ORAL PRESENTATIONS

Dextran-enhanced CEST MRI reveals the size effect of BBB dysfunction associated with neuroinflammation

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Introduction

The blood-brain barrier (BBB) is compromised in multiple central nervous system (CNS) disorders associated with neuroinflammation, including multiple sclerosis (MS). Currently available magnetic resonance imaging (MRI) methods, however, are only able to measure BBB leakage in the lower molecular size range with the use of small molecular tracers, *i.e.,* gadolinium (Gd) agents (<1 kDa)[1,2] and water (18 Da).[3,4] The goal of this study is to adopt a dextran-based chemical exchange saturation transfer (CEST) MRI approach for assessing BBB leakage in the larger size range and studying the size characteristics of BBB dysfunction.

Methods

All animal experiments will be approved by the Animal Care and Use Committee of Johns Hopkins University. *EAE MS mouse model:* C57Bl/6 mice (F/6-10w), were injected s.c. with myelin peptide (MOG35-55, 200 µL, 0.5 mg/mL) emulsified in incomplete Freund's adjuvant supplemented with *M. tuberculosis* H37Ra (5 mg/mL) and i.p. with 300 ng of pertussis toxin on days 0 and 2. Mice were observed daily for signs of paralysis using a 0-5 rating system. Fluorescent imaging. EAE mice (n=3) were injected with the combination of fixable Dex40-TRITC and Dex3-FITC (i.v.) at the dose of 80 mg/kg, and sacrificed at 30 min after injection (without perfusion) to collect brains. Fluorescence microscopy was then performed on tissue sections. *MRI*: all in vivo MRI was acquired using a Biospec 11.7 T horizontal MRI scanner (Bruker, Ettlingen, Germany). According to our previously reported protocol,[5] CEST MRI was performed before and after the i.v. injection of 200 µL dex40 saline solution (750 mg/kg b.w), using parameters: B_1=1.8 µT, T_{sat}=3 s, Δω=-3 to +3 ppm with a step size of 0.2 ppm. $MTR_{asym}=(S_{-\Delta\omega}-S_{+\Delta\omega})/S_0$ was computed after the B_0 correction using the WASSR method. ΔMTR_{asym} (1 ppm) at each time point was calculated by MTR_{asym} (t)- MTR_{asym} (pre).

Results

1. The size-dependent BBB disruption in MS can be detected by fluorescent dextran-tracers of different sizes: Immunofluorescent results show dextrans of smaller sizes (*e.g.*, 3 kDa) penetrated the brain parenchyma deeper than larger sizes (*e.g.*, 40 kDa). Our study proves the feasibility to use dextrans as a group of tracers with different sizes for probing the size

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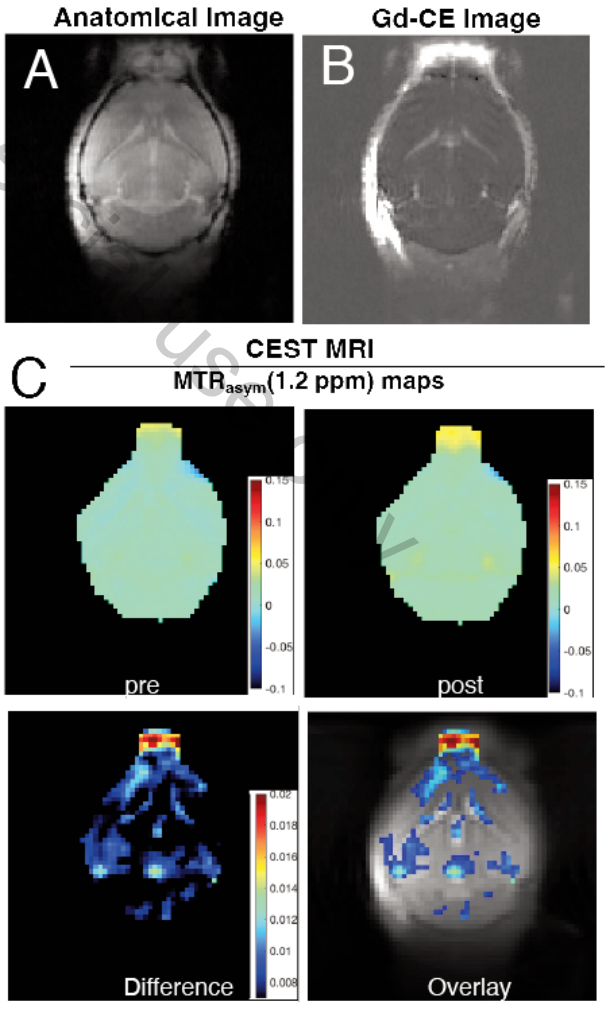

Figure 1. Dex-enhanced CEST MRI results of a representative mouse (score= 1.5) at 20 min post- injection.

effect of BBB dysfunction.

2. Dex-enhanced CEST MRI: As shown in Figure 1, mice with high clinical disability scores have BBB impairment in the mouse brain, confirmed with Gd-enhanced MRI (Figure 1B). Dex-enhanced MRI results (Figure 1C) showed substantial contrast enhancement in the corresponding brain regions. Interestingly, while the size of Dex (40 kDa) is larger than the size of Gd-DOTA (559 Da), the area showing enhanced Dex-CEST signal is slightly larger than that of Gd-enhancement, suggesting that, besides size, other particle properties such as shape and surface properties of a given agent/particle may also contribute to the permeation across BBB.

Conclusions

We have established a dextran-based imaging protocol for assessing the biodistribution of dextrans in the brains of EAE mice. We will continue studying the size effect of dextrans and determining the optimal dextran size for accurately mentoring the disease progression.

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