

# Quantifying the Permeability of Blood-Brain Barrier in MS patients under Conventional Treatment

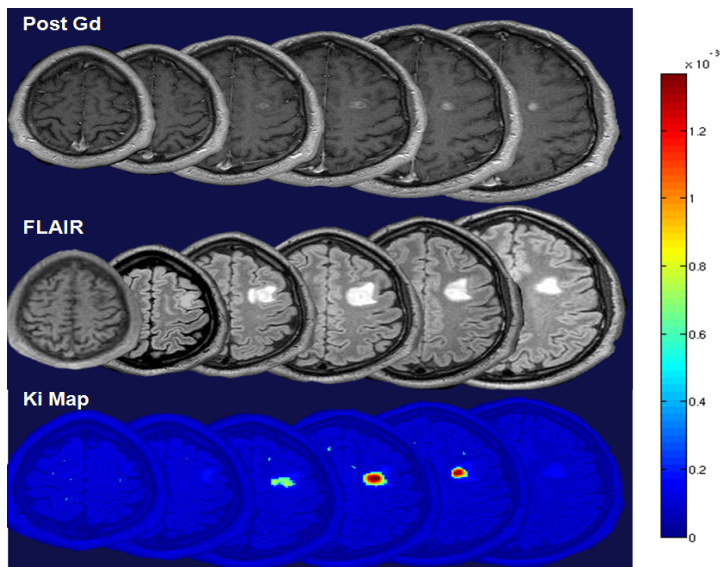
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**Introduction:** Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system. In MS, a complex inflammatory cascade of lesion development includes: T cell migration into the central nervous system, macrophage recruitment, blood-brain barrier (BBB) breakdown, demyelination, axonal damage, remyelination and gliosis. Damage to the BBB in patients with MS is frequently seen with Gadolinium-enhanced MR. Reduction of T1 relaxation time in contrast-enhanced MRI (CEMRI) allows for the qualitative assessment of focal BBB abnormalities in patients with multiple sclerosis (MS)<sup>1, 2</sup>. Although by this method enhancing lesions can be counted and their volume measured, little is known about quantitative values of BBB permeability in the MS brain<sup>3, 4</sup>. An *in vivo* quantitative measurement of BBB alteration in neurovascular diseases, such as MS, would enhance options for monitoring treatments. The objective of this study was to quantify the permeability of BBB in MS patients by employing dynamic CEMRI (DCEMRI) and the Patlak<sup>5</sup> modeling technique, to analyze MS patients and normal subjects.

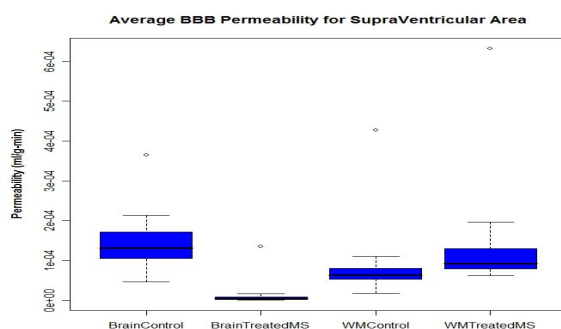
**Materials and methods** Ten MS patients under conventional treatment and 17 controls were recruited for BBB permeability studies. The MRI investigation was performed using a 1.5 - Tesla Siemens whole-body clinical scanner with a standard eight channel array headcoil (Siemens AG, Erlangen, Germany). DCE-MRI scans were conducted with a fast T1 mapping technique (TAPIR) and a reduced dose of Gd-DTPA (1/4 of standard dose of 0.1 mmol/Kg). By using TAPIR a series of echo signal obtained. Then we used a method which first proposed by Look and Locker to calculated T1 values. T1 images representing changes in T1 values were related to the change in concentration of contrast reagent being washed out from the plasma. TAPIR was performed with the following parameters: TR=15ms; banded readout scheme with 3 echoes at TE1:TE2:TE3=2.8:5.1:7.4ms;  $\alpha=25^\circ$ ; FOV =220 mm x 220 mm, slice thickness= 5.0 mm, slice gap= 5 mm, number of slices= 6, number of averages=1, Matrix size=128 x 128, receiver bandwidth= 50 kHz; 20 time-points sampled on the relaxation curve; T1=30ms and preparation delay  $\tau=2s$ . With sagittal sinus as reference point for the concentration of Gd-DTPA in plasma, Patlak multi-compartmental modeling technique was employed to derive a pixel-based BBB permeability map from the data.

**Results and discussion:** DCEMRI distinguished between high grade and low grade levels of BBB permeability in MS patients. **Figure 1** represents an example of an MS patient with a single enhancing lesion. In this patient, the abnormal leakage of BBB was quantified; abnormal BBB leakage was confined to the lesion volume, which is also visualized by FLAIR and Gd-DTPA enhanced T1w images.



**Figure 1.** Three sets of MR-based images representing an enhancing lesion in a 32 years old patient with MS. Top row shows a series of T1 images acquired after the injection of 0.1 mmol/Kg of Gd-DTPA representing the volume of an enhancing lesion. Middle row shows T2 FLAIR images highlighting abnormalities in white matter as hypointense area. Bottom row shows the BBB permeability map for white matter area which is overlaid with the anatomical image to show the location of leakage. Color-coded BBB permeability map shows pixel-wise permeability values. In this case the permeability map quantifies the permeability of lesion corresponding to the volume which was visible with both post Gad images and FLAIR. Using statistical analysis, we found that in control subjects, the BBB permeability coefficient within a %95 confidence interval is less than  $3 \times 10^{-4}$  (ml/g-min). In generated permeability maps abnormal values classified with this threshold.

Comparing average permeability of gray and white MS brain tissue with controls (see **Fig. 2**), we found a statistically significant reduction in average brain permeability in MS patients under treatment ( $p < 0.001$ ). However, we did not find a statistically significant difference in permeability of BBB in WM alone of treated MS compared to the WM of controls ( $p = 0.25$ ). Our results could be caused by an effect of the drugs or be normal component of the MS attack. It is possible that the drug treatments affects the endothelial cell tight junctions by an action of transforming growth factor-beta ( $TGF-\beta$ ), which is increased in MS modifying drugs and reduces BBB permeability. Permeability maps, reconstructed from the data acquired by DCEMRI, provide more information about the state of the BBB in MS patients compared to the standard Gad-enhanced images. Further study is needed to determine its usefulness diagnostically and in clinical trials.



## References:

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**Figure 2.** Average permeability of BBB as calculated by DCEMRI in WM and a volume of brain located above ventricular area of controls and MS under conventional treatment.

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