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Effect of hormonal changes on the neurological status in the menstrual cycle of patient with multiple sclerosis

Yuksel Guven Yorgun[a,*], Serkan Ozakbas[b]

[a] Odemis State Hospital, Izmir, Turkey
[b] Faculty of Medicine, Department of Neurology, Dokuz Eylul Univesity, Izmir, Turkey

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ABSTRACT

Objectives: Premenstrual worsening has been often complained by patients with multiple sclerosis (MS). However, there is no quantitative study in the literature regarding premenstrual worsening and there are only a few studies for its reasons. In diseases such as MS, which there are limited evidence about the etiology and the triggers, detection of the variables in menstrual period, which is defined relatively easy, has a great potential to shed light to the disease. In the present study, we aimed to detect whether there was a deterioration in premenstrual period of patients with MS and to measure the observed deterioration and the relationships between demographics, physical and hormonal variables.

Patients and methods: This study included 44 patients with MS, who were diagnosed according to McDonald criteria, and 14 healthy controls. For two consecutive cycles, cases were evaluated on the basis of neurological functions in the premenstrual and ovulation phases. In each examination, blood samples were obtained for detection of the levels of sex hormones (FSH, LH, E2, Progesterone). In the first and the fourth examinations, we applied Multiple Sclerosis Functional Composite (MSFC).

Results: Patients with MS showed poor performance in all used measurements than the healthy controls. Premenstrual period was worse based on cognitive aspects than the ovulation period in both MS patients and healthy controls. This was more evident in patients with MS. Patients treated with immunomodulatory agents had better cognitive performance than those were not given these agents.

Conclusion: In our study, the patients with MS were found to be worse in cognition, and physical performance when compared with the healthy group. In premenstrual period, cognitive functions, and physical performance deteriorated in patients with MS. Healthy people seemed to be deteriorated on cognition measured with Paced Auditory Serial Addition Test.

1. Introduction

Multiple sclerosis (MS) is probably an autoimmune disease characterized with demyelination, axonal loss and gliosis in a genetically predisposed individual. It is the most common cause of neurological disability after trauma in young adults [1–4]. Usually starts between the ages of 20–40 years. It is more common in women than men [5–7], and has a better prognosis in women [3].

The etiology has not been elucidated, however T lymphocytes are known to be effective in immunopathogenesis. Helper CD4 + T lymphocytes are located intensively around MS plaque and the surrounding veins. These cells are functionally divided into two as T helper 1 (TH-1) and T helper 2 (TH-2). CD4 + TH-1 cells are reactive to myelin antigens [8].

There is a strong relationship between autoimmune diseases and sex hormones [9]. TH-1 cell response is more dominant in women than men; which may explain the higher incidence of MS and other autoimmune diseases in women than men [9–13]. Low estrogen levels support TH-1 type proinflammatory response. High levels of estrogen and progesterone support the TH-2 response [14]. MS attack rate changes due to pregnancy is thought to be closely related to fluctuations in the sex hormones [14–21].

The onset of experimental model of MS, experimental allergic encephalomyelitis (EAE) is delayed, severity and incidence decreases when treated with estrogen or estriol, because estrogen therapy causes a shift from TH-1 to TH-2. The increased severity of EAE in experimental animals, which underwent oophorectomy, creates a strong evidence for the effect of estrogen on experimental model [9–22]. Also,

* Corresponding author.
E-mail addresses: yuksel.yorgun@gmail.com (Y. Guven Yorgun), serkan.ozakbas@gmail.com (S. Ozakbas).

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subjective symptomatic deterioration in MS patients with menopause has been reported [23,34].

Premenstrual exacerbation of MS patients is a condition often noted and is likely related to sex hormones. Elaboration of the relationship between hormonal situation and clinical profile can be a guiding light in the elucidation of disease pathogenesis as well as both the nature and extent of this relationship may introduce prophylactic and/or symptomatic treatment options. In MS where there is limited evidence regarding etiology and triggering factors, identification of variables related to menstrual period that is the relatively easy to define, has potential contributions in elucidating the disease. The primary aim of the present study is to compare the premenstrual and ovulation periods on the basis of physical and cognitive clinical parameters in order to investigate whether there is a deterioration in patients with MS during the premenstrual period. The secondary objective of this study is to identify relationship between clinical parameters and demographic (such as age, education) and disease-related features (such as duration of disease, number of attacks etc.), to detect whether there is correlation between these parameters and sex hormone levels, and to compare healthy women with MS patients in terms of these features.

2. Materials and methods

2.1. Patients and control group

This study Patients included patients followed-up in our Demyelinating Diseases outpatient clinic, aged above 18 years, and who were diagnosed according to revised McDonald criteria (2010) [24]. The patients were selected if they had regular menstrual cycle, and cognitive levels to give history and were able to sign the informed consent forms.

Patients were randomly selected in order of admission to the clinic. Patients who had MS attack within the past month; who have used drugs (corticosteroid use within the past month or intensive immunosuppressive therapy in the last three months), or had additional neurological disease that may affect the clinical evaluation; who had psychiatric disorders that might affect cognitive tests; who had other medical illnesses that may affect sex hormone levels; and who would not be able to attend regular follow-ups, were excluded. The patient group was compared with age and education-matched healthy women of reproductive age.

2.2. Clinical evaluation

Timed 25-Foot Walk (T25-WT) is used for lower-extremity functions, 9- Hole Peg Test (9-HPT) is used for upper extremity functions, Paced Auditory Serial Additional Test (PASAT)-3 s version (PASAT-3) was used for evaluation of cognitive status [25–27]. Cognitive level was also evaluated by visual analog scale (VAS) which helped us to understand the cognitive level from the patients' perspective.

2.3. Hormonal evaluation

FSH, LH, E2, progesterone levels were measured in 5 mL venous blood drawn from the arm. Hormone levels were examined in Endocrinology Laboratory of our hospital, which had long time experience and had a large normative data.

2.4. Procedure

Written informed consents were obtained from all the patients after informing the patients about the aim and the design of the study, and then detailed medical history was obtained. The last menstrual period (first day of the last menstrual bleeding), the average duration of menstruation and cycle duration, were questioned retrospectively. In patients who could not provide this information or the exact details, precise information was obtained by allowing to experience the subsequent cycle. After determining menstrual periods in all cases, dates of visits were set, and patients were given appointments for the first visits. The two visits were arranged at premenstrual period (the period between a week before menstruation and the first day of menstruation) and the other two visits were at ovulation period (13–16 days before the expected menstruation). Also during the visit, patients were questioned again whether they are in the exact period. Blood sampling (5 mL) was performed from the arm veins, and FSH, LH, E2 and progesterone levels were measured. All patients were evaluated for four times during their 2 cycles, including 2 times in the premenstrual and two times in the ovulation periods.

In the first and fourth visits; Neurological inspection (EDSS was calculated), PASAT, T25-WT and 9HPT were performed.

Thus, as approximately one and a half months elapsed between the repeated cognitive test (PASAT), it was avoided that patients could learn test structure so that they could get higher score in the next visit. It was provided that test performances of patients were independent from adaptation mechanisms by selecting the first visit randomly in premenstrual or ovulation period.

If the first visit was initiated in premenstrual period, the fourth visit was scheduled in the second ovulation period. If the first visit was initiated in ovulation period, the fourth visit was scheduled in the second premenstrual period.

2.5. Statistical analysis

Patients and healthy subjects were compared using the non-parametric tests. Mann-Whitney U test was used in comparison of variables in either ovulation or premenstrual periods. Wilcoxon test was used in comparison of these two periods in terms of specified variables. The difference between patients and healthy subjects (Delta - Δ) in each menstrual periods was compared with the Mann Whitney U test. Wilcoxon test was used to compare the difference between ovulation and the premenstrual periods (Delta - Δ) for each variable.

Cognitive correlations between patients and healthy subjects in both premenstrual and ovulation periods were performed using Spearman correlation test. In correlation analysis, it was accepted that $r < 0.40$ indicated weak correlation; $r = 0.41–0.59$ moderate correlation; $r = 0.60–0.80$ strong correlation; and $r > 0.80$ as excellent correlation.

EDSS and EDSS functional systems in ovulation and premenstrual periods were compared using Friedman ANOVA test. A p value < 0.05 was considered statistically significant.

3. Results

Sixty five patients with regular menstrual cycle who met inclusion criteria were invited for the study. Of patients, 17 rejected to participate to the study. The study was started initially with 47 patients, but one patient had an attack at the first visit and another one at the third visit, thus they were excluded. Another patient left the study after the first visit. A total of 44 patients completed the study by regularly attending all visits. Control group consisted of 14 subjects. Of the patients, 21 were in the premenstrual period, and 23 in the ovulation period at the first visit. Seven subjects in the control group were in the premenstrual period, and 7 in the ovulation period when they attended the first visit. Demographic characteristics of the patients and controls are presented in Table 1 and clinical characteristics of patients in Table 2.

3.1. Cognitive evaluation

When ovulation and premenstrual periods were compared, significant differences were determined in PASAT between the patients and healthy subjects (Table 3). There was a significant difference in PASAT both in the ovulation and premenstrual periods. While

Table 1
Demographic Characteristics of the Subjects.

	MS Group	Control Group	P
N	44	14	
Age	31.10 ± 7.12	29.13 ± 5.34	NS
Total Education time *(year)*	14.01 ± 3.46	15.43 ± 4.1	NS
Education n *(%)*			
Primary school	4 (1)	1 (7)	
High school	15 (35)	4 (29)	
University	25 (64)	9 (64)	
Total number of pregnancy	0.84 ± 1.05	0.38 ± 0.61	NS
Number of children mean ± SD	0.66 ± 0.8	0.36 ± 0.63	NS
Marital Status %			
Married	38.6	35.7	NS
Unmarried	61.4	64.3	NS
Total breastfeeding time (month)	5.8 ± 8.9	5.4 ± 10.18	NS
PMDD Criteria rating (%)	20.45	7,14	NS
PMDD score	6.34	5.5	NS

SD: Standard deviation, EDSS: Expanded disability status scale.
PMDD: Premenstrual Dysphoric Disorder, NS: Non Significant.

Table 2
Clinical Characteristics of the Patient Group.

Age of Disease Onset, *mean ± SD*	26.68 ± 6.28
Disease duration, *mean ± SD*	7.15 ± 6.2
Number of Attacks, *mean ± SD*	2.95 ± 1.44
Mean Number of Annual Attacks, *mean ± SD*	0.67 ± 0.47
EDSS Score, *mean ± SD*	1.44 ± 1.18
Immunomodulator use *n*	
Non-user	8
Interferon Beta-1b	14
Interferon Beta-1a subcutaneous	14
Glatiramer acetate	8

SD: Standard deviation.
EDSS: Expanded disability status scale.

deterioration was found in patients at the premenstrual period when compared with those in the ovulation period (Table 3p3), mild deterioration reaching statistically significant level was also detected in PASAT in the healthy group (p = 0.046) (Table 3p4).

There was a statistically significant difference between the ovulation and premenstrual periods in deterioration of PASAT (ΔPASAT) (P = 0.007). It was found that the significant difference in PASAT as a cognitive test between patients and control group increased in the premenstrual period, indicating more markedly deterioration in the premenstrual period than in the ovulation period (P = 0.009).

3.2. Physical evaluation

A significant difference was identified in the 9-HPT scores (duration) for both dominant and non-dominant manual functions during the ovulation period between the patient and control groups (Table 4). This difference became more marked in the premenstrual period. In the T25-WT test evaluating the lower extremity functions and ambulation, significantly longer durations were recorded in the patient group than in healthy subjects during both premenstrual and ovulation periods. The difference between the ovulation and premenstrual periods was evaluated for the patients, and it was detected that while no marked change was identified in the dominant hand, statistically significant deterioration was recorded in the non-dominant hand (Table 4p3). No similar change was identified in the healthy subjects (Table 4p4). In terms of T25-WT durations, significant deterioration was recorded in patients during the premenstrual period, but changes in healthy subjects did not reach statistically significance level.

No difference was detected in the disability measured by EDSS between the ovulation and premenstrual periods in patients, as well as no difference in EDSS functional system scores.

When the differences were compared for the ovulation and premenstrual periods on the basis of 9-HPT between the patient and control groups, the difference in the premenstrual period was significantly higher (P = 0.004) than the ovulation period.

When 36 patients who had used immunomodulators were compared to 8 patients who had not, the users had better scores both in 9-HPT and T25-WT in the ovulation period. The 9-HPT scores both for dominant and non-dominant hands were lower in the immunomodulator users when compared with the non-users (P = 0.023, P = 0.004, and P = 0.007, respectively). The T25-WT scores were also lower in the immunomodulator users when compared with the non-users (P = 0.012). Comparisons in the premenstrual period showed the disappearance of this difference and that there was no significant difference in the scores between the immunomodulator users and non-users. When compared with the healthy subjects, E2 and LH were significantly lower in the MS patients during the ovulation period, whereas FSH and LH were higher during the premenstrual period (Table 5).

3.3. Correlation analysis

While no correlation was identified among patients between physical (EDSS, 9-HPT, T25-WT) and cognitive parameters (PASAT); correlations were identified between the duration of the disease and all before mentioned parameters except (EDSS) (EDSS: r = 0.012, 9-HPT: r = 0.347, T25-WT: r = 0.0430, PASAT: r = −0.400). There was no correlation between age and PASAT in the control group. Also, 9-HPT and T25-WT did not deteriorate significantly with the increasing age.

In the patient group, a significant negative correlation was determined between numbers of pregnancies and miscarriages, and PASAT (r = -0.296 and r = 0.349, respectively, P < 0.05). The positive correlation was determined between the T25-WT and the number of pregnancies and total number of children. The correlation for the total number of children (r = 0.398, P < 0.01) was more marked than the one for number of pregnancies (r = 0.301, P < 0.05). In the control group, no similar correlation was determined with the pregnancy history.

Table 3
Cognitive Test Scores of the Patient and Control Groups in the Ovulation and Premenstrual Periods.

	Ovulation Period		*p1*	Premenstrual Period		*p2***	*p3****	*p4*****
	Patient	*Healthy*		*Patient*	*Healthy*			
PASAT	48.16 ± 11.07	53.36 ± 9.32	*0.003*	46.2 ± 9.93	51.79 ± 8.71	*0.001*	*0.016*	*0.046*
VAS	82.68 ± 13.55	89.38 ± 9.197	*0.006*	79.95 ± 13.59	86.57 ± 15.321	*0.008*	*0.038*	0.057

*p1: Comparison of the patient and control groups in the ovulation period.
**p2: Comparison of the patient and control groups in the premenstrual period.
*** p3: Comparison of the patient group in the ovulation and premenstrual periods.
****p4: Comparison of the control group in the ovulation and premenstrual periods.
PASAT: Paced Auditory Serial Addition Test, ACT: Auditory Consonant Trigram.
VAS: Visual Analog Scale.

Table 4
Physical Test (9-HPT and T25-WT) Scores of the Patient and Control Groups in the Ovulation and Premenstrual Periods.

	Ovulation		p1*	Premenstrual Period		p2**	p3***	p4***
	Patient	Healthy		Patient	Healthy			
9-HPT (dominant hand)	18.05 ± 2.46	15.31 ± 1.17	***0.002***	18.48 ± 2.6	15.76 ± 1.70	***0.001***	0.076	0.095
9-HPT (non-dominant hand)	22.60 ± 2.01	17.29 ± 1.98	***0.001***	25.92 ± 4.37	18.01 ± 1.24	***0.000***	***0.004***	0.06
9-HPT (average)	20.32 ± 1.89	16.3 ± 2.65	***0.004***	22.2 ± 3.45	16.88 ± 1.01	***0.002***	***0.028***	0.07
T25-WT	5.02 ± 1.13	4.22 ± 0.32	***0.014***	5.51 ± 2.04	4.4 ± 0.34	***0.003***	***0.006***	0.059

*p1: Comparison of the patient and control groups in the ovulation period.
**p2: Comparison of the patient and control groups in the premenstrual period.
*** p3: Comparison of the patient group in the ovulation and premenstrual periods.
****p4: Comparison of the control group in the ovulation and premenstrual periods.
9-HPT: 9- Hole Peg Test.
T25-WT: Timed 25-Foot Walk Test.

No correlation was determined in duration of breast-feeding neither with patients nor controls.

Significant correlations were identified between disease duration, and all clinical and cognitive variables, as expected ($p < 0.05$). This condition was more marked in the premenstrual period.

While the most marked correlation was determined between the number of attacks and 9-HPT and T25-WT ($P < 0.01$), a weaker correlation was observed with PASAT ($r = 0.209$, $P < 0.05$). No correlation was identified with EDSS. As a noteworthy sign, the shorter interval between the first two clinical attacks, indicated a more significant deterioration in the 9-HPT and T25-WT ($r = 0.305$, $r = 0.342$, respectively) ($P < 0.01$). The correlation was more evident in the premenstrual/menstrual period ($r = 0.341$, $r = 0.395$; $P < 0.01$).

The correlation analysis between the VAS scores, which the subjects evaluated their own performances, and PASAT showed a strong correlations both in patients and healthy subjects, as well as both in the ovulation and premenstrual periods (For patients; $r = 0.606$, $P = 0.001$ in the ovulation period, and $r = 0.815$, $P = 0.000$ in the premenstrual period. For healthy subjects; $r = 0.300$, $P = 0.017$ in the ovulation period, and $r = 0.348$, $r = 0.008$ in the premenstrual period).

4. Discussion

When many unanswered questions about the menstrual period are combined with premenstrual deterioration revealed by observational data, we considered to investigate changes observed during the menstrual period in MS patients. For this reason, we used variables which were effective in clinical examination physically and cognitively. Cognitive functions indicate a very significant area in disability determination, which cannot be revealed by traditionally used disability evaluation scales in MS. In the present study, we measured presence of cognitive function deteriorations in MS using PASAT which is used in cognitive field evaluations. PASAT was significantly worse in the patient group both in premenstrual and ovulation periods. In the healthy group, mild deterioration that reached statistical significance was observed in PASAT too. This finding indicates definitely transient, but significant cognitive effect in MS patients in the premenstrual period. It was determined that the significant difference obtained in cognition in the ovulation period between patients and healthy subjects was increased in the premenstrual period, indicating that patients deteriorated more markedly in the premenstrual period when compared with the ovulation period. These data are supportive for transient effect of deterioration in cognition encountered in the premenstrual period. While no difference was detected in physical disability in patients between ovulation and premenstrual periods by using traditional evaluation tool, EDSS; significant differences were detected in both 9-HPT and T25-WT subscales of MSFC. 9-HPT, which has been proved to be effective in evaluation of lower extremities in MS patients, and T25-WT which has been used in objective evaluation of lower extremity functions were both deteriorated more significantly in premenstrual period compared to ovulation period (test durations were longer in premenstrual period). Comparison of difference (Delta) between ovulation and premenstrual periods indicated similar results. All of these signs showed that premenstrual period was the time interval in which physical disabilities were more marked in MS patients than the ovulation period. The present study is the first study in the literature revealing periodic/transient physical deterioration in MS. While the gender-related differences are well known in MS, the number of studies is limited. MS is encountered in women two to three times more common than in men, and there are strong evidences indicating that its prognosis is better in women compared with men. Symptoms in women may display variations in pregnancy, premenstrual period and menopause. The common characteristic of these periods is that there are changes in levels of sexual hormones. In their study, Zorgdrager and De Keyser evaluated the patients with normal menstrual cycle for deterioration of the symptoms in MS related to menstruation by questioning them thoroughly on changes in MS symptoms, and found that 23% relapsing remitting MS patients reported cyclic deteriorations in MS symptoms just before (until 3 days before the bleeding) or at the beginning of menstruation. [28]. They reported that there were deteriorations in spasticity, paresthesia, lack of coordination, sensorial disorder, pain, visual and ocular symptoms and in sphincter disorder. The study was based on a questionnaire and there was no objective scale for

Table 5
Hormone Levels of the Patient and Control Groups in the Ovulation and Premenstrual Periods.

	Ovulation Period			Premenstrual Period		
	Patient	Control	p	Patient	Control	P
E2	104.3 ± 63.67	122.064 ± 72.5845	***0.026***	65.747 ± 46.1986	68.800 ± 56.1338	0.096
Progesterone	2.99 ± 3.95	2.431 ± 3.6967	0.098	3.118 ± 4.1364	5.336 ± 4.5364	0.06
FSH	7.7 ± 4.61	7.478 ± 4.1851	0.109	6.531 ± 4.4689	4.314 ± 2.0329	***0.031***
LH	11.18 ± 12.84	18.982 ± 18.9603	***0.034***	4.967 ± 2.9379	3.640 ± 2.2697	***0.044***

FSH; Follicle-stimulating Hormone.
LH: Luteinizing Hormone.

evaluation [28]. What is the reason for deterioration in menstrual period? Wingerchuk et al. investigated the role of body temperature increase in premenstrual pseudo- exacerbation in MS, and they investigated whether it could be prevented with aspirin [29,30]. It seems that relapsing course has a triggering effect on menstrual worsening. This conclusion is supported by the study of Zorgdrager and De Keyser.

None of 12 primary progressive MS patients included in that study reported any change in their MS symptoms related to menstruation [28]. In this context, Sicotte et al. showed that administration of 8 mg daily estriol to the patients with clinically definite MS made the gamma interferon levels in peripheral blood reduced; the response against the tetanus antigens delayed; and the number and volume of gadolinium-enhanced lesions in MRI decreased [16]. Similarly, in a broader study performed presently, Annette Langer-Gould et al. investigated risks in breast-feeding and postpartum relapse in 32 women with MS and in 29 healthy women [31]. As a result, marked degree of relapse risk was determined in the year after the delivery in women who did not breastfeed in the first 2 months or who started the supplementation foods in the babies, and relapses were observed earlier. While the difference determined in mean score in 9-HPT was marked for non-dominant hand, it did not reach statistically significant level in the dominant hand. It is not surprising that 9-HPT score of the dominant hand was higher. Similar results were reported in pivotal studies using this test [27,32,33]. The follow ups performed in our clinic both during the attack period [33] and remission period [27] revealed that similar deterioration in the non-dominant hand was markedly more. Possibly, this condition may be explained as that tolerance of non-dominant hands is lower in handicapped situations. Although no statistically significant difference was determined between these two tests in healthy subjects, deterioration of T25-WT was noteworthy in the premenstrual period. This finding indicates that premenstrual period is a physically distressing period also for healthy women. In pivotal studies conducted about use of MSFC subtypes during the follow up, it has been shown that EDSS was not as effective as MSFC subtypes in evaluation of changes in the disability. In a study performed during attack period, methylprednisolone was used and 5-day follow up was performed by MSFC. 9-HPT and T25-WT were performed every day, and it was reported that these two tests showed clinical improvement which could not be determined by EDSS, rapidly and at a very early step [33]. In the study performed in the remission period, it was proved that these tests could show changes which were reported as inadequate after 2-year follow up by EDSS [27]. Data obtained in our study showed that the superiority to EDSS reported in these two studies was also valid when menstrual cycle periods were considered. Although EDSS has been a reliable scale for many years, our data re-confirmed that its efficacy during the follow up and in determination of action was markedly lower than MSFC.

The obtained data were controlled by correlation analyses. During examination of correlation with demographic data, there was no correlation between age and physical clinic (EDSS, 9-HPT, T25-WT) and cognitive variable (PASAT) in the patient group, whereas there was a significant correlation between all variables except disease duration and EDSS, as it was expected. In the healthy subjects, no correlation was determined between age and cognitive parameters, and there was no marked deterioration in 9-HPT and T25-WT with the increasing age.

In the patient group, numbers of pregnancies and miscarriages were significantly negatively correlated by using PASAT. Although this finding requires confirmation by larger size studies that will be performed on larger number of patients, it might be considered as a secondary outcome related to unfavorable effect of having a child on MS, at least on cognitive functions. Thus, if positive correlation between T25-WT, and number of pregnancy, total number of children was combined with detection of no similar correlation in pregnancy history in the healthy subjects; it might be deduced that cognitive condition and gait capacity would be deteriorated in MS patients as number of pregnancy was increased.

Significant correlation was determined between disease duration and all clinical and cognitive variables, as it was expected. It was noteworthy that this condition was more marked in the premenstrual period. Although the most marked correlation in attack number was determined with 9-HPT and T25-WT, a weak correlation was observed with PASAT. No correlation was determined in EDSS. The noteworthy finding was shorter the duration between two clinical attacks, the more marked deterioration was determined in 9-HPT and T25-WT. The correlation was more striking in the premenstrual/menstrual period. This finding indicates the correlation between disease activity and physical disability. It is not surprising that the correlation obtained during premenstrual period was stronger than other data.

It was determined that E2 and LH were significantly lower during ovulation period in MS patients, whereas FSH and LH were higher in the premenstrual period. Large size clinical trials are required for clinical interpretation of these findings. In patients with high estrogen levels, it was determined that there were less fatigue and clinical deterioration, which did not reach statistical significance levels. These findings may be evaluated as evidences for protective effects of estrogen. A more powerful comment may be made about this issue only after larger size population trials.

The present study has some limitations. Detailed evaluation in one visit lasted averagely 1.5 h. Additionally, performance of cognitive test in the morning, and of visits in every 15 days (it was different in every case according to the cycle dates) caused long and tiring processes during the evaluation. The next difficulty was that cases should be invited for a visit with close time intervals along the 2-cycle duration. Therefore, patients who could easily reach hospital and had enough time for the procedures were included in the study. Another limitation is regarding self assessment of cognition. We used VAS for self assessment. Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) was more rationalistic because it seems to be more sensitive. But at the time we realized the study, MSNQ had not been adopted to Turkish yet.

In conclusion, premenstrual period is worse in cognitive aspect both in MS patients and healthy women compared to the ovulation period. This condition is more prominent in MS patients. Although physical performances of patients are deteriorated in the premenstrual period (worsening of upper and lower extremity functions), there was no significant deterioration in healthy individuals. Our results show favorable effects of immunomodulator use in the menstrual period. The present study is the first trial investigating problems of MS patients objectively in all major functional aspects. The obtained results both help improvement of hormone hypothesis of MS etiology, and extend future study spectrum. Moreover, both results, and possible correlation detected between hormone levels and clinical deterioration may build up a sound basis for trials, which would investigate the place of hormone treatment among symptomatic and/or, perhaps, modulatory treatment options.

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