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Sex hormone patterns in women with multiple sclerosis as related to disease activity – a pilot study

Profil hormonalny u kobiet chorych na stwardnienie rozsiane w powiązaniu z aktywnością choroby – doniesienie wstępne

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Abstract

Background and purpose: The influence of sex hormones on immune system activity in multiple sclerosis (MS) has been suggested by clinical evidence. The aim of the study was to analyse the pattern of sex hormones in MS women and to correlate the hormone pattern abnormalities to the disease course as well as to the magnetic resonance imaging (MRI) results.
Material and methods: We studied the serum level of the progesterone, β-oestradiol and prolactin in 46 women with clinical definite MS aged from 19 to 65; mean disease duration was 11.80 ± 9.86 years. The evaluation of the intensity of hormonal changes was done using a scoring system (0-3). On the brain MRI, the presence of brain atrophy, of hypothalamic demyelination as well as demyelination intensity (or degree) were analysed. The evaluation of the degree of demyelination and brain atrophy was done using a scoring system (0-4).
Results: The main hormonal abnormalities consisted of decreased progesterone level, increased oestradiol level or both. The sex hormone pattern was abnormal in 56% of patients. Hypothalamic lesions were found on MRI in 53% of cases. The abnormal hormonal pattern correlated with intensity of MR changes ($p < 0.05$, Fisher's exact test), but neither with presence of hypothalamic changes nor with disease parameters (Expanded Disability Status Scale, relapse rate, disease duration).

Streszczenie

Wstęp i cel pracy: Dane z piśmiennictwa sugerują częste występowanie zaburzeń hormonalnych u kobiet chorych na stwardnienie rozsiane (SR). Celem pracy była analiza profilu hormonalnego w zakresie hormonów płciowych u kobiet z SR w powiązaniu z przebiegiem klinicznym i obrazem rezonansu magnetycznego (RM) mózgowia.
Materiał i metody: Badano stężenie progesteronu, β-estradiolu i prolaktyny w surowicy u 46 pacjentek z klinicznie pewnym SR, w wieku od 19 lat do 65 lat, o średnim czasie trwania choroby 11,80 ± 9,86 roku, niestosujących żadnej terapii hormonalnej. Stopień zmian w profilu hormonalnym oceniano półilościowo wg przyjętego arbitralnie przez autorów systemu punktacji (0–3).W analizie RM brano pod uwagę obecność ognisk demielinizacji w obrębie struktur podwzgórza, nasilenie demielinizacji w obrębie mózgowia oraz współistnienie zaniku mózgu. Stopień zmian w RM oceniano także półilościowo wg przyjętego arbitralnie przez autorów systemu punktacji (0–4).
Wyniki: Nieprawidłowe stężenia hormonów stwierdzono u 26 pacjentek (56%). Nieprawidłowości polegały na zmniejszonym stężeniu progesteronu, zwiększonym stężeniu 17-β-estradiolu bądź na łącznym występowaniu obu tych zaburzeń. W badaniu RM w 53% przypadków stwierdzono

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Conclusions: It is important to check the hormonal pattern in MS women because according to our results it may be related to the disease activity and probably affects the type of therapeutic intervention. This pilot study will be extended in a larger population.

Key words: sex hormones, MRI, multiple sclerosis.

obecność zmian demielinizacyjno-zapalnych w obrębie podwzgórza. Stopień zaburzeń hormonalnych oceniany półilościowo korelował ze stopniem zmian w RM mózgowia ($p < 0,05$; test dokładny Fishera), nie był natomiast związany z obecnością zmian w obrębie podwzgórza czy parametrami klinicznymi (punktacja w *Expanded Disability Status Scale*, częstość rzutów, czas trwania choroby).

Wnioski: Stan hormonalny kobiet chorych na SR powinien być brany pod uwagę w analizie klinicznej choroby i przy decyzjach terapeutycznych, gdyż wydaje się mieć związek z aktywnością SR. Badania te, w celu potwierdzenia uzyskanych wyników, należy kontynuować na szerszym materiale.

Słowa kluczowe: hormony płciowe, rezonans magnetyczny, stwardnienie rozsiane.

Introduction

Multiple sclerosis (MS) is an autoimmune disease, characterized by a chronic inflammatory demyelinating process in the central nervous system (CNS). Females have an increased risk of developing autoimmune diseases such as rheumatoid arthritis (RA) and MS compared to males. Relapsing-remitting MS (RRMS) affects females two to three times more often than males [1-3]. Although the mechanism for gender disproportion related to susceptibility and disease progression in MS is unclear, increasing evidence suggests that sex hormones play an important role [4-8]. For example, the clinical signs of MS usually appear in young adults, after sexual maturity. Other periods of change in serum sex hormone concentrations, such as during menstruation and the menopause, may also negatively affect the course of MS [9-11]. Little is known about the influence of oral contraceptives on the modulation of the disease activity in MS [12]. More evidence for a role of sex hormones in MS is observed during pregnancy [13-15]. Indeed, increased level of sex hormones produced during pregnancy have been reported to reduce the severity of MS, whereas in a period of time marked by reduced sex hormones, such as the postpartum period, clinical symptoms of MS often increase. Pregnancy is associated with enhanced humoral and decreased cellular immune activity [16,17].

The goal of this article is to analyse the pattern of sex hormones in MS women and to correlate the hormonal pattern abnormalities with the clinical course of the disease and to the magnetic resonance imaging (MRI) results.

Material and methods

Subjects

The study group included 46 women with clinically definite MS diagnosed according to the criteria proposed by McDonald *et al*. [18]. The control group for hormonal study consisted of 50 healthy women matched for age and hormonal status (premenopausal and postmenopausal).

Sex hormone levels obtained in the control group of healthy women were usually accepted as normal; if in a given case results markedly exceeded the limits obtained in the control group ("outsiders") that person was not included in the control group. The hormone mean values and ranges found in controls are presented in Table 1.

The patients were recruited from MS Outpatient Clinic and MS Unit, Department of Neurology, The Medical University of Warsaw. Their characteristics are provided in Table 2. There were 27 patients with RRMS, 12 with secondary progressive course (SPMS) and 7 with

Table 1. Hormone value ranges in controls

Menstrual cycle phases	17-β-oestradiol	Progesterone
	Mean and range (pg/mL)	Mean and range (nmol/L)
Follicular phase	102.0 (35.0-169.0)	2.10 (1.21-2.99)
Ovulation	238.0 (49.0-427.0)	Not detectable
Luteal phase	122.0 (53.0-191.0)	55.31 (24.71-85.90)
Postmenopausal period	64.0 (18.0-110.0)	1.08 (0.60-1.56)

Table 2. Demographic characteristics of multiple sclerosis patients

Characteristics	Multiple sclerosis patients
Number of patients	46
Age [years]; mean ± SD (range)	39.28 ± 11.67 (19-65)
Multiple sclerosis duration [years]; mean ± SD (range)	11.80 ± 9.86 (0.5-39.0)
Relapse Index; mean ± SD (range)	2.24 ± 2.60 (1-12)
EDSS; mean ± SD (range)	3.51 ± 1.71 (1-7)

SD – standard deviation, EDSS – Expanded Disability Status Scale

Table 3. Magnetic resonance imaging (MRI) analysis: scoring system

MRI abnormalities (scores)	
0	Normal brain MRI
1	Moderate multifocal demyelination
2	Marked multifocal demyelination
3	Marked diffuse demyelination
4	Marked diffuse and multifocal demyelination and brain atrophy

Table 4. Hormone pattern analysis: scoring system

Hormone abnormalities (scores)	Progesterone serum level	7-β-oestradiol serum level
0	Normal	Normal
1	Decreased	Normal
2	Normal	Increased
3	Decreased	Increased

relapsing-progressing MS (RPMS). Hormonal and MRI studies were performed during thet follicular phase in 14 patients, during the luteal phase in 12 patients, during ovulation in 1 woman. In 19 women hormonal evaluation has confirmed postmenopausal state. Neither patients nor controls have received any hormonal therapy, including hormonal contraception. There was no relevant gynaecological history in the control group. The patients' gynaecological symptoms and signs were also insignificant except for mild menstrual disturbances occurring in 50% of patients, consisting of irregular menstruation. All subjects gave their informed consent prior to their inclusion in the study. Brain MR as well as hormonal panel are a part of the standard procedures performed in the MS Unit.

Magnetic resonance imaging

On MRI examination, conventional spin echo sequences were used to obtain proton density and T2-weighted images of the brain. The T1-weighted images were also analysed. The MR images were evaluated according to an arbitrarily proposed semi-qualitative scoring system used in our MS Unit. Such evaluation was performed by an experienced neuroradiologist. It was impossible to perform qualitative MRI analysis for technical reasons. The evaluation of the degree of demyelination and brain atrophy was done using a scoring system (Table 3). In addition, on 36 scans it was possible to analyse the presence and then to assess the number of T2-weighted hypothalamic lesions.

Hormonal studies

At the day of MR study (± 7 days), serum levels of 17-β-oestradiol (pg/mL), progesterone (ng/L) and prolactin (ng/mL) were determined. Blood samples were stored at –20°C until analysis. Single measurement of the level of sex hormones is insufficient from an endocrine and gynaecological point of view to make a precise diagnosis of possible disturbances and in this study it serves only as a basis for preliminary conclusions and for comparison with the control group. Hormonal evaluations were blinded and performed in a single radioimmunoassay for each hormone. The evaluation of the intensity of hormonal changes was done using a scoring system (Table 4). The hormone levels were analysed separately for each hormone and for each hormonal phase. For example, the progesterone level was considered abnormal in the follicular phase if it was < 1.21 nmol/L or > 2.99 nmol/L.

Statistical analysis

Values are presented as mean ± SD as well as means and ranges. The Spearman correlation coefficients test was used to study the correlations between the following variables: Expanded Disability Status Scale (EDSS), age, disease duration, relapse index and MRI as well as hormonal scores. Wilcoxon rank-sum test was used to analyse the differences between patients and controls. Fisher exact test was used to study the associations between different parameters, i.e. hormonal and MR scores in different subgroups. Statistical significance was defined as $p < 0.05$.

Results

Hormonal changes

The mean hormone levels in the MS patient group were as follows: 137.7 ± 144.26 pg/mL for oestradiol, 6.41 ± 11.59 nmol/L for progesterone and 93.29 ± 344.21 ng/mL for prolactin (prolactin level ranges in controls were from 1.2 to 29.93 ng/ml). These results in different cycle phases (hormones' mean values and ranges) compared with the control group are presented in Fig. 1. The oestradiol level was abnormal in 12 patients (26.1%), the progesterone level in 21 (45.6%) and the prolactin in 5 cases (10.9%). Because of the small number of patients in each subgroup, statistical comparison of the sex hormone level differences between MS patients and the control groups in particular phases of the menstrual cycle was not possible. The distribution of the degree of hormonal changes (in scores) is presented in Fig. 2. In general, hormonal abnormalities were found in 26 MS women (56.5%) and were usually of mild intensity (score 1).

Magnetic resonance imaging changes

Hypothalamic lesions were found on MRI in 17 of 36 analysed cases (53%). The distribution of the degree of MR changes (in scores) is presented in Fig. 3. This distribution was almost equal for scores 1, 2 and 4.

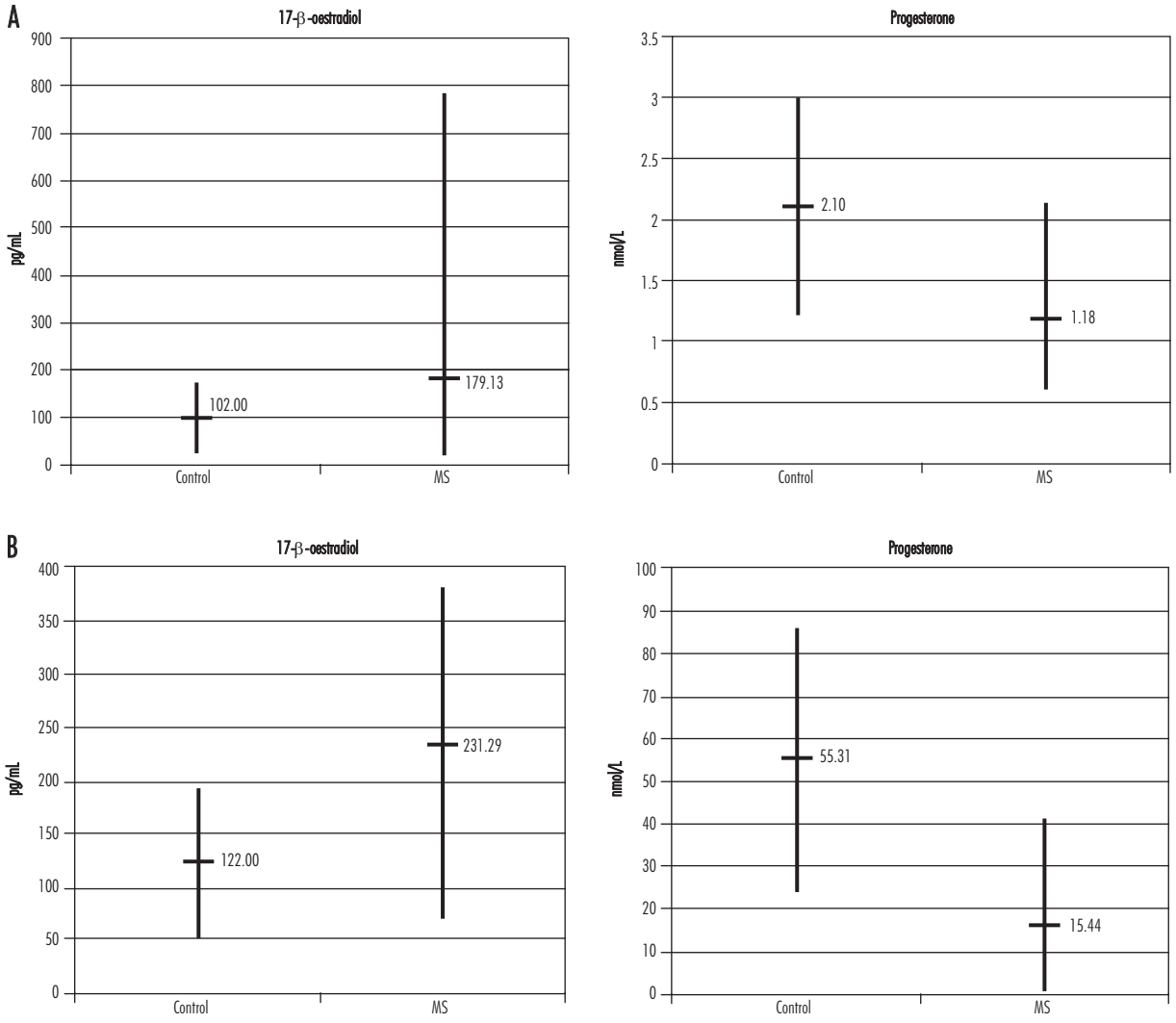

Fig. 1. Hormone levels in multiple sclerosis (MS) patients and controls (means and ranges): A) follicular phase and B) luteal phase

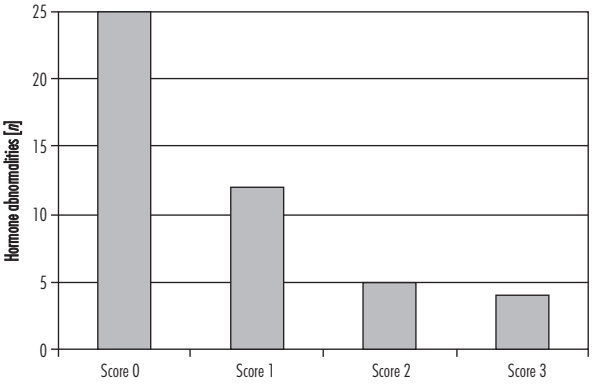

Fig. 2. Hormonal abnormalities distribution (in scores) in multiple sclerosis patients

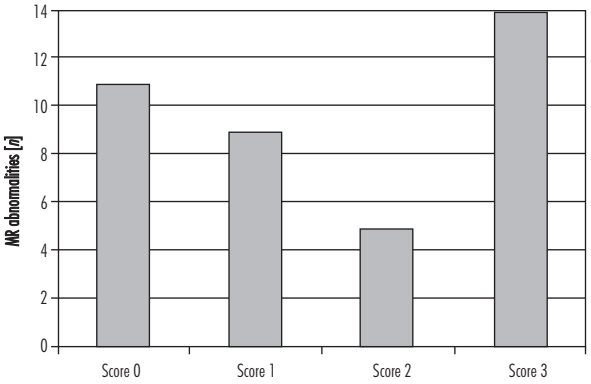

Fig. 3. MRI abnormalities distribution (in scores) in multiple sclerosis patients

Hormonal versus MR changes

The significant associations were found between hormonal and MR score distribution if studied by Fisher's exact test ($p < 0.05$).

Neither the hormonal nor MR scores were related to the clinical parameters (i.e. the age of the patients, the MS duration, the EDDS value as well as the relapse index).

There was no correlation between the presence and the number of hypothalamic lesions on MR and the hormonal change scores. Especially the presence and the number of hypothalamic lesions were not closely related to the prolactin level if studied by Wilcoxon two samples and by Kruskal-Wallis test.

Discussion

It seems that sex hormones play an important role in susceptibility to MS and in disease progression. In our material the oestradiol level was abnormal (increased) in about one-fourth of patients, whereas both oestrogen (high) and progesterone (low) levels were abnormal in about half of patients.

Oestrogen has a dichotomous effect on the immune system [19]. For example, T cell development in the thymus is suppressed, whereas antibody production is stimulated by oestrogen [20,21]. Furthermore, oestrogen decreases T-cell mediated delayed-type hypersensitivity [21,22], granulocyte-mediated cytotoxicity and natural killer-mediated cytotoxicity [22,23]. Oestrogens are considered to differentially affect immune responses during pregnancy, during the menstrual cycle, and in postmenopausal women [6,19]. During pregnancy, oestrogens play an important role in regulating physiological events essential to the maintenance of the fetus and the protection of the mother, but may also influence the clinical course of MS [24-26]. Indeed, in MS it is well known that late pregnancy affords temporal remission of MS attacks [27]. The clinical remission is also associated with a decrease of the disease activity on the MRI [28-30]. Women who first developed symptoms of MS during pregnancy experience less subsequent disability than women who developed the disease at any other time [31]. Besides the possible immune modulation by oestrogen during pregnancy, it can be anticipated that oral contraception similarly affects the immune system. Although no data in MS have been reported about the long-term effects of oral contraception, the effects of oral contraception in rheumatoid arthritis (RA) have been debated. No definite conclusion could be drawn, since a beneficial effect has been documented in some earlier studies, while in others oral contraception has no effect [32-35]. This may reflect the reduced amount of oestrogen in more recent oral contraceptives and the use of synthetically modified oestrogen [36].

The exact role of progesterone in MS remains unclear [37,38]. It might modify the cytokine production in MS [39]. Pozzilli *et al*. [40] found that increased ratio of progesterone/17-β-oestradiol during the luteal phase was associated with both a high number and volume of enhancing lesions on MRI. In our study we have confirmed the relationship between this ratio and the degree of MR changes. During pregnancy, the placenta produces a high level of progesterone responsible for the immunosuppressive effect. Contrarily, Correale *et al*. [14] found in MS that progestrone, in concentrations similar to that found in the peripheral circulation during the normal menstruation, during pregnancy, as well as in pharmacological doses, enhanced secretion of IL-4 by peripheral CD4+T cells. Since IL-4 plays an important role in

the development of Th2 cells, progesterone seems to be a good candidate for their promotion.

In our study we analysed the MR abnormalities in relation to hormonal changes. The clinical remission in MS is usually associated with a decrease of the disease activity on the MRI [28]. Some studies revealed gender-associated differences in clinical evolution of MS as well as in the evolution of MRI findings. Female patients are more likely to develop more inflammatory but less destructive lesion pathology. There was a trend toward higher lesion volume in T1-weighted images and higher ratio T1/T2-weighted lesions when comparing male to female with RRMS. Women showed a smaller number of Gd-enhancing lesions [41]. These results indicated a gender effect on MRI findings in MS using conventional MRI techniques [42].

We tried to correlate the MRI findings and clinical MS parameters. Our results were unrelevant. Particularly there was no relationship between hormonal abnormalities and presence and/or number of hypothalamic lesions.

Conclusions

The molecular basis for explaining the hormonal pattern related differences in MRI findings in women with MS and the underlying pathological process translating the disease activity in general, as well as in our study, in MRI-related measures remains unclear, although a divergent imbalance between demyelination, inflammation and neurodegeneration related to hormonal patterns is proposed. To confirm the obtained results our pilot study should be extended to a larger patient population.

Disclosure

Authors report no conflict of interest.

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