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Short-term accrual of gray matter pathology in patients with progressive multiple sclerosis: an in vivo study using diffusion tensor MRI

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The mechanisms underlying the progressive course of multiple sclerosis (MS) are not fully understood yet. Since diffusion tensor (DT) MRI can provide quantitative estimates of both MRI-visible and MRI-occult brain damage related to MS, the present study investigated the value of DT MRI-derived measures for the assessment of the short-term accumulation of white and gray matter (GM) pathology in patients with primary progressive (PP) and secondary progressive (SP) MS. Fifty-four patients with PPMS and 22 with SPMS were studied at baseline and after a mean follow-up of 15 months. Dual-echo, T1-weighted, and DT MRI scans of the brain were acquired on both occasions. Total lesion volumes (TLV) and percentage brain volume changes (PBVC) were computed. Mean diffusivity (MD) and fractional anisotropy (FA) maps of the normal-appearing white (NAWM) and gray matter (NAGM) were produced, and histogram analysis was performed. In both patient groups, a significant increase of average lesion MD ($P = 0.01$) and of average NAGM MD ($P = 0.007$) was found at follow-up. No significant differences between PPMS and SPMS patient groups were found for the on-study changes of any MRI-derived measure. No significant correlations were found between the percentage changes of DT MRI-derived measures and those of TLV and PBVC. No significant changes of DT MRI-derived measures were observed in age-matched healthy controls over the same study period. Over a 1-year period of follow-up, DT MRI can detect tissue changes beyond the resolution of conventional MRI in the NAGM of patients with progressive MS. The accumulation of DT MRI-detectable gray matter damage does not seem to merely depend upon the concomitant increase of T2-visible lesion load and the reduction of brain volume. These observations suggest that progressive NAGM damage might yet be an additional factor leading to the accumulation of disability in progressive MS.

Keywords: Multiple sclerosis; Magnetic resonance imaging (MRI); Diffusion tensor MRI; Gray matter

Introduction

Patients with primary progressive (PP) multiple sclerosis (MS) experience accumulation of irreversible neurological disability since the onset of the disease, without an initial period of clinical relapses and remissions (Thompson et al., 1997). Conversely, when the progression of disability begins after a purely relapsing-remitting course, which may have lasted several years, the disease course is named secondary progressive (SP) (Lublin et al., 1996). Although it is likely that diffuse axonal loss and persistent demyelination may play a role in

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increasing the clinical impact of MS-related damage, the pathological mechanisms underlying the progressive course of MS remain, at least partially, unclear (Noseworthy et al., 2000).

Conventional MRI has given a relevant contribution to the in vivo monitoring of MS evolution, by allowing us to detect signs of disease activity and increasing lesion burden over time with a greater sensitivity than the patients' assessment on a solely clinical ground (Miller et al., 1993). However, conventional MRI aspects are poorly correlated with MS clinical progression and have a limited prognostic value for the short- and long-term disease outcome (Brex et al., 2002; Losseff et al., 1996; Molyneux et al., 2001; Rovaris et al., 2003b). Quantitative MR-based techniques, able to provide a more accurate in vivo estimation of MS pathology, may overcome some of the limitations of conventional MRI (Filippi and Grossman, 2002). Among these techniques, diffusion tensor (DT) MRI allows the quantitative measurement of different aspects of tissue microstructure, obtained by exploiting the properties of water diffusion in the brain (Basser et al., 1994; Le Bihan et al., 1986, 1991). The diffusion coefficient of biological tissues, which is influenced by their various components, including cell membranes and organelles, is always lower than the diffusion coefficient in free water and, for this reason, is named apparent diffusion coefficient (ADC). Since some cellular structures are aligned on the scale of an image pixel, the measurement of diffusion is also dependent on the direction in which diffusion is measured. As a consequence, diffusion measurements can give information about the size, shape, orientation, and geometry of tissues. A measure of diffusion which is independent of the orientation of structures is provided by the mean diffusivity (MD), the average of the ADCs measured in three orthogonal directions. A full characterization of diffusion can be obtained in terms of a tensor, a 3×3 matrix which accounts for the correlation existing between molecular displacement along orthogonal directions. From the tensor, it is possible to derive MD, equal to the one third of its trace, and some other dimensionless indexes of anisotropy. One of the most used is the fractional anisotropy (FA). The pathological elements of MS can alter the permeability or geometry of structural barriers to water diffusion in the brain, thus typically causing increased MD and decreased FA values (Hajnal et al., 1991). Since "inflammatory" changes and gliosis can potentially restrict water molecular motion, myelin and axonal loss seem to be the most likely contributors to MS-related DT MRI abnormalities (Mottershead et al., 2003). Using histogram analysis (Cercignani et al., 2001b), the DT MRI characteristics of large portions of the brain, as well as of the gray and white matter (WM) compartments, can be investigated. In MS, those pixels corresponding to T2-visible lesions can be excluded from the analysis, thus allowing a selective assessment of the normal-appearing white (NAWM) and gray matter (NAGM) to be performed in isolation (Cercignani et al., 2001a).

To the best of our knowledge, no longitudinal DT MRI studies have been conducted in patients with progressive MS yet. The present study was therefore performed to assess the value of DT MRI for the in vivo assessment of the short-term accumulation of NAWM and NAGM damage in patients with PP and SP MS, with the ultimate aim to investigate whether DT MRI-derived metrics may reliably serve as paraclinical measures of outcome to monitor the evolution of progressive MS.

Materials and methods

Patients

All patients were selected from the populations attending the outpatient MS clinics of the participating institutions. The disease course was classified as PP or SP according to international criteria (Lublin et al., 1996; Thompson et al., 2000). Other neurological conditions were always carefully excluded by performing the appropriate investigations, including cerebrospinal fluid (CSF) examination in all patients (Thompson et al., 2000). At study entry and follow-up, patients underwent a complete neurological examination, with rating of the expanded disability status scale (EDSS) scores (Kurtzke, 1983). This was done by a single observer, who was unaware of the MRI results, within 3 days from the corresponding MRI session. At follow-up, patients were considered clinically worsened if they had an EDSS score increase $\geq$1.0, when baseline EDSS was <6.0, or an EDSS score increase $\geq$0.5, when baseline EDSS was $\geq$6.0. EDSS changes had always to be confirmed by a second visit after a 3-month, relapse-free interval.

Fifty-four PPMS patients (women/men: 27/27) were studied. Forty-five patients were affected by definite and nine by probable PPMS (Thompson et al., 2000). All patients with probable PPMS had negative CSF examination and positive MRI findings. Forty-three PPMS patients had had a spinal cord presentation at disease onset, the remaining 11 had had other uni- (10 patients) or multifocal (1 patient) presentations, with motor (3 patients), visual (1 patient), cerebellar (4 patients), brainstem (3 patients), or sensory (1 patient) disturbances. Mean age was 51.3 (range: 25–68) years, median disease duration was 10.0 (range: 2–26) years, and median EDSS score at study entry was 5.5 (range: 2.5–7.5). Thirty-six PPMS patients did not undergo any disease-modifying treatment during the study period, nine were treated with azathioprine, five with pulses of intravenous mithoxantrone, and four with methotrexate. Twenty-two clinically definite MS patients (women/men: 13/9) with a SP disease course were also studied (Lublin et al., 1996). Their mean age was 48.3 (range: 34–60) years, median disease duration was 17.9 (range: 6–29) years, and median EDSS score at study entry was 6.0 (range: 4.0–7.0). During the study period, seven SPMS patients were not treated with disease-modifying drugs, eight were treated with interferon beta-1b, three with pulses of intravenous mithoxantrone, two with azathioprine, and two with glatiramer acetate.

To test the stability of conventional and DT MRI measurements, eight sex- and age-matched controls with no previous history of neurological diseases and with a normal neurological examination underwent the same scanning procedures as patients at study entry and follow-up.

All the subjects signed a written informed consent prior to study entry, and the study was approved by the local Ethical Committees of all the participating institutions.

Image acquisition

Using a 1.5-T magnet, the following scans of the brain were acquired at baseline and follow-up, after a mean interval of 15.0 (range: 12–23) months: (1) dual-echo turbo spin echo (repetition time [TR] = 3300, echo time [TE] = 16/98, echo train length = 5); (2) T1-weighted conventional spin echo (TR = 768, TE = 14); 3) pulsed-gradient spin-echo echo-planar (PGSE) (interecho