

High incidence of hyperandrogenism-related clinical signs in patients with multiple sclerosis

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Abstract

A mild prevalence of multiple sclerosis (MS) is present in females (2:1). To elucidate the pathogenetic role of sex steroids on the disease, we studied 76 women affected by MS, compared to 50 healthy women (mean age \pm SD, 34.9 ± 0.9 vs 33.4 ± 1.7 years). The menarche was at mean age of 12.3 ± 0.2 vs 12.4 ± 0.2 . Interval between menses was 28.0 ± 0.3 vs 27.8 ± 0.3 days, with duration of menstrual flow of 5.0 ± 0.2 vs 5.0 ± 0.2 days. Oligo- or amenorrhea was present in 20% of patients and in 16% of controls. Oral contraceptives were assumed by 21% of patients and 34% of controls (n.s.).

Premenstrual symptoms were found in 43% of patients and in 46% of controls (n.s.). The incidence of hyperandrogenism (greasy skin, acne and hirsutism), evaluated by a specific questionnaire, was higher and statistically significant in MS patients than in controls (28% vs 10%, $p < 0.05$). Further studies, including a complete clinical and laboratory evaluation of gonadal function, are necessary in order to clarify whether hyperandrogenism may influence MS disease activity.

Abbreviations

MS:	multiple sclerosis
X ² :	chi-square
HyperA:	hyperandrogenism

Introduction

A pathogenetic role for sex steroids on immune system activity in Multiple Sclerosis (MS) has been suggested.

Evidence in the literature shows a mild prevalence in females (2:1), a lower disability in younger patients using oral contraceptives, a reduced frequency of exacerbations during pregnancy followed by relapses in post-partum period and a correlation between sex hormone levels and disease activity evaluated by magnetic resonance imaging during the menstrual cycle [1–5].

Material and methods

We investigated the menstrual history, the use of oral contraceptives, the presence of premenstrual symptoms and hyperandrogenism in female MS patients compared to controls, by means of a questionnaire. Seventy-six patients affected by MS, according to Poser criteria [6], and 50 healthy women from the hospital staff were interviewed about their men-

strual history, in terms of interval between menses (days) and duration of menstrual flow (days), and the use of oral contraceptives; moreover the same physician noted MS patient and control complaints with regard to premenstrual symptoms and hyperandrogenism. All subjects were fully informed of the purpose of the study and gave their approval.

Amenorrhea and oligomenorrhea were assumed as more than 6 months since last menstrual period and cycle length of more than 35 days, respectively.

Hyperandrogenism was divided into three items (greasy skin, acne and hirsutism). The degree of each item was evaluated using a 4-point scale (0=absent, 1=mild, 2=moderate and 3=severe degree). Hyperandrogenism was defined positive if at least one item, with degree ≥ 2 (moderate and severe degree), was present in the same subject.

We investigated 7 premenstrual symptoms (depression, irritability, drowsiness, breast tenderness, abdomen swelling, headache and weight gain) and subjects were considered positive when they reported ≥ 4 positive answers.

Statistical analysis was performed by using X²-test. The Mantel-Haenszel procedure was applied to evaluate the differences between MS patients and normal subjects, after adjustment for the possible effects connected with the examined factors.

Tabel I. Disorders of gonadal function and use of oral contraceptives in MS patients (n=76) and controls (n=50).

	MS patients	Controls	
Oligo-amenorrhea	20%	16%	n.s.
Premenstrual symptoms	43%	46%	n.s.
Hyperandrogenism	28%	10%	p<0.05
Oral contraceptives	21%	34%	n.s.

Tabel II. Association between multiple sclerosis (MS) and hyperandrogenism (HyperA) in subgroups of subjects assuming oral contraceptives, according to the Mantel-Haenszel procedure.

Group	MS patients			Controls			MS patients and controls		
	with HyperA	without HyperA	Total	with HyperA	without HyperA	Total	with HyperA	without HyperA	Total
with Contraception	7	9	16	1	16	17	8	25	33
without Contraception	14	46	60	4	29	33	18	75	93
Total	21	55	76	5	45	50	26	100	126

Corrected X²=5.1, with 1 degree of freedom, p<0.025

Results

Patient and control clinical characteristics were not significantly different, respectively considering age (34.9 ± 0.9 vs 33.4 ± 1.7 years) (mean \pm SD), age of menarche (12.3 ± 0.2 vs 12.4 ± 0.2 years), interval between menses (28.0 ± 0.3 vs 27.8 ± 0.3 days) and duration of menstrual flow (5.0 ± 0.2 vs 5.0 ± 0.2 days).

Oligo- and amenorrhea were present in 20% of patients and 16% of controls (n.s.). Premenstrual symptoms were found in 43% of patients and in 46% of controls (n.s.). The incidence of hyperandrogenism was higher and statistically more significant in MS patients (28%) than in controls (10%) ($X^2=4.988$, with 1 degree of freedom, $p<0.05$). Oral contraceptives were assumed by 21% of MS patients, compared with 34% of controls (n.s.) (tabel 1).

Since the use of estrogens/progestagens combinations for contraception could differently reduce the clinical appearance of hyperandrogenism in MS patients and controls, we applied the Mantel-Haenszel procedure to evaluate such a possibility. This approach confirmed that the association between MS and hyperandrogenism was statistically significant (corrected $X^2=5.1$, $p<0.025$), after adjustment for the possible effects connected with the use of oral contraceptives (tabel 2).

Discussion

In our results, 20% of MS patients referred a history of oligo-amenorrhea, without statistically significant difference in comparison with controls (16%) (tabel 1). A similar result has been previously observed [7–9].

The incidence of premenstrual syndrome was comparable between MS patients and controls. A wide range of incidence (5–100%) of premenstrual symptoms was described in the literature, depending on number and intensity of symptoms investigated [10].

We found a higher incidence of hyperandrogenism-related clinical signs in MS patients than in controls. Clinical aspects of hyperandrogenism in MS patients are only marginally reported in the literature. Grinstead et al. showed increased circulating androgen levels of ovarian origin (delta4-androstenedione and testosterone) and normal adrenal androgen (dehydroepiandrosterone sulphate) concentrations in fertile women with MS [8]. The same authors reported that none of MS patients revealed clinical symptoms of hyperandrogenism. However they only investigated the menstrual cycle pattern and fertility problems in MS patients. On the contrary, we examined other clinically relevant aspects of hyperandrogenism itself, not clearly investigated before. Further studies are necessary in order to confirm our data by the means of the diagnostic tools used for hyperandrogenism (as the

Ferriman-Gallwey scale for hirsutism and laboratory assays for serum sex hormone evaluations).

Experimental data have shown that the hormonal environment may influence the immune activity [1]. The presence of sex hormone receptors was demonstrated in immune cells [11, 12] and all the three major classes of sex steroids (estrogens, androgens and progesterone) may influence cytokine secretion, demonstrating different modulatory effects [1].

Therefore a complete clinical and laboratory evaluation of gonadal function seems necessary in studies investigating correlations between sex steroids and disease activity in MS patients.

Regarding exogenous sex steroids, oral contraceptives were assumed by 21% of MS patients and 34% of controls, probably reflecting a more usual practice among normal subjects.

In conclusion, our results show that MS patients more frequently present clinical signs of hyperandrogenism, in comparison to controls. Further studies are necessary in order to clarify whether hyperandrogenism may influence MS disease activity.

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