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Age independently affects myelin integrity as detected by magnetization transfer magnetic resonance imaging in multiple sclerosis

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ABSTRACT

Background: Multiple sclerosis (MS) is a heterogeneous disorder with a progressive course that is difficult to predict on a case-by-case basis. Natural history studies of MS have demonstrated that age influences clinical progression independent of disease duration.
Objective: To determine whether age would be associated with greater CNS injury as detected by magnetization transfer MRI.
Materials and methods: Forty MS patients were recruited from out-patient clinics into two groups stratified by age but with similar clinical disease duration as well as thirteen controls age-matched to the older MS group. Images were segmented by automated programs and blinded readers into normal appearing white matter (NAWM), normal appearing gray matter (NAGM), and white matter lesions (WMLs) and gray matter lesions (GMLs) in the MS groups. WML and GML were delineated on T2-weighted 3D fluid-attenuated inversion recovery (FLAIR) and T1 weighted MRI volumes. Mean magnetization transfer ratio (MTR), region volume, as well as MTR histogram skew and kurtosis were calculated for each region.
Results: All MTR measures in NAGM and MTR histogram metrics in NAWM differed between MS subjects and controls, as expected and previously reported by several studies, but not between MS groups. However, MTR measures in the WML did significantly differ between the MS groups, in spite of no significant differences in lesion counts and volumes.
Conclusions: Despite matching for clinical disease duration and recording no significant WML volume difference, we demonstrated strong MTR differences in WMLs between younger and older MS patients. These data suggest that aging-related processes modify the tissue response to inflammatory injury and its clinical outcome correlates in MS.

1. Introduction

Multiple sclerosis (MS) is a clinically heterogeneous disease most commonly presenting in young adults with a relapsing–remitting (RRMS) course. For the majority, the course of disease eventually becomes progressively disabling (secondary progressive, SPMS).

Natural history studies have demonstrated that age affects disease progression independent of disease duration (Koch et al., 2007; Scalfari et al., 2011). Latency to development of SPMS is reduced in older patients, with age of onset representing an independent predictor for time to progression (Koch et al., 2007). Indeed, the effects of age on progressive disability occur despite variation in the initial disease pattern preceding SPMS (Confavreux and Vukusic, 2006). Aging-associated delay in remyelination may underlie this phenomenon. Complete remyelination of gliotoxin-induced demyelination occurs faster in younger rats when compared with older rats (Shields et al., 1999) and by pairing their circulatory systems, it was demonstrated that exposure of older mice to the circulatory systems of younger mice led to a restoration of youthful remyelinatory potential (Ruckh Julia et al., 2012).

Abbreviations: MTR, magnetization transfer ratio; NAWM, normal appearing white matter; NAGM, normal appearing gray matter; WM, white matter; GM, gray matter; WML, white matter lesion; GML, gray matter lesion.

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Although magnetic resonance imaging (MRI) has revolutionized clinical practice in MS (McDonald et al., 2001; Polman et al., 2011) parameters derived from conventional MRI have limited correlations with clinical measures of disability (Filippi et al., 1995a). While MRI is sensitive in identifying focal white matter MS lesions, conventional T1- and T2-weighted MR protocols cannot readily detect subtle changes in normal appearing white matter (NAWM) (Filippi and Agosta, 2007) nor cortical gray matter lesions, which have been demonstrated at post-mortem (Evangelou et al., 2000). Magnetization transfer (MT) parameters have been used to detect and quantify changes occurring outside lesions identified on conventional MRI. MT contrast represents proton interactions between free fluid and macromolecules, such as myelin (Filippi and Agosta, 2007) and provides a potential in vivo biomarker of ultrastructural integrity which is sensitive to pathology in vivo in a variety of neurological diseases, including MS. The most widely examined MT contrast parameter is the magnetization transfer ratio (MTR), representing the percentage reduction of MR signal when applying off-resonance radiofrequency irradiation. Reduced MTR suggests reduced exchange between macromolecular-associated and free water, most likely due to a reduction in the size of the macromolecular pool.

Mean MTR signals in NAWM are lower in MS patients, compared with controls (Filippi et al., 1995b), and MTR in the GM has been shown to predict disability progression (Agosta et al., 2006). The precise nature of tissue damage associated with MTR abnormalities is under contention; some studies have demonstrated strong correlations between myelin content and MTR (Schmierer et al., 2004), while others have demonstrated correlations between MTR and axonal density in both lesions and NAWM (van Waesberghe et al., 1999).

Here, in order to investigate the biological substrates underlying the clinical effects of age in MS, we examined to what extent CNS tissue injury differs amongst older and younger MS patients. We therefore selected two groups of MS patients differing by age but not by the duration of their disease and one healthy control cohort age-matched to the older MS patients to account for and interpret any age-related differences from normal aging. We examined the MTR distribution in visible white matter lesions and normal appearing gray and white matter.

2. Materials and methods

2.1. Patients

Forty patients with rapidly evolving MS enrolled in the Medical Research Council-funded Patient Research Cohort Rapidly Evolving Multiple Sclerosis study (PRC-REMS [http://clinicaltrials.gov/ct2/show/NCT01044576]) and thirteen healthy controls enrolled in GSK-sponsored EMI115241 were selected for inclusion. The studies had ethical approval from the London — Chelsea NRES Committee (NHS REC Ref. 09/H0708/61) and Essex 1 Research Ethics Committee (Ref: 11/EE/0026), respectively, and all subjects gave full informed consent in writing. All MS patients included had a diagnosis of MS according to the revised McDonald's criteria (Polman et al., 2011) with RRMS or SPMS, disease duration ≤5 years from clinical diagnosis, EDSS score 2.0–6.0 at screening and meeting criteria for highly active and/or treatment-refractory MS activity defined as: (a) Two or more clinical exacerbations in the previous 12 months, regardless of treatment; OR: (b) one clinical exacerbation and sustained increase in EDSS of at least 1 point in the previous 12 months after receiving, declining or not tolerating immune-modifying treatment, OR: (c) evidence of gadolinium (contrast)-enhancement or increase of T2 lesion load at MRI after receiving, declining or not tolerating immune-modifying treatment. Patients were assigned to one of two cohorts depending on their age: 'young MS' aged 25–35 years [n = 20] or 'older MS' 45–60 years [n = 20], both ranges inclusive. Healthy control subjects were included in the 'older control' cohort to age-match the 'older MS' group. Cohort demographics common for all three groups are reported in Table 1. MS-relevant characteristics for the two MS groups are reported in Table 2. At the blinded MRI data quality check, two patients from the 'older MS' group had excessive movement artifacts and two healthy control subjects had incidental findings. These four subjects were excluded from their respective groups prior to analysis.

2.2. MRI acquisition

MRI images were acquired on a 3 Tesla Magnetom Verio scanner (Siemens Healthcare, Erlangen, Germany) at software version VB17 using a 12-channel phased array head coil with an 8-channel phased array neck coil. The following sequences were obtained in a single imaging session at a single site (Fig. 1).

Pre- and post-contrast T1-weighted 3D MPRAGE volumes were acquired based on the ADNI-GO recommended parameters (Jack et al., 2008): 256 × 192 mm field of view (FOV), 1 mm^3 isotropic resolution, parallel imaging (PI) factor of 2, in 5 m: 21 s. Gadolinium injection (Gadoterate meglumine, Dotarem, Guerbet, 0.1 mmol/kg) was given <5 min prior to the acquisition of the post-contrast volume.

A T2-weighted fluid-attenuated inversion recovery (FLAIR) 3D volume with 1 mm^3 isotropic resolution for the delineation of white matter lesions was acquired, using a 3D T2w variable-refocusing angle TSE readout (Mugler and Brookeman, 2003). 160 sagittal sections in a single 3D slab were acquired with the following parameters: echo time (TE) 395 ms, repetition time (TR) 5 s, inversion time (TI) 1800 ms, 250 × 250 mm FOV, and a PI factor of 2 in 5 m: 52 s.

Magnetization transfer (MT) images were acquired using two pseudo proton density weighted (PDw) 3D spoiled gradient echo acquisitions (fast low angle shot (FLASH)). Common parameters include: 256 × 240 mm FOV, 192 sagittal sections per 3D slab, 1 mm^3 isotropic resolution, parallel imaging factor of 2, TR of 27 ms with a flip angle of 5° in 7 m: 20 s, and 6 echoes acquired using 630 Hz/pixel bandwidth with TEs every 1.95 ms from 1.95 to 11.7 ms. Each high-bandwidth echo was summed to increase SNR without introducing off-resonance effects of low readout bandwidth (Helms and Dechent, 2009). One of these PDw volumes used an off-resonance MT pulse to add MT weighting (MTw), with a 12.24 ms duration Gaussian pulse at 2.2 kHz off resonance with a nominal flip angle of 540°.

All volumes were co-registered using the FSL Linear Image Registration Tool (FLIRT) (Jenkinson et al., 2002) to the MPRAGE volume to account for any movement between the acquisitions. MTR maps were calculated using the MTw and PDw acquisitions by the equation:

$$MTR = 100 \cdot (S_{PDw} - S_{MTw})/S_{PDw}. \quad (1)$$

2.3. MRI segmentation

Lesion segmentation in the MS cohorts was performed by a semi-automated thresholding technique with manual correction (Jim Version 6.0, http://www.xinapse.com/software.html) performed by a trained observer and corroborated by a second experienced observer, both blinded to age and clinical status. Areas were segmented from T1-weighted MPRAGE and T2-weighted FLAIR images to produce regions of interest (ROIs) representing white (WML) and gray matter lesions (GML). The FLAIR was used in conjunction with the MPRAGE due to advantages with respect to lesion conspicuity and detectability (Rydberg et al., 1994; Filippi et al., 1996).

Brain extraction and white/gray matter segmentation in all three groups was performed on T1-weighted images by an automated technique based on prior probabilities (Smith et al., 2002), subtracting the lesion masks from the tissue classifications in the MS groups to give normal appearing gray matter (NAGM) and white matter (NAWM). Segmentation masks were visually inspected by a trained observer, blinded to group, for assessment of the quality of segmentation.