

Migraine: is it related to hormonal disturbances or stress?

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Background: Common neurological syndrome (migraine without aura) is more common among women than men. Migraine is among the top 20 causes of disability. Menstruation is known to be a powerful trigger for migraine, and so is stress, but the presentation of headache is similar in both. Also, women are more vulnerable to stress as well as migraine, and this makes a complex relationship of menstruation, stress, and migraine.

Objective: This study was done to understand the association of hormonal fluctuation in menstruation and stress with common migraine.

Materials and methods: A cross-sectional comparative study was conducted in 40 young adult females, of whom 20 participants were cases of migraine without aura (18–35 years old), and the remaining 20 participants were age-matched controls. The study was done in Maulana Azad Medical College, New Delhi. Study participants were selected on the basis of International Headache Society (ICHD-IIA1.1) (2004) classification. Study participants with neurological disorders, chronic diseases, and disease suggestive of any hormonal disturbances were excluded. Clinically diagnosed migraine cases were asked to maintain a headache diary and to fill in the Depression Anxiety Stress Scales questionnaire. Biochemical assessment of hormonal status for thyroid-stimulating hormone, triiodothyronine, thyroxine, estrogen, follicle-stimulating hormone, luteinizing hormone, and prolactin was also done on the second day of their menstrual cycle. We used the Mann–Whitney *U* test to compare hormonal levels and the χ^2 test to compare anxiety- or depression-related stress among the migraine and nonmigraine groups.

Results: Significantly higher values of prolactin were observed in cases (mean \pm standard deviation, 152.7 mIU/L \pm 30.5) compared to controls (76.1 mIU/L \pm 8.7), with a *P*-value <0.001 . There was no statistically significant difference observed in levels of thyroid-stimulating hormone (*P*=0.081), estrogen (*P*=0.086), luteinizing hormone (*P*=0.091), or follicle-stimulating hormone (*P*=0.478). Also, anxiety with stress or depression with stress was significantly higher among the migraine group than the controls (*P*=0.002). Odds of any stress in migraine were higher in the migraine group than in the nonmigraine group (odds ratio 12, 95% confidence interval 2.7–53.33).

Conclusion: Migraine, particularly without aura, in women is mainly associated with stress-related anxiety or depression, and are more susceptible to stress in the premenstrual period.

Keywords: migraine, menstruation, stress

Introduction

Common neurological syndrome (migraine without aura) is more common among women than men. The Global Burden of Disease study conducted by the World Health Organization in 2000 and the World Health Report 2001 showed that mental and neurological disorders collectively account for 30.8% of all years of healthy life

lost to disability, and among them migraine accounts for 1.4%, which places it among the top 20 causes of disability worldwide.¹ The male:female ratio for migraine among adults varies from 1:2 to 1:3, which proves that women have more vulnerability to migraine. At all ages, migraine without aura is more common than migraine with aura, with a ratio of between 1.5:1 and 2:1. Incidence figures show that the excess of migraine seen in women of reproductive age is mainly migraine without aura. That is the reason we chose young females having migraine without aura in the present study. According to Zwart et al,² Rasmussen,³ and Jensen and Stovner,⁴ it was estimated that migraine sufferers losses are more than 157 million workdays, and have reduced productivity and quality of life.

The length of the attack can last from several minutes to several days, and includes throbbing pain on one side of the head, accompanied by nausea and vomiting or sensitivity to light, sound, and odors. The International Headache Society (IHS) Classification of Headache Disorders (ICHD) includes specific definitions for pure menstrual migraine (code ICHD-II A1.1.1) and menstrual-related migraine (code ICHD-II A1.1.2).⁶ Lipton and Bigal⁵ said that

Although migraine is one of the commonest reasons for patients to consult their doctor and despite its enormous impact, it is still under-recognized and under-treated.

This has various reasons. On one hand, there are no biological markers to confirm the diagnosis, the etiology is controversial and there is a lack of knowledge, time, interest, or all three to manage migraineurs. On the other hand, there is no cure for migraine, and although effective therapies do exist, they have only partial efficiency and are not accessible to all.

Stress, anxiety, hypoglycemia, fluctuating estrogen, certain foods, smoking, and other factors can trigger migraine, but the etiology of migraine is still not known. Many believe that stress and migraine have the same pattern of headache. Stress does not actually trigger a migraine, but makes us more susceptible to our triggers.⁷ Sometimes, the migraine occurs with no apparent “cause”. The trigger theory supposes that exposure to various environmental factors precipitate or trigger individual migraine episodes. Menstruation is known to be a powerful trigger for migraine, but the headache precipitated by it is not different than those triggered by stress, which itself is also a powerful trigger. Epidemiological studies suggest the existence of close but complex relationships between estrogens, migraine, and stroke in women before menopause. Migraine, particularly without aura, is strongly influenced by estrogens, as illustrated by the increased

frequency of onset at puberty of menstrual migraine and of improvement during pregnancy increased by tobacco smoking and oral contraceptive use.⁸ Pattern suggested relationship of menstrual migraine with estrogen fluctuations. Since young women fall under both these categories, this made us keen to study migraine with these two factors.

Hypothesis

The primary trigger for migraine during menstruation may be the withdrawal of estrogen or stress.

Aims and objectives

This study was done to understand the association between hormonal fluctuations in menstruation and stress with common migraine.

Materials and methods

A cross-sectional comparative study was conducted in 40 young adult females, of whom 20 participants were cases of migraine without aura (18–35 years old), and the remaining 20 participants were age-matched controls. The study was done in Maulana Azad Medical College, New Delhi. Study participants were selected from among those presenting to the Neurology Outpatient Department on the basis of ICHD-II A1.1.1 (2004) classification. Informed consent was obtained after explaining the nature of study to the subjects, and ethical clearance was obtained from the institutional ethical committee. Study participants with neurological disorders or any other chronic disease, along with conditions suggestive of hormonal disturbances such as pituitary tumor, hypogonadism, infertility, galactorrhea, were excluded from this study, as well as pregnant or lactating women. These are the secondary causes of increased prolactin level and increased prolactin level also considered as stress marker by Ohlson et al.⁹

Diagnosis was based on a thorough history, including headache, medication, family history, and on the basis of IHS diagnostic criteria for each case. Clinically diagnosed migraine cases were asked to maintain a headache diary. Subjects from both groups were then called 2 hours after a light breakfast in the morning of the second day of their menstrual cycle, and a blood sample was withdrawn for biochemical assessment of their hormonal profile.

Hormonal assay included assessment of levels of thyroid-stimulating hormone, triiodothyronine, thyroxine, estrogen, follicle-stimulating hormone, luteinizing hormone, and prolactin serum component, and serum samples were transported to the Department of Biochemistry on the same day. Biochemical analysis was done using the electrochemiluminescence method (Elecys 2010).

Study participants, both cases and controls, were also evaluated for the number of stressful events, daily hassles, domestic and nondomestic stress, anxiety, and depressive tendencies by asking them to fill in the Depression Anxiety Stress Scales (DASS) questionnaire.⁹ The DASS questionnaire is made up of 42 self-report items to be completed over 5–10 minutes, each reflecting a negative emotional symptom. Each of these is rated on a 4-point Likert scale of frequency or severity of the participants' experiences over the last week, with the intention of emphasizing states over traits. These scores range from 0, meaning that the client believed the item "did not apply to them at all", to 3, meaning that the client considered the item to "apply to them very much, or most of the time". Scoring of DASS was done as per guidelines. Study cases were asked to record pain features, symptoms, and their disability, such as days missed at work or reduced productivity, by maintaining their headache diary for three consecutive cycles.

Statistical analysis

Analysis was done with SPSS 21 software, and numerical variables are presented as mean, standard deviation, median, and interquartile range. We used the Mann–Whitney *U* test to compare hormonal levels and the χ^2 test to compare anxiety- or depression-related stress among the migraine and nonmigraine groups. *P*-values less than 0.05 were considered statistically significant. We also calculated odds ratios for the presence of stress in participants. Then, we performed multivariate analysis using logistic regression. We entered statistically significant variables on univariate analysis as predictor variables and migraine as the dependent variable.

Results

Table 1 shows descriptive statistics of hormonal levels in both groups. Significantly higher values of prolactin were observed in cases (migraine sufferers) (mean \pm standard deviation, 152.7 mIU/L \pm 30.5) compared to controls (76.1 mIU/L \pm 8.7), with a *P*-value <0.001 (Figure 1). There were no statistically significant differences observed in levels of thyroid-stimulating hormone (*P*=0.081) (Figure 2), estrogen (*P*=0.086), luteinizing hormone (*P*=0.091), or follicle-stimulating hormone (*P*=0.478) (Table 1). Anxiety with stress or depression with stress was significantly higher among the migraine group than the controls (*P*=0.002). The odds of any stress in migraine were higher in the migraine group than in the nonmigraine group. (odds ratio 12, 95% confidence Interval 2.7–53.33). (Table 2).

Then we performed multivariate analysis by using logistic regression. We entered free thyroxine, free triiodothyronine,

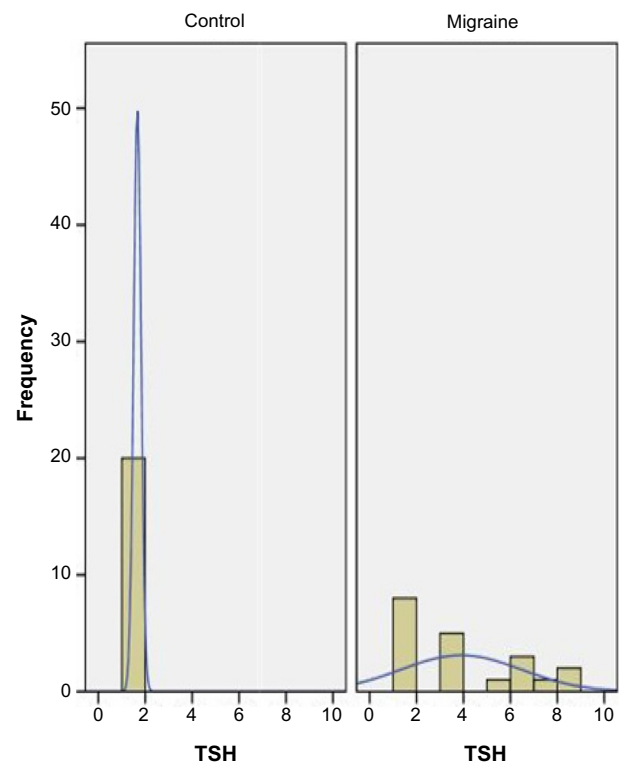


Figure 1 Depicting level of thyroid-stimulating hormone (TSH) in milli-international units per liter among cases of migraine and control.

prolactin, and stress as predictor variables and migraine as the dependent variable in a forward (conditional) stepwise model. The omnibus test result for model coefficients was statistically significant ($P<0.001$), and the Hosmer–Lemeshow test result

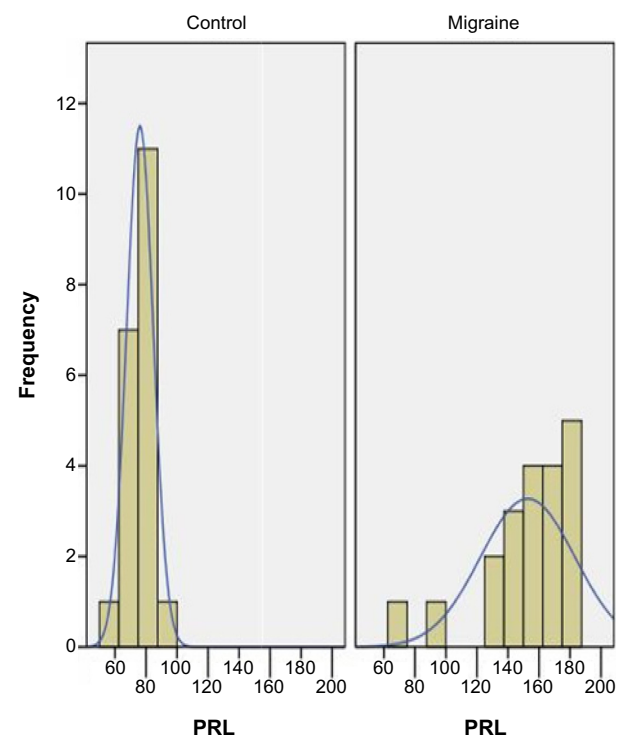


Figure 2 Depicting higher levels of prolactin (PRL) in milli-international units per liter among cases of migraine without aura in females.

Table 1 Distribution of hormone levels on second day of menstruation among migraine and control groups

Hormone	Control		Migraine		Mann-Whitney test P-value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
TSH (mIU/L)	1.67 (0.16)	1.65 (1.51–1.81)	3.90 (2.56)	3.30 (1.51–6.39)	0.081
FT ₄ (mIU/L)	15.07 (0.93)	15.13 (14.25–15.75)	19.01 (1.35)	18.96 (18.76–19.98)	<0.001
FT ₃ (mIU/L)	6.09 (1.09)	6.00 (5.20–6.60)	5.19 (0.45)	5.25 (4.85–5.45)	0.004
E ₂ (mIU/L)	58.89 (7.52)	58.78 (53.50–65.98)	61.37 (26.46)	48.89 (44.34–96.72)	0.086
PRL (mIU/L)	76.07 (8.67)	77.13 (67.57–83.00)	152.70 (30.46)	159.65 (144.15–172.30)	<0.001
LH (mIU/L)	5.97 (1.04)	6.13 (5.34–6.72)	4.63 (2.69)	4.73 (2.10–6.63)	0.091
FSH (mIU/L)	8.98 (11.12)	6.55 (5.81–7.07)	8.38 (4.16)	6.76 (5.51–8.11)	0.478

Abbreviations: SD, standard deviation; IQR, interquartile range; TSH, thyroid-stimulating hormone; FT₄, free thyroxine; FT₃, free triiodothyronine; E₂, estrogen; PRL, prolactin; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

was nonsignificant ($P=0.162$), indicating fit of model. Only prolactin levels were a statistically significant ($P=0.021$) independent predictor of migraine.

Discussion

Hormone changes

According to the National Headache Foundation, 60% of women among menstrual migraine suffer from headache a few days prior to their cycle, during their menstrual cycle, or during ovulation. As estrogen levels drop throughout a woman's cycle, the number of migraines can increase.

Stress triggers

Stress and anxiety can affect the occurrence of migraines, notes Womenshealth.gov. Daily emotional and physical stressors, such as financial worries, poor nutrition, lack of sleep, limited exercise, smoking, or job and relationship concerns can trigger migraine attacks in some people. Migraine is believed to be related to cyclic changes in female sex hormones, but the headache is not any different than those triggered by stress, which itself is a powerful trigger. Since women are more prone to suffer stress because of daily hassles in the work place and at home, and lots of responsibility burden is shared by women in this male-dominated world.

Table 2 Distribution of stress among study participants

Variables	Migraine, n (%)	Control, n (%)	P-value (χ^2 test)
Stress category			
No stress	5 (25)	16 (80)	0.002
Stress with anxiety	10 (50)	3 (15)	
Stress with depression	5 (25)	1 (5)	
Total	20 (100)	20 (100)	
Presence of any stress			
Present	15 (75)	4 (20)	<0.001
Absent	5 (25)	16 (80)	

Note: Odds ratio for stress =12 (95% confidence interval 2.7–53.33).

In the present study, as a case control, we evaluated the stress markers and hormonal status in women having migraine without aura. There are two emotional states that often increase the stress level and thus increase migraines. One is depression. This condition often reduces a person's bodily ability to respond to medication. This is especially true for women, who seem to suffer more from depression. It has been determined that even moderate depression can reduce the effectiveness of migraine medication and treatment methods, such as relaxation and biofeedback.

Anxiety is another emotional state that can increase stress levels and therefore migraine. Anxiety is a state of tension or nervousness that often occurs with no apparent reason, and as with depression, it can prevent the medicine from working well. It also sometimes increases the amount of pain that is experienced. Therefore, many migraine sufferers find it necessary to treat not just the migraines but also the anxiety to get maximum relief.¹⁰ With the preceding discussion, it is clear that stress is a major contributory factor for migraine, which is justified with the results of our study, in which the DASS questionnaire revealed stress-related anxiety in 70% of cases and higher prolactin levels ($P<0.001$). Sobrinho¹¹ demonstrated that prolactin and cortisol are measurable markers of two different and alternative coping strategies to "psychological stress" in which cortisol surges were related to surprise and shock and were negatively associated with prolactin.

Stress can be physical, psychological, or due to other positive stimuli. It is not the stress that harms your body, but the reaction to it is more important. Subtle variations in individuals make reactions to stress different in various individuals. Stress leads to activation of the sympathetic adrenal axis by descending pathways to the hypothalamus through the cortex, which was also reported in animal studies with increased prolactin levels.¹² It is a well-known fact that stress can also induce various heat-shock proteins,

which can bind to various deoxyribonucleic acid-binding domains that can alter the transcription. Another theory related to gene polymorphisms was found to be more prevalent in migraineurs,^{13,14} as various gene polymorphisms were found to be more prevalent in migraines. The genetic load, ie, the “migraine-susceptibility genes”, can be cumulative and determines a critical attack threshold that can be modulated by external (psychosocial stress, preventive therapies) and internal factors (hormonal status, anxiety). Triggers, such as alcohol and stress, are more likely to induce an attack when the migraine threshold is lowered, eg, in the perimenstrual period in many female migraineurs. If the threshold is reached, the cellular and molecular cascade leading to activation of the trigeminovascular system is ignited in the brain and/or brain stem. The genetic load is likely to determine the severity of the migrainous disorder, as well as complications like chronification by medication overuse, which need to be further studied as well as the role of stress in vascular endothelium.

Conclusion

Menstruation is known to be a powerful trigger for migraine. Since women fall under both these categories, this made us keen to study migraine with these two factors, which was found not to be different from stress headache with the results of our study. We can conclude that stress is a more powerful trigger for migraine than menstruation, or it makes migraine much more susceptible to other predisposing factors, including menstruation.

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Disclosure

The authors report no conflicts of interest in this work.

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