Normal appearing Brain Tissue MTR abnormalities in patients with clinically isolated syndromes and early Multiple Sclerosis

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This study investigated when normal appearing brain tissue (NABT), gray matter (NAGM) and white matter (NAWM) MTR abnormalities begin in the course of MS. 2D-SE MT imaging was performed in 40 clinically isolated syndrome (CIS) patients, 28 early RRMS and 51 controls. Images were segmented using SPM99 and MTR histograms were acquired for NABT, NAGM and NAWM after extracting lesion masks. NABT, NAGM and NAWM mean MTR were significantly reduced in CIS and early RRMS. Subtle NABT abnormality is detected in CIS before the diagnosis of MS and are more pronounced in early RRMS. CIS without T2W lesions also have abnormal NABT MTR despite being at a lower risk of developing MS and disability.

Background:

Magnetization Transfer Ratio (MTR) histogram analysis provide a global measure of disease burden in multiple sclerosis (MS). Previous studies have shown evidence of MTR abnormalities in normal appearing white matter (NAWM) or brain tissue (NABT) in MS patients with well established disease. The earliest development of MTR changes in NABT is not fully defined. Clinically isolated syndrome (CIS) is the first identifiable clinical event in MS, although not all CIS develop clinically definite MS. Previous MTR studies of small series of patients with clinically isolated syndromes (CIS) showed conflicting results, suggesting that these widespread changes may occur latter.

Aim:

To determine if normal appearing brain tissue (NABT), normal appearing gray matter (NAGM) and normal appearing white matter (NAWM) MTR abnormalities occurred early in the clinical course of RRMS or before the diagnosis of MS (CIS).

Methods:

Subjects included 40 CIS patients (within 3 months of the demyelinating event), 28 early RRMS (within 2 years of first MS attack) and 51 matched controls. At the time that the MTR scan was performed, patients had a standardized neurologic examination and disability assessment using the 10-point Kurtzke Expanded Disability Status Scale (EDSS). 2D-SE MT imaging was performed with a GE 1.5 Tesla signa scanner. Slice thickness was 5mm with no gap (TE 30/80 ms, TR 1720 ms, 2kHz off resonance sinc pulse, 0.75 NEX). MTR was calculated for each pixel as ([Mo-Ms])/Mo)x100 percent units (pu). Interleaved T2-weighted (T2W) images were segmented into grey, white matter, or CSF using SPM99. T2 lesion masks were created using Dispimage (Plummer, Department of Medical Physics & Bioengineering, Universtiy College London Hospitals NHS Trust, London, UK). MTR histograms were acquired for NABT, NAGM and NAWM after extracting lesion masks. Brain parenchymal fraction (BPF) was calculated from the segmented images as brain parenchyma (grey and white matter and lesions) divided by total intracranial contents (brain parenchyma and CSF volumes).

Results:

The CIS cohort (N=40) was 58% female with a mean age of 34 years (SD ±9), and 17/40 had no T2W lesions. The RRMS cohort (N=28) were 68% female with a mean age of 36 years (SD ±7) and all had T2W lesions. The early RRMS patients had a larger median T2 lesion load (6.0 ±13.3 vs 0.8 ±1.9 ml) and lower mean lesion MTR (30.6 ±2.2 vs 32.1 ±2.0 pu) than the CIS patients. NABT, NAGM and NAWM mean MTR were significantly reduced in CIS and early RRMS patients compared to gender and age matched controls (Table). Patients without T2W lesions also had a significant decrease in NABT mean MTR. Whole brain atrophy (BPF) was only seen in early RRMS. CIS patients also had a significant decrease in NAWM mean MTR (37.3 versus 37.5 pu, $p = 0.002$) and NAGM (31.4 versus 31.7 pu, $p < 0.05$) compared to controls. Subtle white matter atrophy was also detected in CIS patients (WMF 0.351 ±0.019 versus 0.362 ±0.018, $p < 0.05$) compared to controls.

Table: NABT MTR Histogram findings and atrophy (BPF) in CIS and Early RRMS

Measure	Control N=51	CIS without lesions N=17	CIS with lesions N=23	Early RRMS N=28
BPF	0.854 ±0.016	0.851 ±0.021	0.848 ±0.021	0.843* ±0.027
NABT avg MTR	34.3 ±0.4	34.0** ±0.3	33.9** ±0.5	33.3*** ±0.91
% Decrease		-0.9%	-1.2%	-3.1%
Peak height	10.4 ±0.8	10.0 ±0.7	10.1 ±0.7	10.1 ±0.9
Peak location	37.1 ±0.7	36.7 ±0.6	36.6** ±0.7	36.0*** ±0.9
25th percentile	32.0 ±0.6	31.4** ±0.5	31.4** ±0.6	30.8*** ±1.2
50th percentile	35.2 ±0.5	34.8 ±0.4	34.6* ±0.5	34.2*** ±0.8
75th percentile	37.7 ±0.5	37.3 ±0.5	37.2* ±0.5	36.8*** ±0.8

*$p<0.05$, **$p<0.01$, ***$p<0.001$ Mann-Whitney Test compared to controls. ± Standard Deviation

Conclusion:

Subtle NABT abnormality is detected in patients with CIS before the diagnosis of MS and are more pronounced in patients with early RRMS. Abnormalities are seen both in normal appearing white matter and normal appearing gray matter. Patients without T2W lesions also have abnormal NABT MTR despite being at a lower risk of developing MS and disability. MTR changes may represent a susceptibility to experiencing a demyelinating event, and may not be prognostic for disease progression.

References:

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