Grey matter magnetization transfer ratio reflects clinical evolution in primary progressive multiple sclerosis: a longitudinal study

Z. Khaleeli[1], D. Altmann[1,2], M. Cercignani[1], O. Ciccarelli[1], D. Miller[1], and A. Thompson[1]

[1]Institute of Neurology, London, United Kingdom, [2]London School of Hygiene and Tropical Medicine, London, United Kingdom

Introduction: Reliable surrogate and prognostic markers are needed to address the wide variation in outcome in primary progressive MS (PPMS), particularly in clinical trials. Magnetization transfer imaging (MTI) is a promising technique which may be appropriate to monitor progressive neurological changes. For the first time we examined MTI in early PPMS, over a period of three years, together with T2 lesion load and brain volume. We aimed to determine whether MT changes reflected concurrent clinical changes, and to identify the best baseline MRI predictor of clinical progression.

Methods: *Subjects:* Forty-seven patients with PPMS (19 female; mean age 45.13 yrs, range 19-65; median expanded disability status scale [EDSS] 4.75, range 1.5-7; mean disease duration 3.4 years, range 2-5) and 18 controls (10 females, mean age 34.6 years, range 27-52) were scanned six-monthly over three years, and patients were clinically assessed at each time-point. Age and gender differences between the patient and control group were adjusted for at each stage of the analysis. *Images:* The protocol, performed on a 1.5T scanner, consisted of: (1) MTI using a 2D interleaved dual-echo spin echo sequence[1] (28 contiguous axial slices, TR=1720ms, TEs=30/80 ms, NEX=0.75, acquired matrix 256x128, reconstructed matrix 256x256, and FOV 240x240mm), acquired with and without a saturation pulse. (2) a 3D inversion-prepared fast spoiled gradient recall (3D FSPGR) of the brain (124 contiguous axial slices, TR 13.3 ms, TE 4.2ms, inversion time 450 ms, matrix 256x160, FOV 300 x 225mm, and a slice thickness of 1.5mm). The scanner was upgraded during the study, and the gradient amplifiers, but not the gradient coils, were changed. Maximum gradient strength increased from $22mTm^{-1}$ to $33mTm^{-1}$.The TR of the FSPGR was reduced to 10.9 ms, and all other imaging parameters remained the same. The upgrade was accounted for at each stage of the statistical analysis. *Post-processing:* In patients, lesions were delineated on the unsaturated PD images. Binary lesion masks were created for each patient. In SPM2, the FSPGR was segmented, applying a likelihood threshold of 0.75 to the white matter (WM) and grey matter (GM) segments. This ensured that only voxels with a high likelihood of containing the correct tissue for each segment were included. GM and WM volumes were recorded. The FSPGR was co-registered to the MTI, and the transformation parameters were applied to GM and WM probability maps. In patients, lesion masks were used to remove lesional tissue and produce GM and normal appearing white matter (NAWM) masks. The masks were applied to the calculated MTR images to obtain MTR maps of the GM and NAWM, and normalized MTR histograms were generated for the GM and NAWM segments. The mean, peak height (PH) and peak location (PL) from each histogram in each patient were obtained. *Statistical analysis:* The statistical analysis was carried out using STATA (http://www.stata.com). A piecewise mixed effect linear regression model, adjusted for the upgrade, age and gender, was fitted to calculate the rate of change in MTR, brain volume and lesion load over time, and the association between rate of change in the radiological variables and the EDSS. Multiple proportional odds ordinal logistic regression models determined whether the extent of EDSS deterioration was predicted by baseline MTR, brain volume or T2 lesion volume.

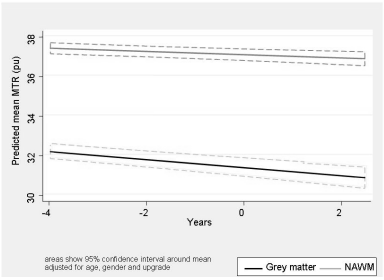

Fig 1. Longitudinal changes in mean grey and NAWM MTR in patients

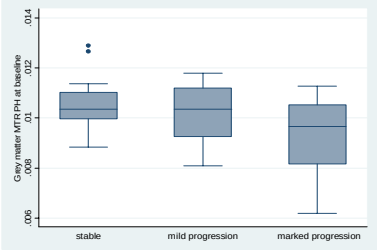

Fig 2. Grey matter PH MTR predicts extent of clinical progression on EDSS

Results: *Longitudinal changes:* In patients, mean GM MTR declined at a rate of 0.20 pu per year and mean NAWM MTR at a rate of 0.087pu per year ($p<0.001$). This was significantly different from controls ($p<0.001$), in whom no changes were seen. In patients, mean GM volume decreased at a rate of 3.98ml per year ($p<0.001$) which was significantly different from controls ($p=0.005$), in whom there was no significant change; decrease in NAWM volume was not significant in patients or controls. T2 lesion volume increased by 2.8ml per year ($p<0.001$). *Correlation between rates of change in radiological and clinical variables:* In the GM, more rapid progression on the EDSS was associated with more rapid decrease in mean MTR ($p=0.032$, 95%CI -0.82 to -0.003, coefficient -0.04) and PL MTR ($p=0.008$, 95%CI -0.12 to -0.2, coefficient -0.07). Rate of change in GM and NAWM volume was not associated with rate of change in EDSS. Greater rate of increase in T2 lesion load was associated with faster progression on EDSS ($p=0.024$, 95% CI 0.09 to 1.31, coefficient 0.70). *Baseline radiological predictors of clinical progression over three years:* In the GM, lower baseline mean MTR (OR 2.33, $p=0.015$, 95%CI 0.21 to 0.844) and PH predicted extent of progression (OR 2.44, $p=0.008$, 95%CI 0.215 to 0.79). In the NAWM, PL significantly predicted progression (OR=2.5, $p=0.039$, 95%CI 0.17 to 0.96). Lower baseline GM volume (OR 1.46, $p=0.039$, 95%CI 0.50-0.98) and lower baseline NAWM volume ($p=0.032$, 95%CI 0.56 to 0.97, odds ratio 1.36) predicted the extent of clinical progression. T2 lesion load predicted also predicted progression(OR 1.03, $p=0.022$, 95%CI 1.00 to 1.06). However, when all significant univariate predictors were modeled together, only GM PH MTR remained significant ($p=0.037$, 95%CI 0.23 to 0.96, OR 2.2).

Conclusions: We have shown for the first time that GM MTR can be used as a surrogate marker to monitor and predict medium term clinical progression in early PPMS. GM MTR is a very practical tool for use in clinical trials: our images were acquired on a standard 1.5T scanner over 20 minutes, and the technique has the potential to be reproducible across multiple centres (2). Further work is now necessary to validate this measure in larger studies, and for the wider application of the technique in other MS subtypes and other diseases.

References: (1)Barker GJ, Tofts PS, Gass A. An interleaved sequence for accurate and reproducible clinical measurement of magnetization transfer ratio. *Magn Reson.Imaging* 1996;14:403-11 (2) Tofts PS, Steens SC, Cercignani M, dmiraal-Behloul F, Hofman PA, van Osch MJ, Teeuwisse WM, Tozer DJ, van Waesberghe JH, Yeung R, Barker GJ, van Buchem MA. Sources of variation in multi-centre brain MTR histogram studies: body-coil transmission eliminates inter-centre differences. *MAGMA.* 2006;**19**:209-22.