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Longitudinal changes in myelin water fraction in two MS patients with active disease

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ABSTRACT

Multiple sclerosis (MS) is characterised by focal areas that undergo cycles of demyelination and remyelination. Although conventional magnetic resonance imaging is very effective in localising areas of damage, these techniques are not pathology specific. A newer technique, T_2 relaxation, can separate water from brain into three compartments: (1) a long T_2 component (>2 s) arising from CSF, (2) an intermediate T_2 component (~80 ms) attributed to intra- and extra-cellular water and (3) a short T_2 component (~20 ms) assigned to water trapped in between the myelin bilayers (termed myelin water). Histological evidence shows that myelin water is a specific marker of myelination. The goal of this work was to follow changes in total water content (WC) and myelin water fraction (MWF) in evolving MS lesions over one year. Multi-echo T_2 relaxation data was collected and used to measure water content and myelin water fraction from three new MS lesions in two patients. WC increased in the three large (>1 cm^3) lesions at lesion appearance and remained elevated in the central core. Two lesions showed low MWF in the core suggesting demyelination upon first appearance. At later time points, one lesion showed a decrease in volume of low MWF, reflecting remyelination whereas the volume of low MWF in the other lesion core remained constant. This work provides evidence that MWF and WC can monitor demyelination and remyelination in MS.

1. Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that is characterised by focal areas of varying degrees of inflammation and demyelination. Individual lesions, while appearing indistinguishable on conventional T_2 weighted images, demonstrate considerable heterogeneity on histopathologic evaluation with varying degrees of demyelination, axonal loss, inflammation and gliosis. Histological studies show evidence that cycles of demyelination and remyelination occurs in lesions [1], however, the timescales are unknown since pathological studies provide only one snapshot of the state of a lesion. Magnetic resonance imaging (MRI), which allows for in vivo measurement of lesions over time, is helpful to investigate chronological changes in MS brain [2]. Visualising demyelination and remyelination over time would add depth to the contribution of MRI to measuring the evolution of MS lesions.

T_2 relaxation is an MRI technique that enables separation of the tissue water signal from brain into three components: (1) a long T_2 component (>2 s) arising from CSF, (2) an intermediate T_2 component (~80 ms) attributed to intra- and extra-cellular water and (3) a short T_2 component (~20 ms) assigned to water trapped in between the myelin bilayers [3–6]. The sum of the signals from all three components is proportional to the total water content (WC) of the tissue and the fraction of signal from the myelin water component is termed the myelin water fraction (MWF). In order to determine quantitative values for WC and MWF, acquisition of T_2 relaxation was done on a single-slice otherwise off-resonance effects from other slices can affect the signal from the different water components [7]. Previous work has shown strong quantitative correlations between luxol fast blue histological staining for myelin and MWF, providing compelling evidence that the short T_2 component is a marker of myelin [8]. Prior work *in vivo* found the short T_2 component was variably decreased in MS lesions [3,9–11], and diffusely reduced in the normal appearing white matter (NAWM) when compared to healthy controls [10,12].

The goal of this work was to study the longitudinal changes in total water content (WC) and myelin water fraction (MWF), obtained from a single imaging slice, in newly appearing MS lesions. The fortuitous appearance of lesions on the slice of interest allowed observation of

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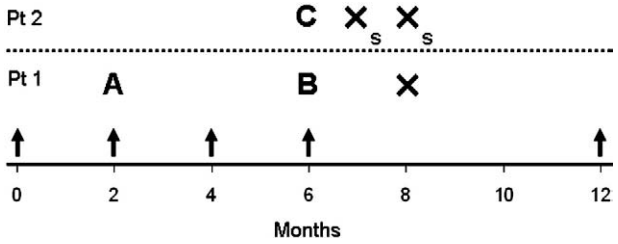

Fig. 1. Diagram of the timeline for scanning, lesion appearance and clinical relapses in both patients. Below the dashed line is data for patient 1 and above the dashed line is data for patient 2. Arrows indicate the time of scans, letters indicate the time of first appearance of new lesions A, B and C, and an X indicates the time of a clinical relapse with a subscript s indicating treatment with steroids.

WC and MWF before, during and after the formation of these new lesions.

2. Materials and methods

2.1. Patient selection

Seven subjects with multiple sclerosis volunteered for this study and signed an informed written consent approved by the Clinical Research Ethics Board of our institution. Of these subjects, two had large (>1 cm^3) lesions and were followed in this paper. Both patients had clinically definite MS according to the Poser criteria [13] and the presence of at least one enhancing lesion on a screening scan performed 4 weeks prior to the start of the study. They were two women aged 36 and 50 years with disease duration of 9 and 10 years, respectively. They both had relapsing MS and had been followed yearly in the UBC MS clinic since diagnosis. They had an EDSS of 2.5 and 3.0 at inclusion in the study. Both had declined disease modifying drugs. Patient 2 had received IV solumedrol 4 months prior to inclusion. They were followed for one year with scans at month 0, 2, 4, 6 and 12. Both had a clinical relapse between month 6 and month 12 scans. Patient 2 received IV methylprednisolone for this relapse 2 months before the final scan. Newly enhancing lesions that were greater than 1 cm^3 and had at least one follow-up scan were studied. Patient 1 had two lesions which qualified (lesions A and B) and patient 2 had one lesion (lesion C). A diagram indicating the time of scans, lesion appearance and clinical relapses for both patients is shown in Fig. 1.

2.2. MRI studies

Images were acquired using a 1.5 Tesla MR scanner (GE Medical Systems, Milwaukee, USA, version 5.7). First, proton density (PD) and T_2-weighted scans (TR 2500 ms, TE 30/90 ms, 22 contiguous slices, matrix 256×192) were obtained using a dual echo conventional spin echo sequence. T_2 relaxation was then measured using a single-slice

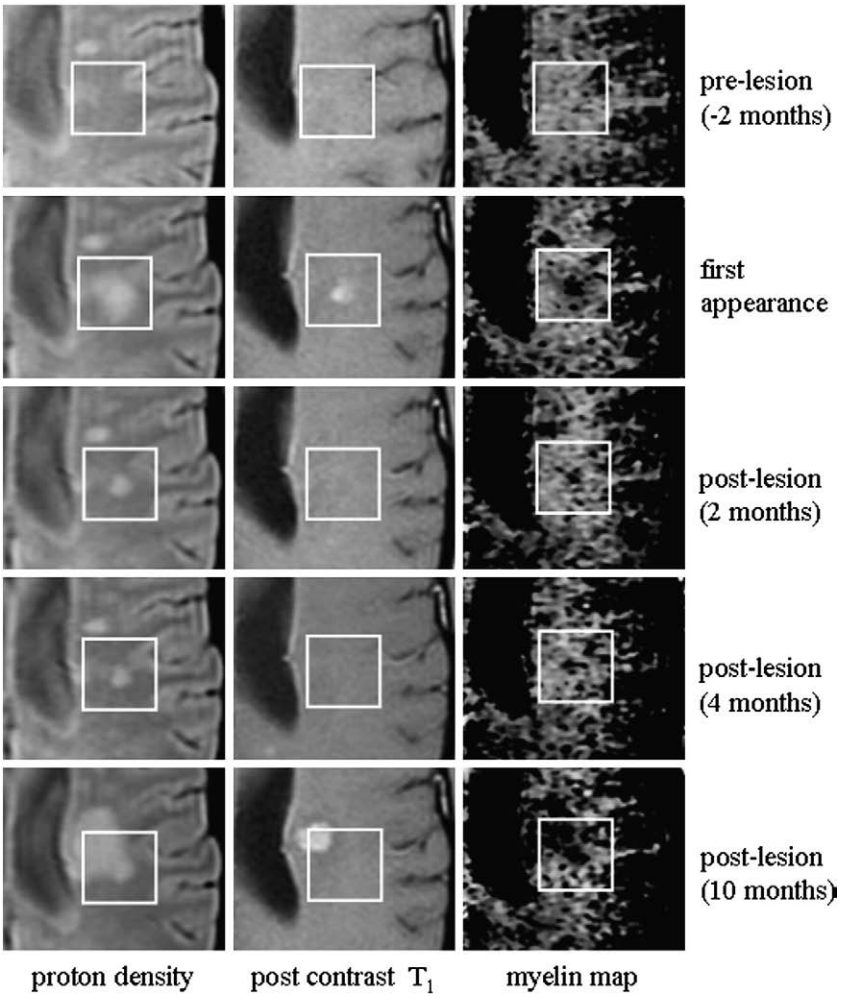

Fig. 2. Images for large lesion A at pre-lesion (1st row), lesion first appearance (2nd row), 2 months post-lesion (3rd row), 4 months post-lesion (4th row) and 10 months post-lesion (5th row). Proton-density (left column), T1-weighted post-Gd-DTPA (middle column) and myelin map (right column) images are shown. The box indicates the location of the lesion of interest.