

Mapping Gd-DOTA leakage kinetics in experimental cerebral malaria

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Target audience: basic scientists, physicians and pharmaceutical companies

Purpose:

Cerebral malaria (CM) is a complication of Plasmodium infection with high mortality, rapidly progressing from drowsiness to seizures and coma. However, the underlying pathophysiological mechanism is poorly understood. Although the role of edema formation in human CM is controversial, ¹ endothelial inflammation and blood brain barrier disruption has been documented in murine experimental CM (ECM) when neurological signs were present. ^{2,3} This study investigates whether quantification of endothelial permeability can be used as an early marker of disease progression.

Methods:

ECM was induced by intraperitoneal injection of 10^6 Plasmodium berghei ANKA infected erythrocytes in eight 8-week-old female C57BL/6J mice (Janvier Labs, France). Body weight, temperature, parasitemia, behavior and clinical symptoms were monitored daily. Hypothermia, unstable gait, paralysis, missing righting reflex and coma were considered symptoms of ECM. Infected mice and 2 uninfected mice underwent dynamic imaging with intraperitoneal injection of 10 mmol/kg Gd-DOTA on up to 4 days using a quantitative technique designed for blood volume and permeability mapping. ⁴ 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) using an inversion recovery prepared 3D gradient echo sequence (TR = 750ms, TI = 305ms, TR_{echo}=6ms, TE=1ms, flip angle = 10°, time resolution 15 s) and a proton density weighted acquisition without inversion pulse (TR = 12s, TR_{echo}=6ms, TE=1ms, flip angle = 10°) for voxelwise normalization (spatial resolution 235 x 235 x 500 μm^3).

Results:

All infected mice progressed to ECM with overt neurological symptoms starting day 7 and reached the terminal stage between day 8 to 9 post infection. Occurrence of Gd-DOTA leakage appeared on day 6 post infection concomitant with general clinical signs such as hunched back and piloerection, preceding specific neurological signs by not more than one day. The degree of Gd-DOTA permeability increased over time and was related to the severity of symptoms. Regional differences in permeability (Figure 1) were observed in the brain parenchyma that were consistent between animals. The apparent distribution volume fraction DVf ⁴ of Gd-DOTA in the brain 1 hour after injection was highest in rostral brain regions where it exceeded 0.8 at the terminal stage. The kinetics of Gd-DOTA accumulation in brain parenchyma was markedly different from those in high-grade tumors or extracerebral tissues such as muscle or skin (Figure 2), mainly governed by passive exchange between two compartments and reaching an apparent DVf of up to 0.4.

Discussion/Conclusion:

This study confirms the link between blood brain barrier impairment and ECM ^{2,3} at an earlier stage of disease development in C57BL/6J mice. In addition, this in vivo study demonstrates quantitative differences in endothelial permeability to Gd-DOTA among brain regions as well as over time by following the same animals during disease progression. It also evokes a complex transport mechanism of Gd-DOTA across the blood brain barrier. This study might contribute to the understanding of the pathophysiological mechanism of CM. Moreover, it reveals a non-invasive quantitative and highly sensitive biomarker of ECM that can be used for follow-up and treatment monitoring.

References:

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Figure 1: Regional differences in Gd-DOTA permeability

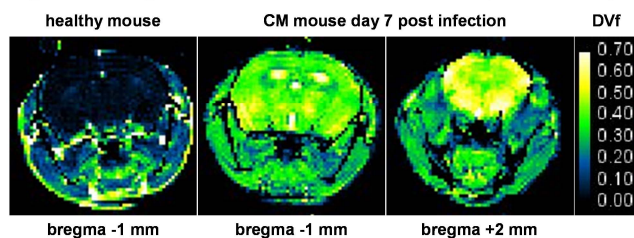


Figure 2: Kinetics of Gd-DOTA accumulation

