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Female sex hormones in men with migraine

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Abstract

Background: Several in vitro antimicobial activity experiments were performed on apple (Malus domastica), banana (Musa parasidica), and wild plants (Zimia spinosa, Saeuda aegyptica, Chenopodium mural, and Caltropis procera). Chemical investigation has shown that each of these plant extracts has a unique combination of active compounds. Methanolic extracts inhibited (staphylococcus. aureus) and (escherichia.coli) growth in preliminary testing of their antibacterial action, whereas salmonella. enterica proved resistant to most extracts. Apple and banana skins, as well as the aerial portions of the plants Zizea spinosa, Saueda aegyptiaca, Chenopodium mural, and Caltrpis procera, were removed to test for the presence of potentially active crude compounds (dis.water,acetone, and methanol). The mic (minimum inhibitory concentration) values of banana and chenopodium methanolic extracts were found to be 1.562 mg/ml and 3.124 mg/ml for Escherichia coli and 6.25 mg/ml and 1.25 mg/ml for Staphylococcus aureus, respectively. Experiments were then conducted to confirm that bananas and chenopodium contain highly active compounds (tests for antioxidant activity, biofilm development and reduction, and antihemolytic action). Banana methanolic extract had a significant inhibitory effect on staph.aureus and e.coli, as shown by a transmission electron microscopy (tem) experiment.

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

1. Introduction

Migraine is a distressing neurological condition that commonly manifests as recurring bouts of severe headache, accompanying symptoms, and aura in one-third of patients. [1] Affective and physical warning signals may precede episodes in as many as two-thirds of migraineurs. [2] Age, sex, and in women, events linked with notable oscillations in female reproductive hormones all have a significant role in migraine prevalence, frequency, duration, and severity. There is some evidence that sex hormones may affect migraine risk and severity [3]. [4] this is shown in the fact that the use of oral contraceptives, either before or after a migraine episode, might have an effect on the severity of the attack. Migraine is a common side effect of oestrogen and anti-androgen medication, which is why many male-to-female transsexuals experience them. Some women reported a lessening in migraine frequency and intensity after receiving testosterone treatment. [6] Whether or whether sex hormones affect migraine risk and activity in males is not understood. In this study, we measured 17-estradiol, free testosterone (Tf), and the ratio of Tf to 17-estradiol in males with migraine throughout interictal and ictal phases.

2. Patients and Methods:

Twenty-five male patients with migraine and twenty-five age-matched healthy male controls were recruited from the neuropsychiatry departments of hospitals affiliated with Benha University for this cross-sectional case control research. Men between the ages of 18 and 74 who met the diagnostic criteria for episodic migraine with or without aura according to the International Classification of Headache Disorders-IIIb [8] were eligible to participate. On the other hand, those who met the following exclusion criteria were not: inability to distinguish migraine from other headaches; headache or use of acute headache medication on more than 10 days per month; daily use of migraine prophylaxis; smoking during participation; and hypertension (defined as blood pressure greater than or equal to 140 Participants were made aware that their data may be used in academic studies.

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

Twenty-five male participants were included in the current investigation. The average age of this group was 38. Plus 25 age- and gender-matched healthy controls. Consistent with our findings, Hansen TF et al. (2018) found that the median age of patients was 42 years old [12]. Although we found no link between migraine and ischemic stroke in our older population, Androulakis XM, et al., 2019 found a correlation between the two in their research of patients with a mean age of 61. This discrepancy may be attributable to the authors' differing case selection criteria. [13] It contradicts Pilati L,et al., 2020, which found a mean age of roughly 20.5 years among its student participants. [14] The current investigation found that the ratio of Tf to E2 was considerably lower in the case group compared to the control group, whereas Tf did not change significantly between the two groups. The AUCs for predicting migraine using interictal E2 or interictal Tf/E2 were modest. There was a 76% sensitivity and a 72% specificity for E2, whereas there was a 68% sensitivity and a 68% specificity for Tf/E2. However, the AUC for accuracy of intrictal Tf in predicting migraine was poor. The reason for this is that while the concentration of E2 grew, the Tf/E2 ratio remained relatively constant. Because of its influence on trigeminovascular activation generated by cortical spreading depression or its interaction with pro and anti-inflammatory mediators and calcitonin gene-related peptide, an elevated E2 level was also shown to be a strong predictor of migraine. Hormonal factors are also reflected in the natural progression of migraine over the course of a person's lifetime, with the incidence of migraines changing around puberty for children and with fluctuations in migraine frequency and severity throughout pregnancy and menopause. However, Shields et al. 2019 observed 14 males between the ages of 26 and 51 who had chronic migraine. Although there was a statistically significant difference between the two distributions [15], our findings that chronic migraine sufferers had lower total testosterone levels compared to published age-matched controls revealed that hypothalamic regulation is disturbed in these individuals. Consistent with the findings of Van Oosterhout et al. (2018), we found that males with migraine had greater oestrogen levels between migraine episodes compared to controls (69 picomoles per litre vs 97 picomoles per liter). Both groups had comparable amounts of testosterone, which meant that the test participants' testosterone-to-estrogen ratio dropped significantly when they were free from migraines [16] This was attributed to the fact that 17-estradiol levels in women whose headaches were not associated with menstruation dropped more quickly during the late luteal phase than in women whose migraines were not associated with menstruation. This might result in an inequity between the long-lasting effects on the genome mediated by nuclear estradiol receptors and the transient effects mediated by intramembranous G protein-coupled receptors. It's possible that this disproportion sets off a chain reaction that causes neural sensitivity and, eventually, migraine episodes. Relative to the control group, the cases in this research had considerably lower libido. Results from the Androgen Deficiency and Acquired Machonism (ADAM) questionnaire showed no statistically significant differences between the two groups. The

questionnaire comprises of 10 items, all of which were completed in our research with a yes or no. This suggests that androgen-deficiency, which has been linked to alterations in mood and anxiety, is much more common among the patients than the controls. In line with the findings of Verhagen et al. 2021, who discovered that male patients with migraine and cluster headaches more frequently reported to have an androgen-deficient state, scored below average on each of the individual sexual items, including decreased beard growth, morning erections, libido, and sexual potency. Moreover, compared to non-headache controls, those who suffer from migraine (18.4%) or cluster headache (20.6%) were more than twice as likely to report at least one of these four sexual symptoms as they were to report a reduction in their overall sexual desire. [7] Furthermore, it is possible that adverse reactions to preventative drugs are responsible in part for the symptoms documented in this research. [7] However, they did not agree on the ADAM score; the Aging Male Symptoms (AMS) and the qADAM scores were different for men who reported migraines, cluster headaches, or neither. For the AMS as a whole, migraine sufferers fared worse than controls. Patients with migraine had lower mean qADAM scores than controls (Verhagen, et al., 2021). [7] This study included age, ictal Tf/E2, and androgen deficiency in ageing men (ADAM) as factors in a regression analysis to predict migraine. It was hypothesised that male migraine sufferers will have lower ictal Tf/E2 and positive ADAM. Twenty of the thirty cases (or 80%) with premonitory signs were found in this investigation, whereas five instances (or 20%) had no such symptoms. Similarly, Laurell et al. (2016) observed that 2223 out of 2714 people had migraines, which is consistent with our findings. Seventy-seven percent (77%) of these people reported having premonitory symptoms (PS), with a mean number of 3.0 symptoms, compared to only 30% (and 491% of people with non-migraine headaches) who did not. [17] Our research contradicts the findings of Kelman L, et al. 2004, who found that only roughly one third (33%) of patients exhibited prodrome or premonitory symptoms, regardless of the kind of migraine. [18] Variability in rates may be due to factors such as research design, patient selection, and the inclusion or exclusion of certain symptoms in the questionnaire. The population under study might also account for some of the variation seen; for example, patients identified in a community-based environment could not have been given information regarding the warning signs of migraine. There were no statistically significant variations in age at the onset of warning signs amongst the patients that were examined[18]. Age, ictal and interictal Tf/E2, and ADAMS were used as factors in a regression analysis to predict positive premonitory symptoms. Not one of them was seen as indicative of a favourable prognosis. This agrees with the findings of Schoonman et al. (2006), who also observed no statistically significant relationship between age, education, or migraine subtype (with or without aura) and the average number of forewarning symptoms experienced by each person. Laurell et al. 2016 verified that the number of PS varied among age groups and that age was a significant predictor in both regression models, therefore this contradicts their findings [19]. [17] Insights into the pathophysiological mechanisms at play in migraine and its societal consequences may be gained through a comprehensive study of sex and gender variations in the disease. Despite ongoing efforts to investigate sex and gender differences across a variety of disciplines (including epidemiology, fundamental science, clinical research, genetics, and neuroimaging), many of the distinctions between the sexes remain poorly understood. Thus, future migraine studies should give sex and gender consideration, think about utilising consistent definitions of these categories, and use appropriate methodologies to study these important variations rather than 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

Our findings should be taken with a grain of salt due to the limited sample size; more research with bigger populations is required to confirm these hypotheses. When doing human clinical trials, women tend to outnumber males, limiting generalizability to the significant male migraine population. Additional breakdowns of migraine features, such as headache frequency, strength, or duration, are not possible due to their similarity. We also cannot rule out the possibility that our findings may be limited to those who already have a severe condition, such as migraine sufferers.

7. Recommendations

We need to confirm these results with bigger and more diverse sample sets. Additional intraindividual follow-up studies spanning several attack cycles are required to determine the precise function of estradiol in males with migraine and if variations in estradiol levels, as in women, could be related with changes in migraine activity. As cultural disparities and stigma surrounding this "feminised" illness should not be overlooked, it is necessary to conduct basic scientific investigations with a more gender-balanced sample. Utilization of feminising and masculinizing hormones is one such unique component of migraine care that has to be considered in future research. Understanding the processes that connect migraine with vascular risk is crucial for the proper therapy of people who suffer from migraine. While sex hormones may have a role in reducing vascular risk, there are presently no established signs that can be used to predict which individuals may be at increased risk.

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There are no conflicts of interest

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