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Female sex hormones in men with migraine.

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Abstract

Background: Migraine is a genetically influenced complex disorder characterized by episodes of moderate-to-severe headache, most often unilateral and generally associated with nausea and increased sensitivity to light and sound. It is a common cause of disability and loss of work. The most common type of migraine is without aura (75% of cases). Migraine is more prevalent in women as compared with men, specifically during reproductive years. Recent studies have found differences in headache characteristics, central nervous system anatomy, as well as functional activation by fMRI between the sexes in migraine patients. Although the cause underlying these differences is likely multifactorial, considerable evidence supports an important role for sex hormones. Estrogen and testosterone regulate a host of biological functions through two mechanisms: nongenomic and genomic. Owing to their lipophilic nature and low molecular weight, sex hormones can cross the blood-brain barrier, resulting in similar concentrations in systemic and cerebral circulation. Female sex hormones modulate the action of many other hormones and vasoactive neuro-mediators implicated in the onset of migraine. Aim of study: To asses interictal, and ictal levels of 17β-estradiol, free testosterone (Tf) and the Tf to 17β-estradiol ratio in men with migraine. Methods : We measured 17β-estradiol (E2) and calculated free testosterone (Tf) in serum of 25 medication-free men with migraine and 25 men without migraine group-matched for age. Blood was sampled for migraineurs interictal, day at 9 AM and measured again when an attack occurred. Clinical androgen deficiency was assessed with the Androgen Deficiency of Ageing Men questionnaire. We analyzed interictal data (mean ± standard error) with analysis of covariance and longitudinal data by generalized estimated equations models. Results: Compared to controls, men with migraine had a lower interictal Tf/E2 ratio (3.5 ± 0.8 vs 4.2 ± 1.1, p = 0.007) due to higher E2 (31.6 ± 7.0 vs 24.3 ± 7.8 pmol/L, p = 0.001) and similar Tf (105.6 ± 19.0 vs 109.3 ± 32.9 pmol/L, p=0.625) levels. Interictal Tf levels were increased in men with migraine reporting premonitory symptoms (p=0.013). Men with migraine more frequently reported symptoms of androgen deficiency (13 of 25 [52%] vs 6 of 25 [24%], p = 0.041). Conclusions: In this study, men with migraine exhibited increased levels of the sex hormone estradiol and showed clinical evidence of relative androgen deficiency. The role of estradiol in modulating migraine susceptibility and activity in men deserves further investigations.

Key words: functional magnetic resonance imaging, 17β-estradiol & free testosterone

1.Introduction

Migraine is a common, disabling, episodic brain disorder, typically characterized by recurrent attacks of severe headache, associated features and in one-third of patients aura.(1) In up to two-thirds of migraineurs attacks may be preceded by affective and physical premonitory symptoms.(2) Migraine prevalence, the frequency, duration, and severity of migraine attacks are highly dependent on age, sex and in women events that are associated with marked fluctuations in female reproductive hormones.(3) Sex hormones might modulate migraine risk and activity(4) that is noticed in : Starting or stopping using oral contraceptives can be associated with either the onset or disappearance of migraine attacks. (5) Many male-to-female transsexuals develop migraine after starting estrogen and anti-androgen therapy.(6) Testosterone administration was associated with reduction in migraine frequency and severity in some women.(6) It is unknown whether sex hormones might modulate migraine risk and activity in men.(7) Here, we assessed interictal, and ictal levels of 17β-estradiol, free testosterone (Tf) and the Tf to 17β-estradiol ratio in men with migraine.

2.Patients and Methods:

This is a comparative cross sectional case control study conducted on 25 male patients with migraine and 25 healthy men without migraine group-matched with age, recruited from neuropsychiatry department in benha university hospitals. Males aged 18 – 74 years, and diagnosed with episodic migraine with or without aura according to the criteria of the International Classification of Headache Disorders-IIIb (8) were included, while excluded if they were unable to differentiate migraine from other headaches, patients had headache or were using acute headache medication on ≥10 d/mo, patients were using migraine prophylactic medication daily, smoking during participation, hypertension (defined as blood pressure >150/90 mm Hg or use of antihypertensive medication), intake of high-fat foods immediately before a measurement, history of hypogonadism, use of any medication or supplements that could affect hormone levels, any liver or kidney

condition, coagulopathies such as hemophilia or a compromised immune system.., . study subjects were informed of the possibility of using the data obtained for academic purpose.

2.1Tools:

All participants (cases & control) were subjected to the following:

1) Medical history taking, semi structured interview questionnaire including each of personal data
2) Blood sample to measure 17β-estradiol (E2) and calculated free testosterone (Tf) and then Tf/E2 ratio was measured.
3) Androgen Deficiency of Ageing Men (ADAM) questionnaire.(9)
4) Clinical evidence of androgen deficiency by items relevant to the reproductive system including frequency of shaving of facial hair, age at dropping of voice in puberty, cryptorchidism, number of children, unwanted childlessness, delay in parenthood despite attempts and help in fertilization (in vitro fertilization, surrogacy)(10)
5) We assessed at each measurement the presence and characteristics of headache and premonitory symptoms which is defined as presence of 1 or more of the above symptoms that was then followed by migraine headache within 24 hours, including less frequent micturition, ankle or wrist edema, changes in defecation, thirst, changes in appetite, craving for specific food, stiffness of limbs and/or face, stiff neck, difficulty with concentrating, mental agitation, physical agitation, fatigue, excessive yawning, hyperirritability, and mood changes such as depression.(2)

2.2Ethical consideration:

An informed written consent was obtained from patients and control subjects before their participation in the current study. It included data about aim of the study, site of the study, study procedure and their acceptance for publication of anonymous data obtained. It was explained to both groups that they can withdraw from the study at any time without any consequences and it will not affect the type and quality of care they are receiving from the facility. It was also assured to all participants regarding the confidentiality of results

2.3Statistical analysis:

The collected data was revised, coded and tabulated using Statistical package for Social Science**.** Shapiro test, Mean Standard deviation (± SD), Student T Test, Mann Whitney Test (U test), Chi-Square test, Fisher's exact test, correlation analysis and regression analysis were used.(11) All reported *p* values were two-tailed and $p < 0.05$ was considered to be significant

3.Results:

Table (1) Comparison of age, interictal Tf, E2, Tf/E2 ratio among studied groups.

	Control N=25 mean±SD	**Cases N=25 mean±SD**	***p***
Age (years)	37±10.8	38.8±8.6	0.526
Interictal Tf (pg/ml)	109.3±32.9	105.6±19.0	0.625
Interictal E2	24.3±7.8	31.6±7.0	**0.001**
Interictal TF / E2 Ratio	4.2±1.1	3.5±0.8	**0.007**

SD, standard deviation; E2, Estradiol; Tf, free Testosterone.

The present study was conducted on 25 male cases. Their mean age was 38.8 years. In addition to 25 healthy control of matched age and gender. Cases showed significantly higher E2, significantly lower Tf/E2 ratio when compared to control group (p=0.001, 0.007 respectively). Tf did not differ significantly between both groups (p>0.05).

Table (2) Regression analysis for prediction of migraine occurrence.

	Univariable				Multivariable			
	p	**OR**	**95% CI**		**p**	**OR**	**95% CI**	
Age	0.516	1.012	0.976	1.049				
ictal Tf/E2	**0.009**	0.595	0.402	0.880	**0.036**	0.641	0.424	0.970
ADAMS	**0.042**	2.152	1.028	4.506	**0.028**	1.624	0.738	3.576

OR, odds ratio; CI, confidence interval.

Regression analysis was conducted for prediction of migraine using age, ictal Tf/E2 and ADAMS as covariates. Lower ictal Tf/E2 and positive ADAMS was considered as predictors of migraine in males.

Table (3) Comparison of clinical androgen deficiency assessment by the Androgen Deficiency of Ageing Men questionnaire (ADAM) questionnaire between cases and controls.

			Control N=25		**Cases N=25**		***p***
			N	**%**	**N**	**%**	
Q1	**Decreased libido**	**No**	22	88%	16	64%	**0.047**
		Yes	3	12%	9	36%	
Q2	**Lack of energy**	**No**	23	92%	24	96%	0.552
		Yes	2	8%	1	4%	
Q3	**Decreased strength and/or endurance**	**No**	24	96%	23	92%	0.552
		Yes	1	4%	2	8%	
Q4	**Lost height**	**No**	25	100%	24	96%	0.312
		Yes	0	0%	1	4%	
Q5	**Decreased "enjoyment of life"**	**No**	25	100%	24	96%	0.312
		Yes	0	0%	1	4%	
Q6	**Sad and/or grumpy**	**No**	25	100%	25	100%	-
		Yes	0	0%	0	0%	
Q7	**Erections less strong**	**No**	22	88%	20	80%	0.702
		Yes	3	12%	5	20%	
Q8	**Deterioration in ability to play sports**	**No**	25	100%	23	92%	0.490
		Yes	0	0%	2	8%	
Q9	**Falling asleep after dinner**	**No**	25	100%	25	100%	-
		Yes	0	0%	0	0%	
Q10	**Deterioration in work performance**	**No**	23	92%	25	100%	0.490
		Yes	2	8%	0	0%	
Total	**Androgen deficiency**	**No**	19	76%	12	48%	**0.041**
		Yes	6	24%	13	52%	

Cases were significantly associated with decreased libido when compared to control group (p=0.047). Otherwise, no significant differences were found regarding answers of ADAM questionnaire (p>0.05 for each). All questions were answered with yes or no. If question 1 or 7 or any 3 other questions are answered positively, the results indicate an androgen-deficient state. So, control group had 24%, while cases group had 52% androgen-deficient state with significant association of androgen-deficiency with studied cases (p=0.041).

Table (4) Premonitory symptoms among studied cases.

		Cases N=25	
Premonitory symptoms	**negative**	5	20%
	positive	20	80%

Among all studied cases, 20 cases had positive premonitory symptoms (80%) and 5 cases had no premonitory symptoms (20%).

Table (5) Regression for prediction of positive premonitory symptoms.

	p	OR	95% CI	
Age	0.764	1.011	0.942	1.085
Interictal Tf/E2	0.114	0.550	0.262	1.154
Ictal Tf/E2	0.460	0.613	0.167	2.245
ADAMS	0.549	1.413	0.456	4.377

OR, odds ratio; CI, confidence interval.

Regression analysis was conducted for prediction of positive premonitory symptoms, using age, ictal and interictal Tf/E2 and ADAMS as covariates. None was considered as predictor of positive premonitory symptoms.

4.Discussion:

The present study was conducted on 25 male cases. Their mean age was 38.8 years. In addition to 25 healthy controls of matched age and gender. Regarding the mean age of patients, it was around 42 years by ***Hansen TF, et al., 2018*** which is consistent with our results(12).On the other side, our study is contrary with ***Androulakis XM, et al., 2019*** with mean age 61 years, this may be due to his different selection of the cases searching here for the association between migraine and ischemic stroke in late life.(13) It is also contrary with ***Pilati L,et al., 2020*** with mean age about 20.5 years, this was because the study was limited and focused on students only.(14) The present study revealed that cases had significantly higher E2, significantly lower Tf/E2 ratio when compared to control group, Tf did not differ significantly between both groups.Interictal E2 and interictal Tf/E2 showed moderate accuracy AUCs for prediction of migraine. E2 sensitivity was 76%, specificity was 72%, while Tf/E2 sensitivity was 68%, specificity was 68%. However, intrictal Tf showed low accuracy AUC for prediction of migraine. This can be explained by almost fixed Tf level and with increased E2 level, the Tf/E2 ratio became significantly lower. Also increased E2 level was found to be a good predictor for migraine which can be explained by its effect on trigeminovascular activation induced by cortical spreading depression or its relation with pro and anti-inflammatory mediators and calcitonin gene-related peptide. Also the natural course of migraine throughout the lifetime reflects hormonal influences, with migraine prevalence diverging at puberty for children, and variations in migraine frequency and intensity with pregnancy and menopause. While ***Shields et al., 2019*** identified 14 men ages 26-51 who suffered from chronic migraine. They had lower total testosterone levels compared to published age matched controls by a median difference of 62.0 ng/dL, which suggested that hypothalamic regulation is altered in patients with chronic migraine with a statistically significant difference between the two distributions (15) which is inconsistent with out study. Our study matches with ***Van Oosterhout, et al., 2018*** that confirmed that in comparison with controls, men with migraine had higher levels of estrogen between migraine attacks (69 picomoles per liter vs 97 picomoles per liter). Testosterone levels were similar among both groups, which resulted in a lower ratio of testosterone to estrogen inbetween migraines for the test subjects (16) This was explained by that women with menstruation-related migraine attacks seem to have a more rapid late-luteal phase drop in 17β-estradiol compared to women without menstruation related migraines. This might cause an imbalance between long-lasting genomic effects of nuclear estradiol receptors and short-lasting non genomic effects via intramembranous G protein–coupled estradiol receptors. This imbalance might activate a cascade leading to neuronal sensitization and ultimately triggering of migraine attacks. The present study found that, cases were significantly associated with decreased libido when compared to control group. Otherwise, no significant differences were found

regarding answers of ADAM questionnaire which consists of 10 questions, all questions were answered with yes or no in our study, if question 1 or 7 or any 3 other questions are answered positively, the results indicate an androgen-deficient state. So, control group had 24%, while cases group had 52% androgen-deficient state with significant association of androgen-deficiency with studied cases which may be due to mood changes and anxiety. Which agreed with ***Verhagen, et al., 2021*** who found that migraine and cluster headache male patients more often reported to have androgen-deficient state, score below average on each of the individual sexual items: decreased beard growth, morning erections, libido and sexual potency, Furthermore, more than twice as many patients with migraine (18.4%) and cluster headache (20.6%) reported to suffer from diminishment of at least one of these four sexual symptoms, compared with non-headache controls.(7) Furthermore, the symptomatology described in this study could partly be explained by side effects of prophylactic medications. (7) But disagreed regarding ADAM score, as differences were found in both Aging Male Symptoms *score* (AMS) and qADAM scores between men with migraine, cluster headache and non-headache controls. The mean AMS scores were higher in patients with migraine compared to controls. Mean qADAM scores were lower in patients with migraine compared to controls (***Verhagen, et al., 2021).*** (7) In current sudy, regression analysis was conducted for prediction of migraine using age, ictal Tf/E2 and Androgen Deficiency of Ageing Men (ADAM) as covariates. Lower ictal Tf/E2 and positive ADAM was considered as predictors of migraine in males. The present study revealed that among all studied cases, 20 cases had positive premonitory symptoms (80%) and 5 cases had no premonitory symptoms (20%). Our study matches with ***Laurell, et al. 2016*** who found that out of 2714 persons, 2223 were diagnosed with migraine. Among these, 77% reported premonitory symptoms (PS), with a mean number of 3.0 symptoms compared to 30% without PS, and 0.5 symptoms among 491 persons with non-migraine headaches. (17) Our study in contrary with ***Kelman L, et al. 2004*** who documented that only about one third (33%) of patients, irrespective of the type of migraine, experienced prodrome or premonitory symptoms. (18) Variability in rates might be explained by differences in study design such as preselection of patients or differences in symptoms that are included in the questionnaire. Another source of variability might be the studied population, it may be that patients identified in a population-based setting are not informed about premonitory symptoms in migraine and therefore are less aware of these symptoms.(18) No significant differences were found regarding age according to incidence of premonitory symptoms among studied cases.Regression analysis was conducted for prediction of positive premonitory Symptoms, using age, ictal and interictal Tf/E2 and ADAMS as covariates. None was considered as predictor of positive premonitory symptoms. This matches with ***Schoonman, et al, 2006*** who found that the effect of age, education and migraine subtype (with or without aura) on the mean number of premonitory symptoms per individual were not statistically significant.(19) This is inconsistent with what was found by ***Laurell, et al. 2016*** who confirmed that the number of PS differed across age groups and age was a significant predictor in both regression analyses. (17) A thorough understanding of sex and gender differences in migraine provides important insights into the pathophysiological processes involved in migraine as well as implications on a population level. Though research into these aspects in the domains of epidemiology, basic science, clinical research, genetics, and neuroimaging continues, several observed sex and gender differences remain unexplored. Therefore, future studies in migraine research should prioritize sex and gender aspects, consider using consistent definitions of these concepts, and employ suitable methods to explore these relevant differences instead of controlling for them.

5.Conclusion:

In this study, men with migraine exhibited increased levels of the sex hormone estradiol and showed clinical evidence of relative androgen deficiency. The role of estradiol in modulating migraine susceptibility and activity in men deserves further investigations.

6.Limitations:

The small number of cases involved which made our results biased, further studies of larger populations are needed to validate these findings. Human clinical studies typically have an overrepresentation of women, limiting generalizability to the still sizable proportion of men with migraine. The migraine characteristics are too homogeneous for additional analyses by headache frequency, intensity, or duration. We also can not fully exclude that, possibly as a result of self-selection, our results may apply only to patients with, for example, severe migraine.

7.Recommendations:

Further studies in larger and additional populations are needed to validate these findings. What exactly the role of estradiol is in men with migraine and whether fluctuations in estradiol levels, as in women, might be associated with changes in migraine activity deserve further intraindividual follow-up studies over multiple attack cycles. Basic science studies with a more representative distribution of sexes are warranted as societal differences and stigma surrounding this "feminized" disease should not be underestimated. Next studies should take into account unique aspects of migraine management including use of feminizing and masculinizing hormones. Generally, thorough understanding of the mechanisms linking migraine and vascular risk is essential for appropriate management of patients with migraine. There are currently no validated indicators that can be used to predict which patients may be at greater risk and if there is a role for sex hormones in coping with such vascular risk.

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Conflicts of interest:

There are no conflicts of interest

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