Sex hormones modulate brain damage in multiple sclerosis: MRI evidence

V Tomassini, E Onesti, C Mainero, E Giugni, A Paolillo, M Salvetti, F Nicoletti, C Pozzilli

Background: Sex related differences in the course and severity of multiple sclerosis (MS) could be mediated by the sex hormones.

Objective: To investigate the relation between serum sex hormone concentrations and characteristics of tissue damage on conventional magnetic resonance imaging (MRI) in men and women suffering from relapsing-remitting MS.

Results: Serum testosterone was significantly lower in women with MS than in controls. The lowest levels were found in women with a greater number of gadolinium enhancing lesions. A positive correlation was observed between testosterone concentrations and both tissue damage on MRI and clinical disability. In men, there was a positive correlation between oestradiol concentrations and brain damage.

Conclusions: The hormone related modulation of pathological changes supports the hypothesis that sex hormones play a role in the inflammation, damage, and repair mechanisms typical of MS.

S everal lines of evidence suggest that gender affects the clinical course of multiple sclerosis (MS), male sex being associated with a more progressive and severe outcome than female sex.1,2 Experimental data in animal models of MS have confirmed a sex related difference in the susceptibility, course, and severity of the disease.3 They have hinted at the fact that vulnerability of the central nervous system (CNS) to damage, as well as the spontaneous recovery, might vary between men and women.4,5

Using magnetic resonance imaging (MRI), it has previously been shown that men with MS are less prone to inflammatory lesions but more susceptible to destructive lesions than women.6,7 An association between sex hormone concentrations and variations in disease activity as assessed by enhanced MRI has been also reported.8,9 The mechanisms by which sex hormones might affect brain damage in MS vary from innate susceptibility to sex related differences in the development of the inflammatory process, limitation of tissue injury, or the repair mechanisms.

Finding an effect of sex hormones on the dynamics of the MS disease process would support the hypothesis that sex hormones play a specific role in brain damage and repair mechanisms typical of MS. In order to clarify whether sex hormones mediate the difference in the MRI characteristics of brain damage, we investigated the relation between serum concentrations of sex hormones and MRI features in a population of subjects suffering from relapsing-remitting MS (RRMS).

METHODS

Patients

We included 60 RRMS patients (35 women and 25 men) with a mean (SD) age of 32.3 (7.6) years, a disease duration of 6.2 (5.4) years (range 1 to 26), and a median (range) expanded disability status scale (EDSS) score of 1.5 (1 to 5.5). The subjects had no history of disease modifying treatments and had not experienced relapses or received steroid treatment in the previous two months. Female patients had normal menstrual cycles and had never employed oral contraceptives or undergone hormone replacement therapy. Thirty six healthy, age matched subjects served as controls.

Study protocol

Serum follicle stimulating hormone (FSH) (mU/ml), luteneising hormone (LH) (mU/ml), 17-β oestradiol (pg/ml), testosterone (ng/ml), and dehydroepiandrosterone sulphate (DHEAs) (μg/ml) were determined in both men and women. In women these hormones were measured during the follicular (third to ninth day) and luteal phases (21st to 28th day) of their menstrual cycle, once at each point, while progesterone (ng/ml) was quantified during the luteal phase.

In parallel, brain MRI was carried out using a 1.5 T superconductive system (Philips Gyroscan NT 15, Erlangen, Germany). The following sequences were obtained:

- conventional dual spin echo: proton density (PD) and T2 weighted images (T2WI); time of repetition (TR) = 2000 ms; time of echo (TE) = 20/90 ms;
- pre- and post-contrast T1 weighted images (T1WI); TR = 550 ms; TE = 12 ms; single 0.1 mmol/kg dose of Gd DTPA (gadolinium diethylenetriaminepenta-acetic acid).

For each sequence, axial contiguous slices with 3 mm thickness, 25 cm field of view, and 256×256 matrix were acquired.

MRI analysis

All MRI scans were archived onto electronic media and transferred to a SUN workstation (Sun Microsystems, Palo Alto, California, USA). For each patient, we determined the number of enhancing lesions as well as the volume of T2 hyperintense (T2-LL) and T1 hypointense (T1-LL) lesions. T1-LL measures the volume of “black holes”, which are lesions with lower signal intensity than surrounding white matter but equal to or lower than grey matter. T2-LL and T1-LL were assessed using a semiautomated contouring technique (Dispim, Dispimage).10,11 The quantification of black holes on post-Gd scans followed standard practice, and was justifiable as many low signal intensity lesions on pre-Gd T1 weighted images were acute lesions that enhanced following Gd administration.

Statistical methods

Differences in serum sex hormone concentrations between MS patients and controls and among MS subgroups were

Abbreviations: DHEAs, dehydroepiandrosterone sulphate; EDSS, expanded disability status scale; FSH, follicle stimulating hormone; Gd, gadolinium; LH, luteneising hormone; RRMS, relapsing-remitting multiple sclerosis.
compared using the unpaired Student’s t test. The Mann–Whitney U test was used to compare MRI derived measures in male and female patients. In both sexes, the relations between MRI derived data and sex hormone concentrations were evaluated by the Spearman rank correlation coefficient.

**RESULTS**

There were no significant differences between women and men in disease duration (mean (SD), women: 6.08 (4.9) vs 6.14 (5.7), NS) or EDSS (women vs men: 2.0 (1.3) vs 2.08 (0.9), NS). The mean number of Gd enhancing lesions was significantly greater in women than in men (women vs men: 3.4 (5.0) vs 1.1 (2.5); p = 0.004). However, the extent of brain damage was similar in both groups, as measured by T2-LL (women vs men: 10.92 (8.2) cm³ vs 10.78 (8.3) cm³, NS) and T1-LL (women vs men: 13.17 (0.2) cm³ vs 15.05 (1.6) cm³, NS).

In women, no significant difference was observed in the frequency of enhancing lesions, T2-LL, or T1-LL between scans obtained during the follicular and luteal phases.

Mean serum hormone concentrations in MS patients and controls are shown in table 1. No significant difference in sex hormone levels was noted between male patients and controls. Women with MS had lower testosterone concentrations than controls in the follicular as well as in the luteal phase of the menstrual cycle.

Considering data on the testosterone levels of healthy women, a normal score for testosterone (within 2 SD of the mean) was calculated. We used this score as a cut off value to identify women with abnormally low testosterone concentrations (more than 2 SD below the mean for the controls). A significantly greater number of Gd enhancing lesions was found in the seven women with abnormally low testosterone levels compared with those with a normal testosterone (7.4 vs 2.5, p = 0.02).

**DISCUSSION**

Several studies have suggested that gender affects the clinical course of MS. Using MRI in a large cohort of patients, we have previously shown that there is a pathological counterpart for the different clinical course, with women having more inflammatory but less destructive lesions than men. Results from this study partially supported previous findings (that is, a greater number of Gd enhancing lesions in women than in men), but failed to detect any difference in the proportion of lesions evolving into “black holes”, probably because of the small sample size.

![Figure 1](http://jnnp.bmj.com/)

**Table 1** Serum sex hormone concentrations in patients with multiple sclerosis and controls

<table>
<thead>
<tr>
<th></th>
<th>Follicular phase</th>
<th>Luteal phase</th>
<th></th>
<th>Follicular phase</th>
<th>Luteal phase</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>MS (n = 35)</td>
<td>Controls (n = 18)</td>
<td>p Value*</td>
<td>MS (n = 35)</td>
<td>Controls (n = 18)</td>
<td>p Value*</td>
</tr>
<tr>
<td>FSH</td>
<td>5.61 (3.7)</td>
<td>8.29 (7.2)</td>
<td>0.08</td>
<td>3.42 (2.7)</td>
<td>3.92 (2.0)</td>
<td>0.49</td>
</tr>
<tr>
<td>LH</td>
<td>5.03 (2.1)</td>
<td>5.53 (3.1)</td>
<td>0.50</td>
<td>4.52 (9.4)</td>
<td>6.60 (7.9)</td>
<td>0.42</td>
</tr>
<tr>
<td>Oestradiol</td>
<td>82.54 (87.1)</td>
<td>56.22 (44.5)</td>
<td>0.24</td>
<td>80.17 (52.4)</td>
<td>150.94 (165.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.49 (0.1)</td>
<td>0.58 (0.1)</td>
<td>0.03</td>
<td>0.47 (0.1)</td>
<td>0.63 (0.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>DHEAs</td>
<td>2.06 (1.2)</td>
<td>2.61 (1.4)</td>
<td>0.14</td>
<td>2.01 (1.2)</td>
<td>2.48 (1.0)</td>
<td>0.16</td>
</tr>
<tr>
<td>Progesterone</td>
<td>0.66 (0.2)</td>
<td>0.82 (0.3)</td>
<td>0.04</td>
<td>6.39 (7.6)</td>
<td>7.03 (7.0)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Values are mean (SD).

*B by Student’s t test.

DHEAs, dehydroepiandrosterone sulphate; FSH, follicle stimulating hormone; LH, luteinising hormone.

To analyse the relation between MRI derived measures and the concentrations of each hormone in women, only the MRI scan acquired during the follicular phase was considered. Higher serum testosterone levels in women with MS were associated with higher T1-LL (r = 0.48, p = 0.006), but not with T2-LL (r = 0.32, p = 0.06). No significant relation was found between MRI data and oestradiol concentrations (T2-LL: r = 0.47, r = 0.49, p = 0.04). No significant relation was shown between MRI findings and testosterone concentrations (T2-LL: r = 0.48, p = 0.006; T1-LL: r = 0.32, p = 0.06). No significant relation was found between the other sex hormone levels and MRI measures of tissue damage.

In women, a trend towards significance was found in the relation between testosterone concentrations and neurological disability as measured by the EDSS (r = 0.29, p = 0.05). In men, EDSS and oestradiol levels were not significantly associated (r = −0.15, p = 0.65).
The primary objective of this study was to determine whether there is a link between the profile of sex hormones and MRI characteristics of brain damage in RRMS. As a first step, we investigated whether MS patients had hormonal patterns that were different from those in healthy controls. The results showed that women with MS had lower testosterone concentrations than normal subjects. Women with hormonal levels more than 2 SD below those of healthy controls had more enhancing lesions than women with normal testosterone concentrations. In autoimmune diseases other than MS, such as systemic lupus erythematosus and rheumatoid arthritis, where the hormonal balance seems to play a pathophysiological role, serum testosterone in women was at its lowest level during exacerbations of the disease. By contrast, we found no significant differences in the sex hormone levels between men suffering from MS and healthy men. Although the small number of controls compared to patients might have obscured a differential effect, it can be argued that testosterone concentration was in the normal range in men with MS because they were less prone to develop inflammatory lesions, as has been found previously. In a study assessing endocrine function in MS, Wei and Lightman reported an overactivation of the hypothalamic-pituitary-adrenal axis in parallel with inflammation. Furthermore, Foster et al. suggested that inflammatory cytokines might stimulate the hypothalamic-pituitary-gonadal axis resulting in a decreased production of testosterone. The fact that lower testosterone levels could also account for lower levels of oestradiol during the luteal phase cannot be excluded as, in the ovarian steroidogenesis, 17-β oestradiol is produced from testosterone in the granulosa cells. Lower luteal oestradiol levels cannot be explained by an abnormality in the menstrual cycle (such as anovulation), as progesterone levels were augmented during the luteal phase in a similar way to the control population.

Moreover, in women affected by MS, higher testosterone concentrations were significantly associated with both T2-LL (r = 0.47, p = 0.02) and T1-LL (r = 0.43, p = 0.04). No significant association was found between MRI findings and testosterone levels (T2-LL: r = -0.08, p = 0.93; T1-LL: r = 0.12, p = 0.57). T1-LL, T1 hypointense lesions; T2-LL, T2 hyperintense lesions.

Figure 2: Relation between sex hormone levels and magnetic resonance imaging (MRI) findings in men with multiple sclerosis. Oestradiol concentrations correlated with both T2-LL (r = 0.47, p = 0.02) and T1-LL (r = 0.43, p = 0.04). No significant association was found between MRI findings and testosterone levels (T2-LL: r = -0.08, p = 0.93; T1-LL: r = 0.12, p = 0.57). T1-LL, T1 hypointense lesions; T2-LL, T2 hyperintense lesions.

Conclusions
Our study indicates that serum testosterone is reduced in women suffering from MS, as in other autoimmune inflammatory syndromes, especially during the active phase of the disease, as documented by brain MRI. We therefore propose that oestrogens and testosterone play a role in modulating the development of brain tissue damage in MS. The respective contribution of these two hormones and their types of actions and interactions deserve further analysis.

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