

ORIGINAL ARTICLE

ARAŞTIRMA YAZISI

THE ROLE OF OXIDATIVE STRESS IN MENSTRUAL RELATED MIGRAINE

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ABSTRACT

INTRODUCTION: Menstrually related migraine (MRM) is a headache disorder occurring in reproductive-aged women relevant to menstrual cycles. Attacks occur with decreases in estrogen and may be relevant to oxidative stress which hasn't been clear yet. Our aim was to investigate oxidative stress markers during menstrual cycle which may be important in pathophysiology of MRM as a vascular type headache.

METHODS: 20 patients with MRM (32.65 ± 8.75 age) and 20 healthy volunteers (30.25 ± 8.6 age) were included in our study. All subjects were examined during an attack-free interval and blood samples were taken in order to study estrogen, progesteron, LH, FSH, nitric oxide (NO), malondialdehyde (MDA), superoxide dismutase (SOD) , glutathione (GSH) and glutathione reductase (GSH-Rd) in midfollicular and midluteal phases of the menstrual cycle.

RESULTS: There was no statistical significant difference between the control and the patient groups in according to age, menstrual cycle duration and hormones. GSH-Rd (62.96±17.22 vs 84.69±38.64, p=0.04) and SOD (3834.44±1423.8 vs 4562.41±1825.3, p=0.003) of MRM group were found elevated in the luteal phase when compared with follicular phase but this couldn't be detected in the control group.

DISCUSSION and CONCLUSION: Our results suggested that the antioxidant system in the follicular phase is inadequate relative to healthy subjects in MRM. The antioxidant defence system have to be taken into account to understand the pathophysiology of MRM and therefore need further studies.

Keywords: migraine, headache, menstruation, oxidative stress, estrogen.

MENSTRUASYON İLİŞKİLİ MIGRENDE OKSİDATİF STRESİN ROLÜ

ÖZET

GİRİŞ ve AMAÇ: Menstruasyon ilişkili migren (MİM) üreme çağı kadınlarda görülen menstruel siklus ile alakalı başağrısı bozukluğudur. Ataklar östrojenin düşmesi ile gelişir ve henüz netlik kazanmamakla birlikte oksidatif stres ile ilişkili olabilir. Amacımız oksidatif stres göstergelerini MİM ve sağlıklı kontrollerde menstrual siklus süresince incelemektir.

YÖNTEM ve GEREÇLER: MİM tanılı 20 hasta (32.65 ± 8.75 yaş) ve 20 sağlıklı gönüllü (30.25 ± 8.6 yaş) çalışmaya alındı. Tüm katılanlar attaksız dönemde değerlendirildi ve kan örnekleri östrodiol, progesteron, LH, FSH, nitrik oksid (NO), malondialdehid (MDA), superoksid dismutaz (SOD) , glutatyon (GSH) ve glutatyon redüktaz (GSH-Rd) çalışılmak üzere menstrual siklusun midfolliküler ve midluteal fazlarında alındı.

BULGULAR: Kontrol ve hasta grubu arasında yaş, menstrual siklus süresi ve hormonlar açısından istatistiksel belirgin fark yoktu. MİM grubunun GSH-Rd (62.96±17.22 vs 84.69±38.64, p=0.04) ve SOD (3834.44±1423.8 vs 4562.41±1825.3, p=0.003) değerleri luteal fazda folliküler faz ile kıyaslandığında artmış bulundu ancak bu kontrol grubunda izlenmedi.

TARTIŞMA ve SONUÇ: Sonuçlarımız MİM'de foliküler fazda antioksidan sistemin sağlıklı bireylere göre yetmezliğini desteklemektedir. Antioksidan savunma sistemi MİM patofizyolojisini anlamada ele alınmalıdır ve bu nedenle ileri çalışmalara ihtiyaç duyulmaktadır.

Anahtar Sözcükler: migren, başağrısı, menstruasyon, oksidatif stres, östrojen.

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INTRODUCTION

Migraine is a prevalent headache disorder affecting three times more women than men during the reproductive years. In over half these women, their headaches are strictly related to their menstrual cycle (1,2). Menstruation is a significant risk factor for migraine. Menstrually related migraine (MRM) is known with attacks most likely to occur on or between 2 days before the onset of menstruation and the first 3 days of bleeding cycle in at least two of three consecutive menstrual cycles. Additional migraine attacks with or without aura can occur at other times of the cycle (2,3).

Among women with migraine, 11% have onset of migraine at menarche and are more likely to experience MRM. Approximately 60% have migraine with menses and at other times during the menstrual cycle. The trigger for MRM attack is the drop in estrogen occurring during the late luteal phase of the menstrual cycle (4). Changes in multiple neurotransmitter systems occur with decreases in estrogen and are purported to be relevant to migraine attacks (5). The other possible mechanisms may be related to prostaglandin release, changes in opioid tonus, increased sensitivity of dopamine receptors and serotonergic transmission (6). The mechanism of how the estrogen decrease triggers migraine is not well understood. One of the possible mechanisms is oxidative stress. Geyik et al. found elevated 8-hydroxy-2'-deoxyguanosine as an evidence of oxidative stress-related DNA damage in migraine (7).

In premenopausal women, one of the primary mechanisms of transient change of arterial reactivity is probably the change in the production of NO which causes vasodilation and oxidative stress that may trigger headache. In literature there are publications about oxidative stress parameters in migraine patients, however there isn't any study examining oxidative stress during a menstrual cycle in MRM.

The aim of this study was to investigate oxidative stress markers including nitric oxide (NO), malondialdehyde (MDA), superoxide dismutase (SOD), glutathione (GSH) and glutathione reductase (GSH-Rd) changes during a menstrual cycle in patients with MRM. The results were compared with healthy controls.

MATERIAL AND METHODS

In our study, 20 patients with MRM (32.65 ± 8.75 age) and 20 healthy volunteers (30.25 ± 8.6 age) who admitted to our neurology headache polyclinic between January and September 2012 were included under informed consent conditions. Diagnosis of migraine type was made according to IHS- 2013 diagnosis criteria (2). Patients with hematologic, endocrinologic disorders, psychiatric illness, hypertension, dyslipidemia, infection, epilepsy, cerebrovascular disease, irregularities in menstrual cycle were all excluded. None of the participants had oral contraceptive use, smoking, migraine prophylaxis therapy, analgesics, alcohol and caffeine intake during in the last 48 hours. All patients were examined during an attack-free interval (at least 5 days after an attack).

The blood samples were taken during follicular (3-8 days of the menstrual cycle) and luteal (18-23 days of the menstrual cycle) phases of the hormonal cycle. Follicular and luteal NO, MDA, SOD, GSH and GSH-Rd blood levels were studied in all participants in order to evaluate oxidative stress. The study was approved by the local ethics committee of our university.

Statistical analyses

Statistical Package for the Social Sciences (SPSS) 14.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were given as mean \pm standard deviation. We tested whether or not the variables which were detected in numeric scales in both groups had a normal distribution by using the Kolmogorov Smirnov test. All variables had normal distribution and parametric Independent Sample T test was used in statistical analysis. Data were analyzed using paired t-tests. Chi square tests were used to analyze categorical variables and $p < 0.05$ was considered statistically significant for all comparisons.

RESULTS

There was no statistical significant difference between the control and the patient groups in according to age and menstrual cycle duration. In comparison of hormones we found no significant difference between groups (Table I). The values of antioxidants, GSH-Rd (62.96 ± 17.22 vs 84.69 ± 38.64 , $p = 0.04$) and SOD (3834.44 ± 1423.8

vs 4562.41 ± 1825.3 , $p=0.003$) of MRM group increased significantly in the luteal phase when compared with follicular phase but this couldn't be detected in the control group (Table II).

Although follicular NO levels were higher than luteal levels in our control group (26.73 ± 11.1 vs 22.14 ± 11.7 , $p>0.05$), there was no statistically significance (Table III).

Table I. Demographic characteristics and menstrual hormones of the groups studied showing no significant difference between groups.

	MRM (n=20)	Control (n=20)	p
Age (year)	32.65 ± 8.75	30.25 ± 8.6	NS
Menstrual cycle length (day)	28.2 ± 1.3	28 ± 0.7	NS
Hormones			
Estradiol-F (pg/ml)	57.23 ± 24.82	52.66 ± 22.46	NS
Progesteron-F (ng/ml)	0.53 ± 0.19	0.49 ± 0.25	NS
LH-F (mIU/ml)	5.65 ± 4.27	4.8 ± 1.77	NS
FSH-F (mIU/ml)	9.2 ± 7.62	7.66 ± 4.43	NS
Estrogen-L (pg/ml)	132.99 ± 52.89	127.46 ± 45.97	NS
Progesteron-L (pg/ml)	6.99 ± 4.19	6.46 ± 3.9	NS
LH-L (mIU/ml)	7.3 ± 6.0	6.07 ± 4.7	NS
FSH-L (mIU/ml)	4.08 ± 2.68	4.46 ± 3.6	NS

Values are given as mean \pm standard deviation. -F: follicular, -L: luteal. NS: not significant $p>0.05$

Table II. Comparison of oxidative stress parameters of MRM and controls showing no significant difference between groups.

	MRM	Control	CI	p	
NO-F ($\mu\text{mol/l}$)	23.65 ± 13.9	26.73 ± 10.4	-10.97	4.8	NS
NO-L ($\mu\text{mol/l}$)	20.63 ± 12.35	22.14 ± 11.72	-9.2	6.2	NS
GSH-F (mg/g Hb)	3.04 ± 0.57	3.11 ± 0.44	-0.39	0.26	NS
GSH-L (mg/g Hb)	3.16 ± 0.56	3.10 ± 0.49	-0.28	0.39	NS
GSH-Rd-F (U/g Hb)	62.96 ± 17.22	67.66 ± 34.09	-22.19	12.8	NS
GSH-Rd-L (U/g Hb)	84.69 ± 38.64	65.75 ± 29.6	-3.16	41.1	NS
MDA-F ($\mu\text{mol/l}$)	11.73 ± 2.9	10.25 ± 1.86	-0.09	3.07	NS
MDA-L ($\mu\text{mol/l}$)	12.20 ± 3.1	10.76 ± 2.35	-0.34	3.2	NS
SOD-F (ng/g Hb)	3834.43 ± 1423.7	3872.65 ± 2115.6	-1197.9	1121.5	NS
SOD-L (ng/g Hb)	4562.40 ± 1825.3	4020.96 ± 1681.1	-582.12	1665	NS

Values are given as mean \pm standard deviation. CI: Confidence interval. -F: follicular, -L: luteal. NS: not significant $p>0.05$

Table III. Comparison of oxidative stress parameters of follicular and luteal phases of MRM and control groups. GSH-Rd and SOD levels in MRM group were increased significantly in the luteal phase when compared with follicular phase but not in the control group.

	MRM (n=20)		t-value	p	Control (n=20)		t-value	p
	Follicular	Luteal			Follicular	Luteal		
NO ($\mu\text{mol/l}$)	23.65 ± 13.9	20.63 ± 12.35	1.65	NS	26.73 ± 10.4	22.14 ± 11.72	1.526	NS
GSH (mg/g Hb)	3.04 ± 0.57	3.16 ± 0.56	-1.48	NS	3.11 ± 0.44	3.10 ± 0.49	0.52	NS
GSH-Rd (U/g Hb)	62.96 ± 17.22	84.69 ± 38.64	-2.24	0.037	67.66 ± 34.09	65.75 ± 29.6	0.201	NS
MDA ($\mu\text{mol/l}$)	11.73 ± 2.9	12.20 ± 3.1	0.668	NS	10.25 ± 1.86	10.76 ± 2.35	-0.919	NS
SOD (ng/g Hb)	3834.44 ± 1423.8	4562.41 ± 1825.3	-2.98	0.008	3872.6 ± 2115.6	4020.9 ± 1681.1	-0.437	NS

Values are given as mean \pm standard deviation. CI: Confidence interval. -F: follicular, -L: luteal. NS: not significant $p>0.05$

DISCUSSION

In our study we found that GSH-Rd and SOD levels were elevated in the luteal phase in migraine patients. This can be the result of the activated antioxidant defence system. GSH-Rd is a ubiquitous enzyme, which catalyzes the reduction of oxidized glutathione to GSH. It is essential for the glutathione redox cycle that maintains adequate levels of reduced cellular GSH which is a critical molecule in resisting oxidative stress and maintaining the reducing environment of the cell (8). GSH serves as an antioxidant, reacting with free radicals and organic peroxides, in amino acid transport, and as a substrate for the glutathione peroxidases and glutathione S-transferases in the detoxification of organic peroxides and metabolism of xenobiotics, respectively (8).

Superoxide anion is dismutated by superoxide dismutases (SODs) to hydrogenperoxide that is catalyzed to water by catalase, peroxiredoxins, or glutathione peroxidases. Similar with GSH-Rd, SOD which is also a part of antioxidant defense system found elevated in luteal phase of menstrual cycle in MRM group. The elevation of GSH-Rd and SOD in the luteal phase couldn't be detected in control group. This may be the result of activated antioxidant defence system of MRM patients especially in luteal phase when migraine attacks mainly aggravated. However, the same antioxidant defense system response couldn't be detected in controls.

Although Alp et al. recently found the decreased total antioxidants with an increase in the levels of total oxidants and the oxidative stress index in patients with migraine without aura (9), its relationship with hormones in MRM is still unknown. In literature there are limited data about the fluctuation of antioxidant enzymes in menstrual cycle. In a larger study fluctuations of GSH-Rd and SOD during menstrual cycle were studied but couldn't be detected in regularly menstruating women. However, in the same study it was shown that lower plasma estradiol concentrations resultant in attenuated erythrocyte SOD inhibition and elevated SOD enzyme activity (10). The exact mechanism of inhibitory estradiol action on SOD activity hasn't been clear yet and this needs further studies. The physiological response of antioxidant defence system to normal ovarian hormones especially estrogen cycle needs to be investigated especially in understanding the

pathologies related to menstrual cycle like MRM. In our study GSH-Rd and SOD levels of control showed no significant difference during follicular and luteal phases of the cycle which is concomitant with literature (10,11,12).

The drop in estrogen occurring during the late luteal phase of the menstrual cycle is accepted as a main reason for MRM attacks (13). It has been also shown in an invitro study that 17 beta-estradiol increased membrane fluidity (a reciprocal value of membrane microviscosity) of erythrocytes and improved the rigidity of cell membranes in women through the NO and cGMP dependent mechanism (14). The mechanism of action of estrogen within the brain is related in part to the vascular system. Estrogen receptors were found in the endothelial and smooth muscle cells in the walls of brain arteries and arterioles (15). Stimulation of these receptors causes relaxation of the microvasculature following the secretion of a variety of vasoactive substances, such as NO (16), prostacyclin, and prostaglandin E2 (17,18). All these data suggesting vasodilator effects of estrogen. In this study, follicular NO levels were higher than luteal levels in our control group, however there was no statistically significance which limited us to make a comment on this.

The altered sensitivity of estrogen receptors in the walls of brain arteries may cause MRM headaches. All these possible mechanisms have not been studied yet and they are the questions that need to be addressed in future studies.

There are also limitations of our study. Despite the fact that MRM patients without migraine attacks at follicular phase with regular menstruation cycle were not so common to be found, our study group wasn't so large. It would be better to have a larger group having more significant results. Additionally, subsequent analysis of studied parameters in different menstrual cycles may strengthened the value of our findings but it was almost impossible to design a study group having regular menstrual cycles with free migraine attacks in the following period, besides it was impossible to predict the next menstrual cycle. Additionally pure menstrually related migraine patients are study of interest. This can be also investigated in further studies with larger study groups. It can be concluded that the antioxidant system in the follicular phase was

inadequate relative to healthy subjects in MRM. To our knowledge there is no study about the changes of oxidative stress markers during menstrual cycle in MRM. Our findings suggest that GSH-Rd and SOD which are important in antioxidant defence system are elevated as a reaction to oxidative stress in luteal phase of MRM. The estrogen induced changes in antioxidant defence system have to be taken into account to understand the pathophysiology of MRM and need further studies.

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