

Non-invasive assessment of blood-brain barrier permeability in multiple sclerosis patients by arterial spin labeling.

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Synopsis

Multiple sclerosis is a demyelinating disease affecting the central nervous system. Although MS lesions can be identified by conventional MRI, the evaluation of active lesions in normal appearing gray and white matter requires measures of blood-brain barrier permeability (BBB), which is commonly assessed through the dynamic contrast enhanced (DCE) acquisition. When repeated scans are needed in the MS patients follow-up, repeated gadolinium injection is not recommended. This study successfully showed the feasibility of advanced arterial spin labeling sequences as an alternative to evaluate BBB permeability, whose results of water-exchange times across the BBB were in agreement with DCE measurements.

Introduction

Multiple sclerosis (MS) is the most inflammatory demyelinating disease that affects the central nervous system (CNS), characterized by focal lesions and diffuse damage of both white and gray matter¹. MS pathophysiology is associated with blood-brain barrier (BBB) permeability deregulation, allowing leakage of auto-reactive T-cells to perivascular compartments². Although macroscopic MS lesions are easily identified as hyperintensities in T2w or FLAIR, it is not possible to differentiate active from inactive lesions solely based on these images. Inflammatory and microstructural changes in MS go far beyond focal lesions, affecting normal appearing white (NAWM) and gray matter (NAGM)². Recent evidence has shown signs of latent inflammation in chronic lesions, the so-called smoldering lesions^{2,3}. In parallel, histopathological studies have reported BBB abnormalities in inactive MS lesions and in NAWM⁴.

Common strategies to evaluate BBB damage in NAWM of MS patients are based on post-contrast T1w-MRI or dynamic contrast-enhanced (DCE) MRI, from which perfusion and permeability information is obtained⁵. Since the chronic nature of MS, repeated MRI scans are necessary, including repeated injection of gadolinium-based contrast agents, which is unwanted due to concerns regarding gadolinium retention. A novel non-invasive alternative to contrast-enhanced methods has recently been proposed employing advanced arterial spin labeling (ASL) sequences^{6,7}, allowing the quantification of water-exchange times across the BBB, beyond classical outputs of cerebral blood flow (CBF) and arterial transit time (ATT).

In this study, we employed Hadamard-encoded pseudo-continuous ASL (pCASL) to acquire images after seven post-labeling delays (PLDs) combined with a multi-echo 3D-GRASE readout to assess BBB permeability in MS patients and compare it to the results of DCE and pre- and post-contrast T1w, T2w and FLAIR.

Methods

Three MS patients (one female, 37.33-13.65 years) were scanned on a Philips Achieva 3T MRI scanner in agreement with local IRB conditions. The total acquisition protocol consisted of pre- and post-contrast T1w, T2w, FLAIR, ASL and DCE (Figure 1). The ASL protocol included seven PLDs (170-1870ms) after eight Hadamard-blocks with labeling duration of 1800, 800, 400, 2x150 and 2x100 ms to capture both angiographic and perfusion phases and eight echo times (13-393 ms) to evaluate the T2-signal decay and separate the contributions of GM and blood.

DCE post-processing was done using the PkModeling extension of 3D-Slicer to obtain Ktrans maps. ASL post-processing was performed with in-house scripts in Julia Language⁸ using a bi-exponential model in two stages: First, CBF and ATT were obtained by fitting the shortest echo signal to the ASL-Buxton model⁹; and second by fitting the multi-echo signal decay considering literature values of T2 for brain and blood, providing the exchange time between blood and GM (Tbldgm)¹⁰.

All images were transformed to ASL space using FSL-FLIRT¹¹. Data analysis was based on the ROIs of inflammatory lesions, defined by FLAIR hyperintensities, and NAWM with active MS identified as CE voxels by DCE-images. Quantitative plots were made in R¹².

Results

For the ROIs of inflammatory FLAIR hyperintensities, lesions were mostly DCE/postGD-T1w non-enhancing (NE), barring a few voxels localized deep within the lesions, manifesting as contrast-enhanced (CE), as illustrated in Figure 2. For NAWM ROI, the analysis revealed contrast-enhancing regions in combination with increased CBF, Tbldgm and Ktrans, but no signs of inflammation in FLAIR (Figure 3). The quantitative measurements of healthy and BBB damaged NAWM are plotted in Figure 4.

Discussion

An important disease activity biomarker in MS patients refers to BBB breakdown, since the leakage of auto-aggressive T-cells advance neuronal demyelination², typically visualized as FLAIR hyperintensities (Fig.2). However, T2-FLAIR hyperintensities are non-specific to underlie pathological processes, and might correspond to active demyelination/inflammation, edema, gliosis or remyelination areas. The BBB permeability evaluation might help to understand the dynamic of pathological processes in MS. Our study revealed that most of T2-FLAIR hyperintense lesions did not show contrast-enhancement, which is the most conventional clinical practice to measure active inflammation. This pattern was replicated by analyzing ASL Tbldgm. In contrast, deep inside some macroscopic lesions, we observed signs of BBB damage in both ASL-Tbldgm and DCE-Ktrans, suggesting BBB dysfunction, which might be a sign of silent inflammatory activity, not detectable by T1-Gd images.

ASL measures of BBB dysfunction in NAWM were in agreement to classical permeability measurements of DCE and postGd-T1w, with the pattern of CBF and Tbldgm values (Fig.4) meeting the NAWM contrast-enhancement foci with increased Ktrans values. The need for repeated BBB permeability measures in the follow-up of MS patients strengthens the necessity of contrast-free approaches, with ASL being a promising alternative. Furthermore, as ASL measures are based on water molecules, it may be more sensitive to detect subtle BBB deregulation than Gd-leakage, but maybe less spatially specific as the water exchange happens between multiple compartments.

Conclusion

This study showed the ASL utility in evaluating perfusion and BBB-permeability in MS patients, providing two-fold contributions. First, since BBB damage in MS lesions is not as dramatic as in e.g. glioma, it can add on as a methodological proof-of-concept regarding the feasibility of ASL for BBB permeability assessment in clinical routine. Second, by providing results comparable to DCE, ASL is an interesting non-invasive alternative to investigate BBB damages in NAWM.

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Figures

	3D T1W	3D T2W	3D FLAIR	ASL	DCE
FOV (mm ²)	240 x 240	240 x 240	240 x 240	240 x 240	240 x 240
Spatial resolution (mm ²)	1 x 1	0.6 x 0.6	1 x 1	3.75 x 3.75	1.25 x 1.25
Slice thickness (mm)	1	3	1.2	6	7
Number of slices	240	240	240	17	17
TR (ms)	7	59	11000	4300	2.7
TE (ms)	3.2	29	2.8	13.56, 67.82, 122.08, 176.33, 230.59, 284.84, 339.1, 393.36	1.4
LD (ms)	--	--	--	1800, 800, 400, 150, 150, 100, 100	--
PLD (ms)	--	--	--	170, 270, 370, 520, 670, 1070, 1870	--
FA (degrees)	8	10	90	90	14
Number of repetitions	1	1	1	2	50
Gd volume (ml)	--	--	--	--	20
Total scan time (min)	4.23	3.22	3.32	20	4.09

Figure 1: Detailed parameters of the MRI acquisition protocol.

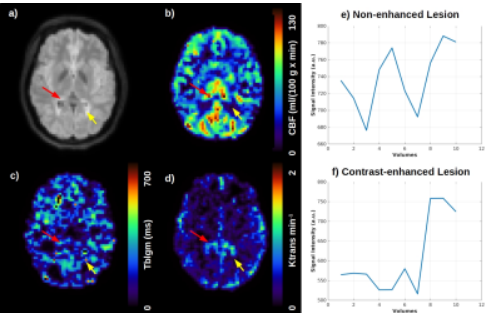


Figure 2: a) Inflammatory MS lesions identified as bright regions in FLAIR-MRI and the perfusion-related parameter: b) CBF in ml/(100 g * min); c) Exchange time across the BBB (Tblgm) measured by ASL in ms and d) Ktrans map measured in min⁻¹, obtained through the contrast-enhanced DCE time-series shown in e) for a non-enhanced lesion (yellow arrow) and f) contrast-enhanced lesion (red arrow).

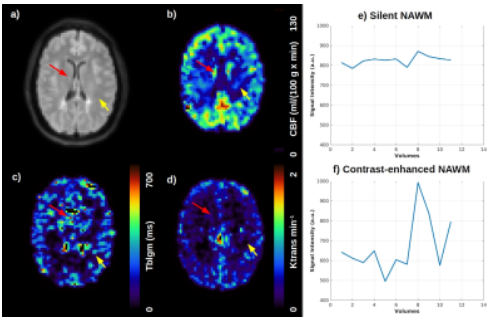


Figure 3: Normal Appearing White Matter (NAWM) analysis. a) FLAIR images showed no inflammatory MS lesions in the regions pointed by the red and yellow arrows and the perfusion-related parameter: b) CBF in ml/(100 g * min); c) Exchange time across the BBB (Tblgm) measured by ASL in ms and d) Ktrans map measured in min-1, obtained through the contrast-enhanced DCE time-series shown in e) NAWM regions with no BBB damages and f) NAWM regions with BBB damage.

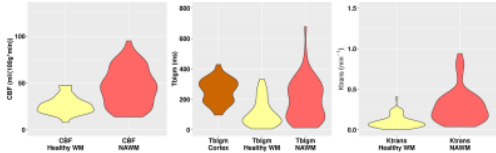


Figure 4: Violin plots of the quantitative measurements of CBF in ml/(100 g * min) and Ktrans in min-1 for a healthy WM region and for a damaged BBB region in NAWM and Tblgm measured in ms in GM cortex, healthy WM and BBB damaged NAWM regions.