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Effects of multiple sclerosis and medications on menopausal age

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Abstract

Objectives: We aimed to determine whether multiple sclerosis (MS) and methylprednisolone and disease-modifying drugs have an effect on menopausal age.

Methods: A total of 86 patients and 98 healthy subjects were included in this study. The natural menopausal age of the patients and healthy subjects were compared. The cumulative dosages of methylprednisolone, beta interferons (IFNβs), and glatiramer acetate were calculated. The effects of the Expanded Disability Status Scale (EDSS), duration of the disease, and cumulative dosage of medications on menopausal age were evaluated.

Results: The patients' mean menopausal age was 45.3 ± 4.8 years and healthy subjects' menopausal age was 46.8 ± 4.3 years, with no significant difference between the two groups. The cumulative dosage of methylprednisolone showed an effect on menopausal age. There was a significant inverse correlation between menopausal age and dosage of IFNβ-1b, while the disease duration and EDSS score showed no correlation with menopausal age.

Conclusions: We conclude that menopausal age is not affected by MS. However, long-term methylprednisolone and IFNβ-1b treatments may change menopausal age in a dose-dependent manner.

Keywords

Multiple sclerosis, disease-modifying drugs, menopause, methylprednisolone, beta interferon, Expanded Disability Status Scale (EDSS)

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Introduction

The effects of multiple sclerosis (MS) on natural menopause are unknown. However, studies have examined the relationship between the course of MS and sex and hormonal status, as well as the effects of hormone treatments. Surprisingly, no information is available concerning the possible influence of treatment agents on natural menopausal age.[1–2]

Therefore, this study aimed to evaluate natural menopausal age in patients with MS. We also examined the effects of methylprednisolone (MP) and disease-modifying drugs (DMDs), which are used for treating MS, on menopausal age.

Material and methods

The study was a randomized, controlled study. The study was approved by the local ethical committee of the University of Health Sciences, Dr. Lütfi Kırdar Kartal Training and Research Hospital, Istanbul. Before the study, verbal consent was obtained from all participants. The patients were followed by our neurology clinic between September 2010 and April 2016.

A total of 86 patients who were diagnosed with relapsing-remitting multiple sclerosis (RRMS) according to the McDonald 2010 criteria[3] and 98 healthy subjects were included in this study. The patients and healthy controls consisted of Turkish women. A questionnaire was filled in by patients. Age, natural menopausal age, onset of RRMS, Expanded Disability Status Scale (EDSS)[4] scores of the patients, agents that were used for treatment (methylprednisolone and DMDs), and dosage and duration of agents were recorded. Inclusion criteria for the study were age between 35–55 years, all volunteer patients, and healthy subjects. Exclusion criteria were having any systemic diseases, receiving any drugs, and having had any previous gynaecological operations.

Menopause was defined as occurring 12 months after the last menstrual period and marking the end of menstrual cycles. The natural menopausal age was compared between the patients and healthy subjects. The cumulative dosages of methylprednisolone, beta interferons (IFNβs: Rebif 44 mcg; Merck KGaA, Darmstadt, Germany and Betaferon; Bayer Pharma AG, Berlin, Germany), and glatiramer acetate (GA; Copaxone Teva Pharmaceutical Industries Ltd, Petach Tikva, Israel) were calculated. The effects of the duration of the disease, the EDSS, and cumulative dosage of using agents on menopausal age were evaluated.

Statistical analysis

Descriptive statistics, comparison of means, and correlation analyses were performed where necessary. Values are reported as mean ± SD. Pearson correlation analysis was used to analyse cumulative methyl prednisolone dosage and Spearman correlation analysis was used for all other variables. The independent samples t test was used for comparison of means. Statistical analysis was performed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows the characteristics of the patients and healthy subjects. The mean age of the patients and healthy subjects was 44.8 ± 6.4 and 45.5 ± 6.4 years, respectively, with no significant difference between the two groups ($p = 0.435$). The mean menopausal age of the patients (45.3 ± 4.8 years) was not different to that of the healthy subjects (46.8 ± 4.3 years, $p = 0.167$). There was no correlation between disease duration and menopausal age. There was no correlation between the EDSS and menopausal age ($p = 0.217$).

Table 1. Characteristics of the patients and healthy subjects

	Patients	Healthy subjects
Age, years	44.8 ± 6.4	45.5 ± 6.4
Menopausal age, years	45.3 ± 4.8	46.8 ± 4.3
EDSS score	3.9 ± 1.7	
Duration of disease, years	8.8 ± 6.8	

EDSS, Expanded Disability Status Scale. Data are presented as mean ± standard deviation.

Table 2. Relations between cumulative dosage of medications and menopausal age

Treatment	Patients (n)	Cumulative dosage (g)	*p* value
Methylprednisolone	86	5849	0.035
Glatiramer acetate	21	539.20	0.138
Interferon beta-1a	21	2.9	0.229
Interferon beta-1b	16	1.36	0.046

During attacks, all patients were treated with high-dose 1000 mg MP intravenously. Table 2 shows the associations between medications and menopausal age. There was an inverse correlation between the dosage of MP and menopausal age ($p = 0.035$). There was no correlation between the dosage of GA and menopausal age ($p = 0.138$). There was no correlation between menopausal age and the dosage of IFNβ-1a ($p = 0.229$). There was a significant inverse correlation between menopausal age and the dosage of IFNβ-1b ($p = 0.046$).

Discussion

Our study showed that MS did not have any effect on menopausal age of Turkish women. Additionally, the duration of disease and EDSS score did not have any effect on menopausal age. However, MP caused an earlier menopause age. While IFNβ-1a did not interfere with menopausal age, there was a correlation between the dosage of IFNβ-1b and menopausal age.

There have not been any studies on the effects of MS on menopausal age. However, Nabavi et al.[5] reported that different types of menstrual disturbances, such as oligomenorrhea, amenorrhea, irregular menstruation, and abnormal duration of menstrual flow, had a higher rate in patients with MS. They also found that mean luteinizing hormone levels in the patient group was higher than those in the control group. Hyperprolactinemia was more prevalent in the patient group than in the control group. They also observed a relation between the type of IFNβ and menstrual irregularities in patients. In the same study, they observed that five of 58 patients started menopause younger than 40 years, and two of them had premature ovarian failure. All of their 58 patients with MS treated with IFNβs.[5]

Golovkin et al.[6] studied 36 women with MS and reported that 16 patients had amenorrhea with hyperprolactinemia. Grinsted et al.[7] reported elevated prolactin and follicle-stimulating hormone levels in patients with MS compared with healthy subjects. The exact cause of irregularities may be complex and probably due to different causes, such as destructive and demyelinating lesions of the hypothalamic–pituitary-adrenal (HPA) axis, effects of the immune system on the HPA axis, and effects of specific symptomatic medication of MS on the HPA axis.[8–14]

Although the effects of MP on menopausal age have not been investigated, the long-term use of MP may be linked to early menopausal age in patients with MS. Short-term, high-dose treatment of synthetic glucocorticosteroids is used in a range of inflammatory and immunological disorders. Two weeks after discontinuation of glucocorticoid treatment in most patients, the adrenal response returns to normal. However, in some patients, the adrenal response remains suppressed for a long time.[15] Among the adverse effects of

glucocorticoid therapy, the most important side effect is suppression of the HPA axis.[16,17]

The effect of DMDs on menopausal age has not been previously investigated. However, there is a relationship between the different subtypes of menstrual irregularities and the types of interferons that are used by patients.[5] Pakulski at al.[18] observed a relationship between using IFNβs and hypermenorrhoea. Because of a lack of research on the relationship between menopausal age and DMDs, we can only speculate on the effects of DMDs on menopausal age. The same mechanism that causes various hormonal changes could affect menopausal age.[19]

In conclusion, menopausal age is not affected by MS. However, the effects of the medications MP and IFNβs may change menopausal age. This issue should be studied with a larger sample size to more accurately estimate menopause age and also clarify the cause(s) and mechanism(s).

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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