Deep Gray Matter 'Black T2' Correlates with Disability in the Minocycline Treated Multiple Sclerosis Patients

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Introduction

MR imaging measures have become the most advanced biomarker candidates for multiple sclerosis (MS) over the last decade. However, clinicians still lack an ideal MRI surrogate that correlates with patient disability strongly. Abnormally decreased signal intensity (SI) on T2-weighted MRI (black T2, BT2) in the deep grey matter (GM) of MS patients has been found to be associated with disease course, duration, and neurological impairment at 1.5T.[1] The BT2, likely due to increased iron deposition, is proportional to the square of MR field strength.[2] Accordingly, a better correlation is observed between disability and deep GM BT2 measured at 3T than that at 1.5T.[3] We have been investigating the role of minocycline as a disease modifying therapy in MS.[4] The goal in the current study was to quantify deep GM BT2 on 3T MRI and its relationship with physical disability over three years in a small group of MS patients treated with minocycline.

Subjects and Methods

Ten relapsing-remitting MS patients [mean age 42.8 years, mean disease duration 11.8 years, median extended disability status scale (EDSS) 2.7] were recruited. All the patients were imaged pre-treatment (at baseline), at 6 months, and then annually during treatment with minocycline on a 3T MR Scanner (GE Signa, WI). T2-weighted MR images were acquired using a fast spin echo sequence with parameters: TR/TE = 2716/80ms, matrix = 512x512, slice thickness = 3mm, no gap. Intrasubject 3D co-registration between time points was applied after image non-uniformity correction. The SI of deep GM structures including the head of caudate, thalamus, globus pallidus, putamen, red nucleus, and substantia nigra (Fig. 1), were measured for each patient.[3] The combined mean deep GM SI (the BT2) at each time point was obtained by averaging the SI in deep GM structures from all patients. The BT2 difference between time points was analyzed using one-way ANOVA. Pearson Correlation was performed to assess the relationship between deep GM BT2 and EDSS. A confidential level of $\alpha = 0.05$ was set as significant in all cases.

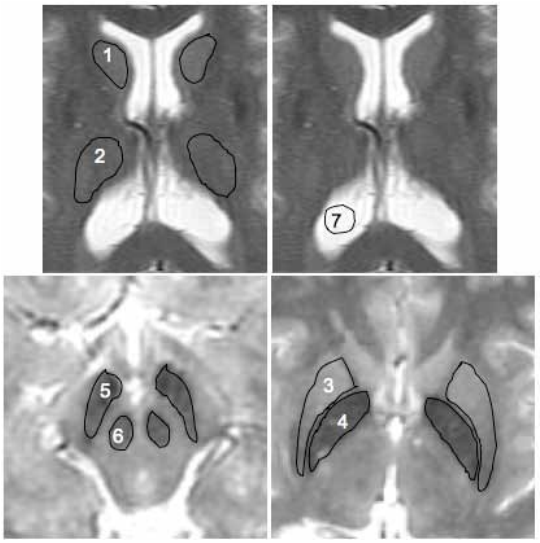

Fig.1 : Example deep GM ROIs drawn on the 3T T2w MRI from a RRMS patient, namely (from 1-6): head of caudate nucleus, thalamus, globus pallidus, putamen, substantial nigra, and red nucleus. The ROI 7 of CSF is used to normalize SI in that of deep GM structures.

Results

Ten patients were enrolled but only eight completed months 12, 24, and 36 scans. There was no significant difference between deep GM BT2 measured at baseline, and at months 6, 12, 24, and 36 on treatment ($P > 0.05$) because of our small sample size. However, a strong correlation between deep BT2 and EDSS was observed in patients treated with minocycline ($P < 0.01$) (Fig. 2).

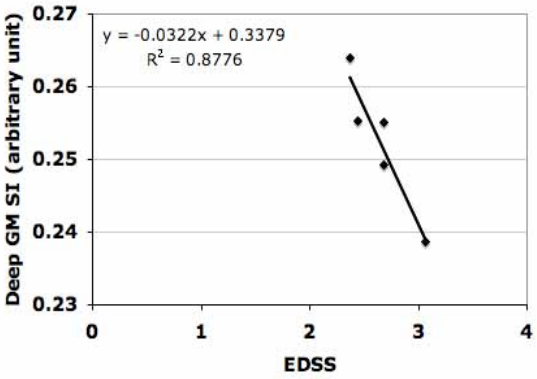

Fig. 2: A strong correlation between deep GM BT2 and patient EDSS score was obtained.

Discussion and conclusions

This small study shows that deep GM BT2 is associated with patient disability in MS. While not directly confirmed in MS, deep GM BT2 is shown to correspond to iron accumulation in other neurological disorders.[5] Iron in the central nervous system is enriched in the oligodendrocytes and myelin. Therefore, oligodendrocyte dysfunction in MS may lead to excessive iron deposition. Although the clinical significance of BT2 is not fully understood, when measured at 3T it explains more of the variance of disability than brain atrophy ($r^2 = 0.08 – 0.17$)[6] in MS. The lack of sustained disability worsening over 3 years is consistent with other beneficial effects of minocycline in MS showing rapid resolution of Gd-enhancing MRI activity,[4] decreased proportion of new T1 black holes[7], and sustained reduction of brain atrophy rate (data in submission). This preliminary study suggests that BT2 has potential to become a MRI surrogate measure of disability in patients with MS. Further investigation is quarantined to confirm the significance of BT2 as a biomarker in MS at high field MR.

References

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