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SHORT COMMUNICATION

'Gender gap' in multiple sclerosis: magnetic resonance imaging evidence

C. Pozzilli[a], V. Tomassini[a], F. Marinelli[a], A. Paolillo[a], C. Gasperini[b] and S. Bastianello[a]

[a]*Department of Neurological Sciences, University 'La Sapienza', Rome; and* [b]*Department of Neurosciences, S. Camillo-Forlanini Hospital, Rome, Italy*

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The authors evaluated the gender difference in the magnetic resonance imaging characteristics of the lesions occurring in the brain of 413 multiple sclerosis (MS) patients. Men had fewer contrast-enhancing lesions ($P = 0.01$), but a higher proportion of lesions evolving into 'black holes' ($P = 0.001$), when compared with women. Thus, our data indicate that men with MS are prone to develop less inflammatory, but more destructive lesions than women. This study results provides support for a modulation of the MS pathological changes by gender.

Introduction

Gender-related differences have been reported in Multiple Sclerosis (MS) as in other autoimmune diseases (Benson, 1994). The disease is two to three times more common in women and both disease course and response to interferon β therapy tend to be more favourable in women (Hawkins and McDonnell, 1999; SPECTRIMS Study Group, 2001).

An analysis of magnetic resonance imaging (MRI) data from the placebo group of a large randomized trial in Secondary Progressive MS (SPMS) have recently shown that men had fewer active lesions and lesser accumulation of T2 lesion burden than women (Li *et al.*, 2001). Although these findings apparently contrast with the better outcome reported in women, it is now widely accepted that increased signal on T2-weighted images has little pathological specificity and its relationship with clinical disability is weak. More recently, hypointense lesions on T1-weighted images, known as 'black holes', have been used as surrogate markers in monitoring destructive pathological processes that most likely relate to MS disease progression (Truyen *et al.*, 1996).

The purpose of this study was to investigate the gender difference in the MRI characteristics of the lesions occurring in the brain as a result of MS.

Methods

Patients

The cohort consisted of 413 consecutive MS patients regularly attending, as outpatients, the MS Centre of our University Hospital, from February 1998 to May 2001. At the time of MRI examination, 266 patients had relapsing–remitting MS (RRMS), as defined by a history of relapses and remissions without gradual deterioration, and 147 patients had SPMS, as defined by an initial RR course with subsequent progressive deterioration for at least 6 months, with or without superimposed relapses.

All patients underwent a full neurological examination with disability assessed using Kurzke Expanded Disability Status Scale (EDSS) score. Patients, who were treated with short courses of intravenous methylprednisolone for relapses, had their MRI scans delayed by at least 30 days in order to avoid the influence of steroids on the scans. Patients treated with immunosupressive or cytotoxic drugs were also excluded from analysis.

In the RRMS group there were 194 females and 72 males (F/M ratio = 2.7/1) with mean (SD) age of 31.8 years (7.9), disease duration of 5.6 (5.1) and EDSS of 2.0 (1.1); SPMS group included 87 females and 60 males (F/M = 1.5/1) with mean (SD) age of 43.3 years (9.3), disease duration of 12.1 (4.9) and EDSS of 5.7 (1.2).

MRI assessment

Brain MRI was obtained using a superconductive 1.5 Tesla magnet (Philips Gyroscan NT 15 Best, The Netherlands). Proton density- and T2-weighted conventional spin-echo (CSE) images (TR = 2000 ms; TE = 20/90 ms), and T1-weighted CSE images (TR = 550 ms; TE = 12 ms) were acquired in the axial plane with 5 mm contiguous slices, field of view = 240 mm and matrix = 256 × 256. The T1-weighted contrast-enhanced images of the brain were obtained after injection of an intravenous bolus of 0.1 mmol/kg of Gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA).

MRI analysis

For each patient, the number of Gd-enhancing lesions, hyperintense lesions on T2-weighted images, and

Correspondence: Carlo Pozzilli, Department of Neurological Sciences, University 'La Sapienza', viale dell'Università 30, 00185, Rome, Italy (fax: +39 06 445 770 5; e-mail: carlo.pozzilli@uniroma1.it).

hypointense lesions on T1-weighted images ('black holes') were counted by a team of experienced observers. A 'black hole' was defined, on post-contrast T1-weighted scans, as a lesion of low signal intensity, compared with surrounding white matter, typically with a signal intensity equal to or lower than grey matter. The proportion of T2-hyperintense lesions that appears hypointense on T1-weighted images, expressed as 'T1/T2 ratio', was also calculated.

Statistical analysis

A comparison of MRI-derived measures between male and female patients was performed using Mann–Whitney *U*-test. Student's *t*-test was used to assess clinical differences between subgroups and chi-square to assess significant association between category data variables.

Results

There was no difference in age, disease duration and EDSS score between men and women. Demographic, clinical and MRI characteristics of the patients are shown in Table 1. There were fewer contrast-enhancing lesions and fewer active scans (i.e. scans with at least one enhancing lesion) in male compared with female patients ($P = 0.01$ and $P = 0.03$, respectively). Female subgroup had lower number of T1-hypointense lesions ($P = 0.09$) and a significantly lower T1/T2 ratio compared with male sugroup ($P = 0.001$). When data of RRMS and SPMS groups were analysed separately, we found a significant gender difference in the T1/T2 ratio (RRMS: 0.36 in men and 0.27 in women, $P = 0.001$; SPMS: 0.40 in men and 0.33 in women, $P = 0.008$), but not in the other MRI measures. There was a trend towards a lower number of enhancing lesions in men when compared with women in both RRMS and SPMS groups. However, the results were not statistically significant, probably because of the small sample size in each group (data not shown). T1/T2 ratio was higher in patients with SPMS than in patients with RRMS (0.36 vs. 0.30, $P = 0.003$).

Discussion

This study provides support for a gender difference in the MRI characteristics of the lesions occurring in the brain as a result of MS. Among patients with MS from our outpatient clinic, men had a lower number of contrast-enhancing lesions, but a higher proportion of lesions evolving into black holes when compared with women. It is now clear that changes on MRI reflect the underlying pathological process typical of MS, with contrast-enhancing lesions representing areas of active inflammation with blood–brain barrier disruption, and black holes surrogate markers of axonal loss (Truyen *et al.*, 1996). Thus, our data indicate that male patients with MS are prone to develop less

Table 1 Summary of demographic, clinical and MRI characteristics

	Men ($n = 132$)	Women ($n = 281$)	*P*-value
Demographic and clinical characteristics			
Age (years)			
Mean–SD	37.7–11.5	36.1–9.9	0.14
Disease duration (years)			
Mean–SD	7.8–6.1	8.1–5.5	0.48
EDSS score			
Mean–SD	3.6–1.9	3.2–2.2	0.10
MRI findings			
Gd-enhancing lesions			
Mean	1.24	1.86	0.01
Median	0	1	
Percentage of patients with active scans	46.2	57.9	0.03
T2-hyperintense lesions			
Mean	48.3	50.1	0.43
Median	43	41	
T1-hypointense lesions			
Mean	19.1	15.8	0.09
Median	11	10	
T1/T2 ratio			
Mean	0.38	0.29	0.001
Median	0.33	0.28	

SD: Standard deviation; MRI: magnetic resonance imaging; EDSS: Expanded disability status scale; Gd: Gadolinium.

inflammatory, but more destructive lesions than female patients.

The observed effect of sex into the dynamic of the disease process is consistent with a previous MRI study. In the placebo arm of a large randomized controlled trial of interferon β-1a in SPMS, Li *et al.* (2001) reported men as having lesser accumulation of active lesions on T2-weighted images than women over 3 years. Our study and the study by Li *et al.* (2001) did agree with the finding that men showed less MRI activity than women, as documented by a reduction of both contrast-enhancing lesions and accumulated lesion burden. Although the presence of enhancing lesions in a single scan is only an isolated snapshot of ongoing disease activity, previous longitudinal studies have demonstrated that the presence of active lesions on a random cranial MRI scan carries a high risk of continuous disease activity on subsequent images (Koudriavtseva *et al.*, 1997; Molyneux *et al.*, 1998).

Furthermore, we found the proportion of T2-weighted hyperintense lesions that developed into T1-hypointense lesions, expressed as T1/T2 ratio, to be higher in men than in women. The T1/T2 ratio varies between 0.13 and 0.5 and it is lower in RRMS than in SPMS (van Walderveen *et al.*, 1999). Factors influencing development of T1-hypointense lesions are partially known. Hypointense lesions may develop as a result of the extent and severity of the inflammatory processes or as a consequence of exhaustion of repair mechanisms (i.e. remyelination). van Walderveen *et al.* (1999) suggest that inflammatory activity, as expressed by Gd-enhancing lesions, is only one of the several factors related to the development of destructive lesions, and other, so far unidentified, factors may independently have a prominent role. The gender itself might play a role explaining part of this observed variability, as suggested by recent evidence indicating a role of sex hormones on brain injury and repair mechanisms (Stein, 2001). In Primary Progressive MS (PPMS), where the female preponderance is not evident, enhancing lesions are infrequently seen, but T1/T2 ratio is similar to other MS patients (Stevenson *et al.*, 2000). Of note, male patients with PPMS have also a higher median T1/T2 ratio than the female subgroup (Stevenson *et al.*, 2000; van Walderveen *et al.*, 2001).

We recognize that our cross-sectional study has certain limitations. Our results are based entirely on single images obtained in men and women with MS at different stages of the disease course. A longitudinal comparative study using multiple serial images might be expected to better define the mechanisms of gender differences in the course/severity of MS.

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