DETERMINANTS OF DISABILITY IN MULTIPLE SCLEROSIS: A CROSS-SECTIONAL, MULTIPARAMETRIC, QUANTITATIVE MR-BASED STUDY OF DISEASE PHENOTYPES

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Introduction

'Magnetic resonance imaging (MRI)-occult', neurodegenerative brain damage, rather than MRI-detectable inflammatory changes, is likely to play an important role for the accumulation of disability in multiple sclerosis (MS) [1] This cross-sectional diffusion tensor (DT) MRI [2] and whole-brain N-acetyl-aspartate (WBNAA) magnetic resonance spectroscopy (MRS) study [3] was performed: (a) to investigate whether these tools can provide us with complementary pieces of information to achieve a better understanding of the nature of disability at different stages of MS; (b) to quantify the extent of the relative contributions of "global" axonal damage/loss and "regional" tissue disruption of the white/gray matter in driving the evolution of MS; (c) to preliminarily evaluate the performance of multiparametric MR-based models [4] as paraclinical correlates of MS disability.

Methods

We studied 27 patients with clinically isolated syndrome (CIS) suggestive of MS (women/men [W/M]: 19/8, mean age: 28.6, median Expanded Disability Status Scale (EDSS) score: 1.0) [5], 21 relapsing-remitting (RR) MS patients (W/M: 13/8, mean age: 35.7, median disease duration: 4.0, median EDSS score: 1.5), 29 secondary-progressive (SP) MS patients (W/M: 15/14, mean age: 45.5, median disease duration: 17.0, median EDSS score: 6.0) and 10 healthy controls (W/M: 3/7, mean age: 33.5, range 24-56 years). The following brain scans were performed using a 1.5 Tesla scanner (Vision, Siemens): dual-echo turbo spin echo (TR= 3300 ms, first echo TE = 16, second echo TE = 98 ms, echo train length = 5, matrix size=256´256, FOV=250x250 mm; 24 contiguous axial slices, slice thickness=5 mm); T1-weighted conventional spin echo (TR= 768 ms, TE= 14 ms, NAC= 2); pulsed-gradient spin-echo echo-planar sequence: inter-echo spacing=0.8 ms, TE=123 ms, number of non-collinear diffusion gradient directions=8; slices: 10, axial, contiguous, 5-mm thick); proton MRS pulse sequence based on a four-step cycle of non-selective 180° inversion pulses (2048 complex points at 0.5 ms/point; recicle time [TR] of 10 seconds, five separate acquisitions for each subject). Total T2 lesion volume (LV), brain parenchimal fraction (BPF), gray matter fraction (GMF) and white matter fraction (WMF), average lesion mean diffusivity (MD) and fractional anysotropy (FA) were calculated; MD and FA histograms were created for the normal-appearing white matter (NAWM) and MD histograms for the normal-appearing gray matter (NAGM). Average MD/FA values and corresponding histogram peak heights were computed. Normalized WBNAA amount for each subject was measured by scaling against phantom data.

	EDSS		Disease Duration	
Independent Variable	**r**	**p**	**r**	**p**
T2 lesion volume [mL]	0.55	<0.001	0.58	<0.001
Average lesion MD [$\times 10^{-3}$ mm^2 s^{-1}]	0.50	<0.001	0.57	<0.001
Average lesion FA	-0.36	0.005	-0.48	<0.001
Average NAWM FA	-0.52	0.001	-0.51	<0.001
NAWM FA peak height	0.42	0.001	0.47	0.001
Average NAWM MD [$\times 10^{-3}$ mm^2 s^{-1}]	0.26	0.02	0.38	0.001
NAWM MD peak height	-0.31	0.007	-0.43	<0.001
Average NAGM MD [$\times 10^{-3}$ mm^2 s^{-1}]	0.52	<0.001	0.54	<0.001
NAGM MD peak height	-0.50	<0.001	-0.50	<0.001
WBNAA [mM]	-0.49	<0.001	-0.74	<0.001
BPF [%]	-0.52	<0.001	-0.50	<0.001
GMF [%]	-0.41	<0.001	-0.32	0.005
WMF [%]	-0.01	0.98	-0.12	0.28

Results

Significant heterogeneity among the three subgroups of patients was found for all MR-derived variables but GMF and WMF (p values ranged from 0.01 to <0.001). At *post hoc* comparisons, CIS patients had significantly lower WBNAA than healthy controls, RRMS patients had significantly higher T2LV, lower average NAWM FA and lower WBNAA than CIS patients, whereas SPMS patients had significantly lower GMF, higher average GM MD and lower GM MD peak height than RRMS patients. Significant correlations were found between patients' EDSS and all MR-derived variables, the strongest being the one with T2 lesion volume (r:0.55, p<0.01) (Table).

A univariate logistic regression demonstrated that disease duration (p<0.001), GMF (p=0.01) and WBNAA (p=0.006) enter a model explaining nearly 70 % ($R^2 = 0.66$) of the observed EDSS variance.

Conclusions

Patterns of MS-related brain damage may vary according to the disease stage and the patients' clinical status: the accumulation of macroscopic lesions and NAWM damage seems to occur mainly during the earlier clinical phases of MS, whereas gray matter pathology is associated to the accumulation of irreversible disability in the late, chronic progressive stage of the disease. Longitudinal multiparametric MR-based studies are warranted to monitor the evolution of MS and to define their actual prognostic value.

References

(1) Miller et al., Brain 2002; 125:1676-1695. (2) Rovaris et al., Neurology 2005; 65:1526-1532. (3) Gonen et al., Neurology 2000; 54:15-19. (4) Mainero et al., Neurology 2001; 56:1331-1334. (5) Kurtzke et al., Neurology 1983 ; 33:1444-1452.