcage coil (diameter 1 inch) and consisted in T_2 weighted high resolution images (80 x 80 x 500 μm^3, RARE factor 8, TR = 5s, effective TE = 36ms, NA= 4, 20 slices, duration 8 minutes) followed by quantitative mapping of T_1 (IR-MDEFT, TR= 30s, TR_{echo}= 6.9ms, NA= 1, excitation flip angle = 10°, duration 5 min for each inversion time TI = 15, 50, 150, 500, 1500, 5000, 15000ms), T_2 (MSME sequence, TR= 15s, TE = 20, 40, 60, …, 200ms, NA= 1, duration 16 minutes) and T_2* (MGE sequence, TR= 15s, TE = 2, 4, 6, …, 80ms, NA= 1, duration 16 minutes) with a spatial resolution of 235 x 235 x 500 μm^3. Parametric maps were calculated pixelwise by a 3-parameter monoexponential fit using the simplex algorithm in ImageJ. [3] Regional relaxation time changes with respect to the values in corresponding regions in healthy brains were analyzed using the Mann-Whitney-Wilcoxon test.

Results:

General signs of disease appeared on day 7 to 8 post infection while neurological symptoms appeared quickly on day 9. Parametric maps as well as T_2 weighted images remained normal until day 7 post infection. On day 8 post infection all three parametric maps showed bilateral relaxation time increases exclusively in the olfactory bulb, with the T_2 and T_2* parameter being significantly ($p<0.05$) elevated (Figure 1 and 2). Well demarcated hyperintensities corresponding to the olfactory limb of the anterior commissure were confirmed on the high resolution T_2 weighted images (Figure 2). At the final stage on day 9 the hyperintensities along posterior white matter tracts (i.e. corpus callosum and external capsule) [1] were observed in the T_2 weighted images along with elevated T_2 but not T_1 parameters. In addition, the dorso-ventral diameter of the trigeminal nerves was decreased at day 9 post infection indicative of cranial nerve damage, another specific sign for CM. [2]

Discussion:

This study shows the involvement of the olfactory limb of the anterior commissure in the development of CM. Importantly, this appears to be the only MRI detectable feature preceding obvious neurological signs which appear abruptly in this mouse strain. Other early signs of CM such as brain swelling or focal hypointensities previously reported for the CBA/J mouse strain, [2] characterized by an earlier and more progressive appearance of neurological signs, were not observed in this study. The observed predominant T_2 increase might reflect accumulation of inflammatory cells or proteins or glial proliferation. However, since T_2 changes are limited to white matter structures, increased free water content due to demyelination can not be excluded. Multicomponent relaxometry analysis [4] might help to differentiate between these pathophysiological mechanisms.

Conclusion:

Despite the small number of animals in this exploratory study we were able to reveal a damage of white matter tracts progressing in the rostro-caudal direction over the time course of CM development. Quantitative relaxometry has the potential to detect this damage without the ambiguity of T_2 weighted signal changes and might also point to the underlying mechanism.

References:

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3. Abramoff MD, Magelhaes PJ, Ram SJ. Image processing with ImageJ. Biophotonics Int 2004;11:36–42.
4. Mackay AL, Vavasour IM, Rauscher A, et al. MR Relaxation in Multiple Sclerosis. Neuroimaging Clin N Am. 2009; 19:1–26.

Figure 1: relaxation parameters in olfactory bulb

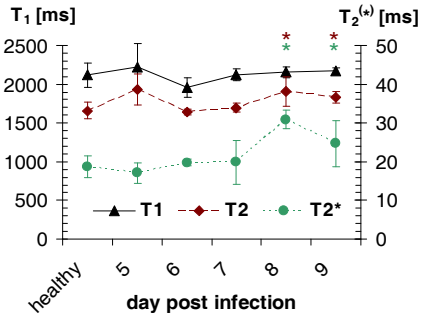

Figure 2: bregma + 3 mm, olfactory limb of the anterior commissure (arrows)