Deep grey matter iron deposition and brain atrophy in early multiple sclerosis: a longitudinal study

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TARGET AUDIENCE: Clinicians, basic scientists interested in disease mechanisms of early multiple sclerosis (MS).

PURPOSE: MS is an autoimmune neurologic disease whose hallmark is inflammatory demyelination of the white matter. In the past decades, a role for dysregulation of iron homeostasis and neurodegeneration has become apparent. Recent MRI studies have demonstrated that iron deposits in deep grey matter (DGM) nuclei are established at first clinical presentation of MS[1]. These findings challenge the commonly held view of MS as a disease primarily of the white matter; however, further work remains to characterize DGM iron accumulation early in MS and any links with neurodegeneration. The objectives of this longitudinal study are (1) to identify DGM structures in which iron accumulates in early MS; and (2) to identify any correlations of iron with a metric of brain volume loss.

METHODS: Imaging. Twenty patients with clinically isolated syndromes (CIS) suggestive of early MS and 15 age- and sex-matched healthy controls (HC) were recruited. Participants were imaged consecutively at 4 month intervals for between 12 and 20 months. Imaging was performed on a 3T system [3D multi-echo GRE (0.5x0.5x1.0 mm^3) and 3D T1-weighted MPRAGE (0.5x0.5x1.0 mm^3)].

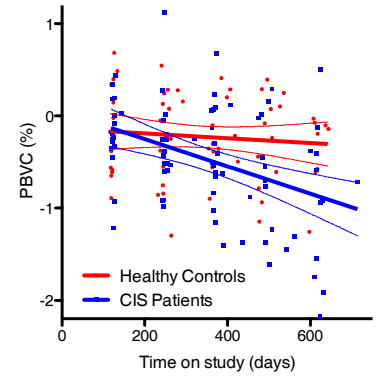
Image processing. To quantify iron, maps of the effective transverse relaxation rate (R2*) were computed from the multi-echo gradient echo data; R2* correlates linearly with iron concentrations[2]. Masks of DGM structures were generated from T1-weighted volumes using an automated segmentation tool. R2* maps were co-registered to T1-weighted volumes so that the same masks could be applied to compute mean R2* in certain DGM nuclei. To quantify atrophy relative to baseline, for each visit other than the first, the percentage brain volume change (PBVC) was calculated from T1-weighted volumes using an automated tool.

Statistical analyses. Mixed model analyses were employed to compare rates of change of R2* or PBVC between groups. The mixed model is a statistical model that models both fixed (within subject) and random (between subject) effects, making it ideal for studying repeated measurements on groups of subjects in a longitudinal study. Terms in each mixed model included group, age, time on study, and an interaction term between group and time on study, thus allowing comparison of rate of change of the dependent variable between groups. Dependent variable was mean R2* in each of four DGM nuclei (thalamus, caudate, putamen, pallidum) or PBVC.

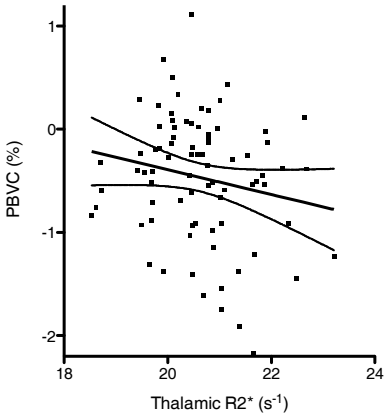
To evaluate an association between PBVC (atrophy) and R2* (iron), additional mixed model analyses were subsequently performed on CIS patients only with PBVC as the dependent variable, and additional terms of age, time on study, and mean R2* in DGM nuclei where a significant interaction term was identified previously.

RESULTS: In the first set of mixed model analyses, rates of change of mean R2* in 4 DGM nuclei or PBVC were compared between HC and CIS. A significant difference in slopes was identified for two DGM nuclei: the thalamus and putamen. Differences in slopes are listed in the Table, as well as the models' solutions for age-adjustment. A significant difference (-0.48 %/year, P<0.001) in slopes between groups was found for PBVC vs. time on study; this is shown in the upper Fig. at right.

	Difference in slopes: [CIS–HC]	Age (covariate)
Thalamus	+0.27 s^{-1}/yr (*P*=0.064)	+0.04 s^{-1}/yr (*P*=0.030)
Putamen	+0.60 s^{-1}/yr (*P*=0.025)	+0.24 s^{-1}/yr (*P*<0.001)



Subsequently, an association between PBVC and mean R2* in thalamus or putamen was evaluated with additional mixed models in CIS patients only (notably, corrected for time on study and age). A significant association was found only for the thalamus (-0.19 %/s^{-1}, P=0.025) which is readily evident from a plot of PBVC vs R2* (lower Fig.). Regressions lines with 95% confidence intervals are shown for illustrative purposes and do not represent the complete mixed model solution.



DISCUSSION: In early MS, iron accumulates in DGM at rates that significantly exceed what is seen in healthy controls due to normal aging. Significant brain volume loss relative to controls is also seen; this is in keeping with previous studies[3]. While the role of iron accumulation in causing/being caused by tissue loss is unclear, it is evident that the two are associated in the case of the thalamus. This is notable, as previous studies have suggested that damage to the thalamus occurs early in MS and may be important in determining the clinical picture[1,4]. An association between iron accumulation and clinical outcomes was not investigated in this study; it remains uncertain if iron deposition will prove a target for future therapies.

CONCLUSION: Enhanced deep grey matter iron accumulation is on-going in early MS. Patients with early MS also have increased atrophy compared to healthy controls. A significant association between thalamic iron and rates of brain volume loss suggests additional disease mechanisms are at play beyond inflammatory demyelination early in MS.

REFERENCES: 1. Quinn et al. MSARD 2013; 3. 2. Yao et al. NeuroImage 2009; 44.
3. Pelletier et al. J Neuroimaging 2004; 14. 4. Minagar et al. Neurology 2013; 80.