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A preliminary study of magnetization transfer and diffusion tensor MRI of multiple sclerosis patients with fatigue

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Abstract To investigate whether multiple sclerosis (MS) tissue damage is associated with the presence and severity of fatigue, we obtained magnetization transfer (MT) and diffusion tensor (DT) magnetic resonance imaging from 28 patients with MS (14 with and 14 without fatigue). MT ratio and mean diffusivity did not differ between fatigued and non-fatigued MS patients. No correlation was found between Fatigue Severity Scale scores and any of the MT and DT MRI-derived quantities. This preliminary study suggests that the severity of overall MS pathology in the brain seems not to be a critical factor contributing to the development of fatigue in MS.

Key words Multiple sclerosis · fatigue · magnetic resonance imaging · magnetization transfer imaging · diffusion tensor imaging

Introduction

Fatigue is a common and disabling feature of multiple sclerosis (MS) [6]. Although a variety of pathogenic mechanisms have been proposed to explain fatigue in MS patients, its genesis remains largely unexplained. Previous studies found no correlation between the presence and severity of fatigue in MS patients and the overall extent of MS lesions seen on conventional magnetic resonance imaging (MRI) scans [2, 4, 7, 10]. However, conventional MRI lacks specificity with regard to the heterogeneous pathological substrates of MS lesions and, as a consequence, does not allow the quantification of tissue damage. In addition, conventional MRI does not delineate tissue damage occurring in normal-appearing brain tissue (NABT), which is known to be damaged in MS [1].

Magnetization transfer (MT) and diffusion-tensor (DT) MRI provide quantitative estimates of MS pathology in lesions and NABT [3, 5]. In this study, we obtained MT and DT MRI from MS patients with and without fatigue to investigate whether the severity of MS tissue damage in lesions and NABT is associated with presence and severity of fatigue.

Patients and methods

We studied 28 patients with clinically definite MS selected from the outpatient Clinics of our Institution. To be included patients had to have: 1) absence of clinical relapses from at least six months prior to study entry; 2) no concomitant therapy with antidepressant, psychoactive, steroid, and other immunomodulant/immunosuppressive drugs; 3) no complaint of mood or sleep disorders; 4) mild neurological impairment. These selection criteria were used to minimize the effect of possible confounding factors (such as the presence of moderate to severe disability) on the assessment of fatigue.

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In all patients, fatigue was assessed and scored using the Fatigue Severity Scale (FSS) [4] within 24–48 hours from MRI acquisition. Fourteen patients who had an FSS score of 25 or higher were considered as fatigued (F), while the remaining with an FSS score lower than 25 were considered as non-fatigued (NF). Thirty sex- and age-matched healthy volunteers served as controls. In Table 1, the demographic and clinical characteristics of MS patients and controls are shown. Approval of the local ethics committee and written informed consent from all subjects were obtained before study initiation.

The following sequences were obtained using a 1.5 T magnet: a) dual-echo turbo spin echo (TR=3300, TE=16/98, echo train length=5); b) 2D gradient-echo (GE) (TR=640, TE=12, flip angle=20°), with and without an off-resonance radio-frequency (RF) saturation pulse (offset frequency=1.5 kHz, Gaussian envelope duration=7.68 ms, flip angle=500°); c) pulsed-gradient spin-echo echo-planar (PGSE) pulse sequence (inter-echo spacing=0.8, TE=123), with diffusion gradients applied in 8 non collinear directions, with a maximum b factor in each direction of 1044 sec mm^{-2}. To optimize the measurement of diffusion only two b factors were used ($b1 \approx 0, b2 = 1044$ s mm^{-2}). Fat saturation was performed using a four RF binomial pulse train to avoid chemical shift artefact. For the dual-echo and GE scans, 24 contiguous, 5-mm thick, interleaved axial slices were acquired, with 256×256 matrix and 250×250 mm field of view (FOV). The slices were positioned to run parallel to a line that joins the most inferoanterior and inferoposterior parts of the corpus callosum. For the PGSE scans, ten, 5 mm-thick slices were acquired with the same orientation as the other scans, positioning the second-last caudal slice in order to match exactly the central slices of the other image sets. These central slices are less affected by the distortions due to B_0 field inhomogeneity, which can affect image co-registration. A 128×128 matrix and 250×250 mm FOV were used. The manufacturer's own phase correction and regridding algorithm was used before Fourier transformation and interpolation to a 256×256 image matrix.

MRI data post-processing was performed by consensus by two experienced observers, who did not know to whom the scans belonged. Hyperintense lesions on dual-echo images were identified and lesion volumes were measured using a local thresholding segmentation technique. MTR, mean diffusivity ($\bar{D}$) and fractional anisotropy (FA) maps were obtained as previously described [3]. From these maps, we measured average lesion MTR, $\bar{D}$ and FA and MTR, $\bar{D}$ and FA histogram-derived metrics of the NABT, as extensively described elsewhere [3, 5].

A two-tailed Student t test for non-paired data was used to compare MR findings between MS patients and controls. An ANOVA model corrected for the level of disability and the duration of the disease was used to compare MR findings between NF and F MS patients. Correlations between FSS and MR quantities were assessed using the Spearman Rank Correlation Coefficient.

Table 1 Demographic and clinical characteristics of MS patients and healthy controls.

	Controls	Non-Fatigued MS	Fatigued MS
Number of subjects	30	14	14
Men/Women	10/20	6/8	3/11
Mean age (SD) years	41.2 (7.1)	37.6 (6.6)	39.1 (8.9)
Median disease duration (range) years	–	8.0 (3–22)	6.0 (1–40)
Median EDSS (range)	–	1.0 (0.0–1.0)	1.0 (0.0–1.0)
Mean FSS score (range)	–	19.7 (13–24)	38.9 (28–55)

EDSS: Expanded Disability Status Scale, FSS: Fatigue Severity Scale, SD: standard deviation. The only significant difference between the two patients'subgroups was that of the FSS scores ($p < 0.0001$).

Results

No macroscopic abnormalities were detected on the brain MRI scans from controls. Mean T2 lesion volumes were 8.9 (SD=10.8) ml in F and 7.2 (SD=4.7) ml in NF MS patients (not significant difference). In Table 2, MR histogram-derived metrics from MS patients and controls are reported. Compared with controls, MS patients had: a) lower MTR histogram peak height (p=0.01) and position (p=0.02); b) increased average $\bar{D}$ (p=0.03) and lower $\bar{D}$ histogram peak height (p=0.003); c) decreased average FA and FA histogram peak position and higher FA histogram peak height ($p < 0.0001$ for all these comparisons). No additional difference emerged when comparing the healthy controls with the two MS subgroups separately. None of the MTR, $\bar{D}$ and FA histogram-derived metrics of the NABT differed significantly between F and NF MS patients. The same was observed when considering the frontal lobe NABT in isolation (data not shown). Average lesion MTR (37.5±1.6 % vs 37.9±1.4), $\bar{D}$ (1.13±0.09 vs 1.14±0.02) and FA (25.0±2.7 vs 24.3±3.0) were also not significantly different between F and NF MS patients. The same was observed when considering the frontal lobe lesions in isolation (data not shown). There was no significant correlation between the FSS score and any of the assessed MR quantities.

Table 2 Mean MTR, $\bar{D}$ and FA histogram derived metrics of the normal-appearing brain tissue from MS patients and controls.

	Controls	Non-fatigued MS	Fatigued MS
Average MTR (SD) [%]	40.6 (1.0)	40.4 (1.2)	40.0 (0.6)
MTR peak height (SD)	115.1 (12.0)	107.5 (12.8)	106.8 (8.8)
MTR peak position (SD) [%]	34.6 (1.5)	35.7 (1.6)	35.3 (1.1)
Average $\bar{D}$ (SD) [10^{-3}mm^2/sec]	0.910 (0.05)	0.960 (0.04)	0.930 (0.06)
$\bar{D}$ peak height (SD)	107.0 (13.6)	95.1 (16.2)	95.3 (12.5)
$\bar{D}$ peak position (SD) [10^{-3}mm^2/sec]	0.760 (0.04)	0.750 (0.03)	0.750 (0.03)
Average FA (SD)	0.23 (0.01)	0.20 (0.01)	0.20 (0.01)
FA peak height (SD)	40.8 (2.9)	48.1 (3.7)	48.2 (4.9)
FA peak position (SD)	0.12 (0.01)	0.08 (0.01)	0.08 (0.01)

MTR: magnetization transfer ratio, $\bar{D}$: mean diffusivity, FA: fractional anisotropy. See text for statistical analysis and further details.

Discussion

Previous MRI studies have consistently shown that, in the best case scenario, the extent of abnormalities seen on conventional MRI is likely to have only a modest role in the pathogenesis of fatigue in MS patients [2, 4, 7, 10]. However, conventional MRI lacks specificity to the heterogeneous pathological substrates of MS lesions, and it is unable to detect MS pathology known to occur in the NABT [1]. These limitations of conventional MRI have led several authors to speculate that the severity of intrinsic lesion damage or the extent and severity of NABT pathology might contribute to the genesis of fatigue in MS [7, 10]. This preliminary study has specifically investigated this issue using quantitative MR technology, and showed that the overall severity of MS pathology in lesions and NABT of the brain from F and NF MS patients is similar, even after correcting for disease duration and level of disability, and, as a consequence, it is likely not to contribute a great deal to the presence and severity of fatigue in MS.

A recent positron emission tomography study has shown that fatigue in MS is associated with frontal cortex and basal ganglia dysfunction [9] and suggested that this might result from disruption of distinct cortical-subcortical circuits. For this reason, we also measured MT and DT MRI changes of lesions and NABT of the frontal lobe taken in isolation and, again, we did not find any significant difference between F and NF MS patients. This suggests that gray matter metabolic abnormalities in fatigued MS patients might be attributed to functional impairment of nerve conduction along frontal cortical-subcortical circuits rather than to their disruption. Demyelination and remyelination might result in impaired capacity of nerve fibers to conduct without leading to detectable changes of water diffusivity (causing increased $\bar{D}$ and decreased FA) and water distribution across the intra- and the extra-cellular compartments (causing decreased MTR). Sublethal axonal injury, which is known to occur in MS, might also determine functional cortical changes, which might be associated with increased perception of fatigue, without altering water diffusivity and distribution. Finally, functional MRI studies [8] have shown a marked inter-subject variability of cortical adaptive reorganisation following MS injury. This variable ability of cortical reorganisation to limit the clinical manifestations of MS might also explain why, although the extent and severity of MS white matter pathology are the same, only some patients develop fatigue.

References

1. Allen IV, McKeown S (1979) A histological, histochemical and biochemical study of the macroscopically normal white matter in multiple sclerosis. J Neurol Sci 41:81–91
2. Bakshi R, Miletich RS, Henschel K, Shaikh ZA, Janardhan V, Wasay M, Stengel LM, Ekes R, Kinkel PR (1999) Fatigue in multiple sclerosis: cross-sectional correlation with brain MRI findings in 71 patients. Neurology 53:1151–1153
3. Cercignani M, Inglese M, Pagani E, Comi G, Filippi M (2001) Mean diffusivity and fractional anisotropy histograms of patients with multiple sclerosis. AJNR Am J Neuroradiol 22: 952–958
4. Colombo B, Martinelli-Boneschi F, Rossi P, Rovaris M, Maderna L, Filippi M, Comi G (2000) MRI and motor evoked potential findings in non disabled multiple sclerosis patients with and without symptoms of fatigue. J Neurol 247:506–509
5. Filippi M, Inglese M, Rovaris M, Sormani MP, Horsfield MA, Iannucci G, Colombo B, Comi G (2000) Magnetization transfer imaging to monitor the evolution of MS: a 1-year follow-up study. Neurology 55:940–946
6. Krupp LB, Alvarez LA, La Rocca NG, Scheinberg LC (1988) Clinical characteristics of fatigue in multiple sclerosis. Arch Neurol 45:435–437
7. Mainero C, Faroni J, Gasperini C, Filippi M, Giugni E, Ciccarelli O, Rovaris M, Bastianello S, Comi G, Pozzilli C (1999) Fatigue and magnetic resonance imaging activity in multiple sclerosis. J Neurol 246:454–458
8. Reddy H, Narayanan S, Arnoutelis R, Jenkinson M, Antel J, Matthews PM, Arnold DL (2000) Evidence for adaptive functional changes in the cerebral cortex with axonal injury from multiple sclerosis. Brain 123:2314–2320
9. Roelcke U, Kappos L, Lechner-Scott J, Brunnschweiler H, Huber S, Ammann W, Plohmann A, Dellas S, Maguire RP, Missimer J, Radu EW, Steck A, Leenders KL (1997) Reduced glucose metabolism in the frontal cortex and basal ganglia of multiple sclerosis patients with fatigue: a ^{18}F-fluorodeoxyglucose positron emission tomography study. Neurology 48: 1566–1571
10. van der Werf SP, Jogen PJH, Lycklama à Nijeholt GJ, Barkhof F, Hommes OR, Bleijenberg G (1998) Fatigue in multiple sclerosis: interrelations between fatigue complaints, cerebral MRI abnormalities and neurological disability. J Neurol Sci 160:164–170