The normal appearing grey matter in primary progressive multiple sclerosis
A magnetisation transfer imaging study

Introduction

In 10–15% of multiple sclerosis (MS) patients, the clinical course is characterised by gradual development of neurological disability [13, 59]. This clinical subgroup is called primary progressive (PP) MS. Certain clinical features partly distinguish it from the more common relapse onset form of the disease – it has an older mean age of onset [55] (40 versus 30 years) a higher proportion of males [42] (1:1 compared with 1:2 in relapse onset MS), and a poorer prognosis with a significantly greater likelihood of more severe disability accruing with follow up [59]. There is currently no therapy proven to favourably
modify the course of PPMS [42]. This subgroup therefore is important in contributing to the overall burden of neurological disability due to MS.

The mechanisms of disability in PPMS are poorly understood. Whereas in relapsing forms of MS, serial magnetic resonance imaging (MRI) studies have revealed a high frequency of new gadolinium enhancing lesions [26, 41], the presence of which is correlated with inflammation [7, 28] and clinical relapses [25, 50], brain MRI findings in PPMS have been striking for the often small overall lesions load and paucity of overt inflammatory (enhancing) lesions [38, 53, 54].

Potential mechanisms for disability in PPMS include: (i) axonal loss in lesions (which is not measurable using conventional MRI); (ii) a diffuse pathological process affecting the normal appearing white matter (NAWM); (iii) a pathological process in the spinal cord (recognising that the most common clinical form of PPMS is a progressive myelopathy). MR studies provide evidence for all of these processes:

1. In brain lesions, there are abnormalities of putative axonal markers (reduced N-acetyl aspartate [NAA, an amino acid largely confined to neurons and axons in the adult central nervous system] and T1 hypointensity) suggesting axonal loss [14, 52].
2. Abnormalities in normal appearing tissues include a reduced magnetisation transfer ratio [32, 48], changes in diffusion characteristics [10, 15, 19], and a decreased NAA [31].
3. Spinal MRI abnormalities include focal lesions, diffuse signal change [36, 38] and atrophy [34, 48].

Previous studies have, however, had little success in identifying conventional or non-conventional MRI features which correlate with functional status in PPMS. This may partly relate to limitations in the scales used to measure disability [8, 27] or to the small size of some cohorts [14, 20, 22, 54]. However, even in a large multicentre study in which both physical and neuropsychological status were assessed, only limited correlations were found with measures of T2 and T1 lesion load and atrophy in the brain or spinal cord [8, 51].

To date, MR studies in PPMS have concentrated on brain lesions, brain NAWM and the spinal cord; there has been little attention given to grey matter. Recent neuropathological studies have demonstrated a higher frequency of lesions in MS cortical grey matter [6, 29] than hitherto appreciated. Such lesions are rarely seen on conventional MRI, probably because the MR parameters that provide image contrast (proton density, T1 and T2 relaxation) are similar for both normal grey matter and grey matter lesions.

Recent developments in MR acquisition and analysis allow for a more detailed examination of normal appearing brain tissues including grey matter (NAGM). These include non-conventional sequences which have a different pathobiological basis from conventional T1- or T2-weighted imaging [40]; MTR (magnetisation transfer ratio) histogram analysis which analyses the whole of a defined region [57]; and segmentation methods for separation of normal appearing white and grey matter as well as lesions [3, 4, 9, 17]. We have applied such techniques in the present study to compare a cohort of PPMS patients with healthy controls, using magnetisation transfer imaging (MTI) which applies an off-resonance radiofrequency pulse to selectively saturate protons bound to macromolecules. The effect of the MT pulse is to produce images from which a quantitative measure, the magnetisation transfer ratio (MTR), can be derived. The MTR provides an indication of the proportion of protons in the tissue that are bound to macromolecules, and by inference the amount of tissue structure [39]. The study describes MTR parameters in lesions, NAWM and NAGM; investigates differences between PPMS patients and controls; and explores, in the patient group, the relationship between the various MR parameters and disability.

Subjects and methods

Subjects

The study was performed in 30 subjects with clinically definite PPMS (20 males, 10 females; mean age 40.7 years, range 25 to 51; mean disease duration 7.3 years, range 2 to 19; median EDSS 5.5, range 2 to 7) and 30 healthy controls (15 male, 15 female; mean age 39.4 years, range 27 to 53). Patients were recruited from clinics at the National Hospital for Neurology and Neurosurgery, London, UK. Primary progressive MS was diagnosed using standard criteria [35, 47]. Disability was measured using Kurtzke's expanded disability status scale [30] (EDSS). The project was approved by the Joint Medical Ethics Committee of the National Hospital and Institute of Neurology, London, UK.

MRI acquisition

MRI was carried out using a 1.5 Tesla Signa Echospeed Horizon system (General Electric, Milwaukee, WI). A dual spin echo sequence was acquired with and without presaturation (using a Hamming apodised three lobe sinc pulse with a duration of 16 ms and a peak amplitude of 23.2µT giving a nominal bandwidth of 250 Hz, applied 1 kHz off water resonance). Scans with and without presaturation were interleaved for each TR period providing precise co-registration [5]. Two sets of 14 5mm axial slices with a 5 mm slice gap were collected and combined to give 28 contiguous slices covering the whole brain. Other parameters were: TE 30/80 ms, TR 1720 ms, 256×128 matrix, FOV 24×24 cm; partial (75%) k-space coverage was used in the phase encode direction to reduce total scan time to 20 min. MTR was calculated in percent units (pu) for each pixel from the expression $\text{MTR} = \frac{(S_{01} - S_{00})}{S_{01}} \times 100$, where $S_{01}$ and $S_{00}$ represent signal intensities with and without presaturation respectively. The T2-weighted images (TE = 80ms) were extracted from these data sets and used for subsequent tissue and lesion segmentation. This allowed us to generate intrinsically registered tissue and lesion masks without the need to acquire further scans.