MTR abnormalities in relapse onset MS patients 20 years after the onset of disease.

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Background: In multiple sclerosis (MS) the relationship between the white matter (WM) lesion load on conventional MRI and clinical disability is only moderate[Brex *et al.* 2002]. Abnormalities within normal-appearing (NA)WM and NA grey matter (GM) as detected by magnetization transfer (MT) MRI occur at the earliest clinical stages of MS [Fernando *et al.* 2005] and increase over time. MT could provide markers reflecting the more disabling features of MS. There are studies suggesting that the GM pathology is one of the key factors associated with disability [Agosta *et al.* 2006].

Aim: To evaluate whether MTR abnormalities within NAGM and NAWM were correlate with clinical disability after 20 years disease duration in a unique cohort of patients who have been followed from first presentation with a clinically isolated syndrome (CIS) suggestive of MS.

Methods: We studied 62 (23 CIS; 3 clinically probable MS; 27 relapsing-remitting and 9 secondary progressive MS) patients after a mean of 19.5 years (range 17.6 – 21.6) from their first episode of CIS (41 women and 21 men; mean age = 51 years, range 39-68); median Expanded Disability Status Scale score (EDSS) for all patients 2.5, (range 0-8) and for MS patients only, 3.0 (range 1-8). MTR was also obtained in 33 healthy controls (20 women and 13 men; mean age = 38.4 years, range 26 – 60). Clinical measures in patients included EDSS and multiple sclerosis functional composite (MSFC).

The following sequences of the whole brain were obtained, using a 1.5 T scanner, from all subjects with matrix=256x256; FOV=24cm^2; 28 5 mm slices: A) 2D interleaved dual spin echo (TR=1720 ms; time TEs=30/80 ms). Both echoes are acquired with and without a MT presaturation pulse to calculate a MTR map [Barker *et al.* 1996]; B) 2D dual echo fast spin echo (FSE) sequences (TR=2000 ms; TE=16/96 ms); C) 2D T_1-weighted spin echo (TR=540 ms, TE=20 ms). Sequences A and B were co-registered using FLIRT (www.fmrib.ox.ac.uk/fsl/).Lesions were outlined on sequence B (short echo) and sequence C using a semi-automated method to calculate T_1 and T_2 (sequence B long echo) lesion volumes (LV). SPM2 was used to segment the long echo images from sequence A into GM, WM and CSF. These were combined to obtain WM, GM, and whole brain masks. Lesions were then removed to obtain NAWM, NAGM and NA brain tissue (BT) masks which were applied to the calculated MTR map. A 10pu threshold was applied and two successive erosions of WM and a single erosion of the GM minimised partial volume effects. Normalized WM, GM, whole brain (WB), NAWM, NAGM, NABT and lesion histograms were generated with a bin width of 0.1 pu and a smoothing window of +/- 0.3pu. The peak height (PH), peak location and average MTR were extracted for WB, GM, WM, NABT, NAGM, NAWM and lesions. A univariate general linear model was used to compare the PH between controls, CIS and MS patients. Spearman rank correlation was used for the correlation between PH of the NABT, NAGM, NAWM, lesions and EDDS and MSFC scores, T_2LV and T_1LV.

Results: There was a difference of the GMPH between MS patients and controls (p=0.005) and MS patients and CIS (p= 0.001) but not between the controls and CIS patients (p=0.93). The GMPH and lesion PH correlated with EDDS and MSFC and with T_2 and T_1LV in the whole patient group and in those who developed MS (see table 1).T_2 and T_1LV correlated moderately with EDSS (r_s=0.49; p<0.001); (r_s=0.53; p<0.001)and MSFC (r_s= - 0.54; p<0.001); (r_s= - 0.50; p<0.001) for all patients as well as in the group of MS patients alone {(r_s=0.56; p<0.001), (r_s=0.57; p<0.001)} and {(r_s=-0.59; p<0.001); (r_s=-0.55; p=0.001)} respectively.

MTR-PH	EDSS	MSFC	T_2LV	T_1LV
NABT (all)	r_s=-0.41; p=0.001	r_s=0.25; p=0.06	r_s=-0.26; p=0.03	r_s=-0.30; p=0.01
NABT (MS)	r_s=-0.38; p=0.02	r_s=0.19; p=0.27	r_s=-0.25; p=0.13	r_s=-0.36; p=0.03
NAGM (all)	r_s=-0.58; p<0.001	r_s=0.47; p<0.001	r_s=-0.46; p<0.001	r_s=-0.43; p<0.001
NAGM (MS)	r_s=-0.60; p<0.001	r_s=0.44; p=0.009	r_s=-0.45; p=005	r_s=-0.49; p=0.002
NAWM (all)	r_s=-0.29; p=0.01	r_s=0.19; p=0.15	r_s=-0.12; p=0.34	r_s=-0.13; p=0.31
NAWM (MS)	r_s=-0.21; p=0.21	r_s=0.10; p=0.56	r_s=-0.30; p=0.07	r_s=-0.34; p=0.03
Lesions (all)	r_s=-0.57; p<0.001	r_s=0.50; p=0.001	r_s=-0.77; p<0.001	r_s=-0.87; p<0.001
Lesions (MS)	r_s=-0.51; p=0.001	r_s=0.44; p=0.002	r_s=-0.71; p<0.001	r_s=-0.81; p<0.001

Table 1: Correlation of the MTRPH with EDSS, MSFC, T_1LV and T_2LV for all patients and for MS group.

Conclusion: This study indicates that the severity of the NAGM damage – inferred from the reduction of MTR-PH - is significantly related to disability in MS patients with a long disease duration (~20 years). WM lesion volume is also related to disability. Because the correlations of GMPH MTR with WMLV are only moderate, (range -0.43 to - 0.51) the contribution of the GM pathology and WM lesions to disability may be partly independent.

Reference List

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