A regression analysis of MTR in early relapsing-remitting MS: evidence that normal appearing white matter abnormality predates symptom onset.

G. R. Davies[1], D. Altmann[1], W. Rashid[1], C. Griffin[1], D. Chard[1], P. Tofts[1], G. Barker[1,2], D. Miller[1]

[1]NMR Unit, Institute of Neurology, London, United Kingdom, [2]Neuroimaging Research Group, Institute of Psychiatry, London, United Kingdom

Introduction The magnetization transfer ratio (MTR) is sensitive to normal appearing white matter (NAWM) abnormality in multiple sclerosis (MS), prior to the onset of permanent disability (1). However, if MTR can also detect a change in NAWM over time, particularly in patients with minimal disability then it might make a useful surrogate marker in clinical trials. A preliminary result suggesting that, in early MS, MTR is sensitive to NAWM change over time has been reported (2). We now present serial MTR data from the same cohort (with additional data points), using a regression analysis to assess the gradient of NAWM change over time.

Methods Twenty three patients with early relapsing remitting MS (RRMS) (4 male and 19 female, mean age 37 mean disease duration at baseline 1.9 years (range 0.5-3.7); median EDSS 1.0 (range 0-3)) and 19 healthy controls (9 male and 10 female, mean age 34) were imaged yearly. Mean follow up was 24 months for MS subjects and 18 months for controls. All imaging was performed on a 1.5 Tesla Signa (GE, USA). For MTR determination a 2D SE magnetization transfer (MT) imaging sequence (3) (TR: 1500ms TE: 19/90 ms. 28 contiguous 5mm axial slices covering the whole brain) were acquired both with and without presaturation. The MT pulse was a Hamming apodised sinc 64 ms in duration and 2 kHz off resonance. Saturated and unsaturated images were interleaved resulting in inherently registered saturated and unsaturated data sets. MTR was calculated from the short echo images on a pixel by pixel basis according to {[Mo-Ms]/[Mo]} x 100 percent units (pu). Lesions were contoured on the unsaturated proton density weighted images using Dispimage (Plummer, UCL). T_2 weighted images from the MT data set were processed in SPM99 to create white matter (WM), grey matter (GM) and CSF probability maps. The WM and GM maps were then combined to create whole brain masks and, using these, non-brain parenchyma was removed from the MTR map. A maximum likelihood algorithm using the three SPM probability outputs then extracted the WM segment from the MTR map and the signal intensity of lesions was set to zero to leave only NAWM. Partial volume voxels were minimized with a 10 pu threshold and 2 successive boundary erosions. Normalized NAWM histograms were generated with a bin width of 0.1pu and a smoothing window of +/- 3pu and mean MTR was calculated from the histogram. A hierarchical regression model was used to assess the gradient of decrease (and the patient vs control difference in gradient) in MTR with time allowing for intra- and inter-subject variability. An ordinary least squares regression was used to assess the difference at baseline in mean MTR between MS patients and controls. There was no evidence of age or gender confounding, and these terms were omitted from final models.

Results The mean NAWM MTR at baseline in MS patients was 37.8pu, (SD 0.5pu) versus 38.3pu, (SD 0.4pu) in controls, $p = 0.002$. In controls there was no significant change in MTR over time: rate of change per day = +0.0001pu, $p = 0.26$, 95% CI: -0.0001pu, +0.0003pu. In MS patients, there was a significant reduction in MTR with time: rate of change per day = -0.0003, $p < 0.001$, 95% CI: -0.0004pu, -0.0001pu. (There was also a significant rate of change relative to controls, $p < 0.001$.) There was no evidence of non-linearity in MTR changes detected by the model and so, assuming linearity and a zero gradient in controls, backwards extrapolation of the gradient suggests that NAWM MTR abnormality was present 1180 days (95% CI bootstrap: 4740 days, 340 days) prior to clinical onset.

Conclusions The study indicates that MTR is sensitive to progressive NAWM changes in early RRMS in the absence of significant disability. MTR is likely to be sensitive to a number of pathological processes known to occur in MS NAWM including inflammation, gliosis and axonal loss (4,5). Such processes may be contributing to the ongoing changes seen in MTR. The backward extrapolation of NAWM MTR change suggests that the NAWM abnormality predates symptom onset by 3.2 years and this implies that a subtle disorder of NAWM may be one of the earliest events in the pathogenesis of MS. Alternatively, if the linear assumption is not correct, only a substantially steeper decline in NAWM MTR during early pathogenesis would be consistent with this data.

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