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ORIGINAL ARTICLE

Hormonal effect on the relationship between migraine and female sexual dysfunction

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Abstract It is not a well-established finding in migraine that female sexual dysfunction (FSD) emerging as a natural course of disease, as a result of accompanying depression/anxiety, or an underlying endocrinological abnormality. Our aim is evaluating the relationship among frequency and severity of migraine, FSD, depression, anxiety, and related hormones in migrainous women. We examined 80 migrainous female and 62 controls cross sectionally. Beck Depression and Anxiety Inventories, Female Sexual Dysfunction Inventory, Migraine Disability Assessment Test, and hormonal analysis were done. Independent risk factors were identified by logistic regression analysis and cut-off values were measured with Receiver Operating Curve. FSD was not related to frequency or severity of migraine. Although depression and anxiety was related to arousal and lubrication, they had limited effect in FSD. There were correlations between prolactin (PRL), desire and lubrication, follicular-stimulating hormone FSH and orgasm, luteinizing hormone (LH), and pain. Also FSH-LH combination and PRL were found as independent factors for FSD. FSH-LH combination and PRL were found as independent factors which had effect on FSD in migraine. Our study is a precursor study about the effect of several hormones on FSD and migraine relationship. Hormonal effect on FSD in migraine will be clearer with future studies.

Keywords Migraine · Female sexual dysfunction · Prolactin · Follicular stimulating hormone · Luteinizing hormone

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Introduction

Persistent, recurrent problems with sexual response including six domains such as desire, arousal, lubrication, orgasm, satisfaction, and pain which causes distress and/or strains relationship with the partner is known medically as female sexual dysfunction (FSD) [1]. FSD is a common health problem worldwide with the prevalence ranging between 43 and 90% [2, 3]. There is a genetic susceptibility for FSD that is influenced remarkably by environmental factors [4]. FSD reflects a dynamic interplay of central and peripheral nervous, vascular, and endocrine systems [5]. Several endocrinopathies such as polycystic ovary syndrome (PCOS), obesity, metabolic syndrome, diabetes mellitus (DM) and some hormonal contraception methods are associated with FSD [6, 7]. Also hormonal replacement therapies particularly estrogen and testosterone are used for FSD in postmenopausal women [8].

In recent years, studies discuss about the impact of chronic pain on FSD as an environmental factor [4, 9]. Primary headaches especially migraine is a common cause of chronic pain [4]. Migraine is a chronic disorder affecting lots of women all over the world which is associated with sexual dysfunction and different psychological disorders such as depression and anxiety [10]. Prevalence of migraine in women is approximately 17% [11]. Several studies identify that women with migraine have higher sexual pain, satisfaction disorders, difficulties in lubrication, and orgasm [4, 12]. In a large population based study in USA, the frequency and quality of sexual

relationships were affected in 86% of migrainous patients, and it resulted in divorce in 26% of the cases [13]. Sexual dysfunction such as decreased libido, difficulty in arousal resulting in vaginal dryness, and absent or delayed orgasm are also commonly seen in psychiatric disorders such as depression and anxiety and/or due to antipsychiatric medicine usage [14]. And it is known that depression and anxiety are oftenly seen in migraine sufferers [15]. It has not yet been clearly identified that FSD in patients with migraine occurs as a natural course of disease, as a result of accompanying depression and/or anxiety, or due to an underlying endocrinological abnormality. A few studies have been done to understand the relationship in between FSD, migraine and comorbid psychiatric disorders such as depression and anxiety recently. But relationship with hypothalamic and sex hormones in females with migraine who were suffering from FSD have not been studied yet.

Our aim in this study is evaluating the relationship among frequency and severity of migraine, FSD, depression, anxiety, and related hypothalamic and sex hormones in females with migraine for identifying a new perspective.

Method

Patients

The study was performed between March 2015 and December 2016, cross sectionally. We selected 80 female migraine patients between the ages of 18–45 years old from Neurology outpatient clinics in Bakirkoy Research and Training Hospital who had been examined in the Obstetric and Gynecology Department of the same hospital before. The inclusion criterion was diagnosis of migraine with or without aura according to the International Headache Society (IHS) International Classification of Headache Disorders-II (ICHD-II) (IHSD-II), which continued for at least 1 year in sexually active females for at least 1 year. We excluded patients who had secondary headaches, other primary headaches, other forms of migraine, diagnosis of depression, anxiety and other psychiatric disorders, PCOS, DM, hypertension, obesity, metabolic syndrome, hepatic or renal failure, endocrinological diseases and any other medical condition which may affect sexual function, patients who were pregnant, breastfeeding, or postmenopausal. Also, patients who were using antidepressants, antipsychotics, oral contraceptives (OC), antiepileptics, or any other medications that may affect sexual function were excluded from our study. Medication overuse headache was also excluded. The control group was selected from healthy females who were between 18 and 45 years of age with no disorder.

Instruments

Migraine patients and healthy individuals in the control group were asked to complete the questionnaires consisting of Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Female Sexual Dysfunction Inventory (FSFI) after sociodemographic features were noted. Migraine patients were also subjected to Migraine Disability Assessment Test (MIDAS) and Visual Analog Score (VAS). MIDAS is a 5-item, open-ended questionnaire evaluating frequency and duration of headache, as well as how often these headaches limited patient's ability to participate in daily activities [16]. BDI is a 21-item, multiple-choice, self-reported questionnaire that measures the severity of depression [17]. BAI is a 21-item, multiple-choice, self-reported questionnaire that measures the severity of anxiety [18]. FSFI is a 19-item, multiple-choice, self-reported questionnaire assessing the key dimensions of sexual function in women [19]. Patients and controls who needed assistance due to a reading and/or writing problem were supported when necessary while they were filling the questionnaires. During administration of the questionnaires, any incomprehensible questions and answers were explained without giving any guidance as to the response they should give.

Then, all patients and controls were subjected for blood sampling for analyzation of biochemistry, complete blood count (CBC), estrogen (E), progesterone (P), follicular stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL). If any disorder was detected in biochemistry and/or CBC, those patients were excluded from our study.

Firstly, sociodemographic characteristics; scores BDI, BAI, and FSFI; and hormone levels were compared between migraine patients and controls. VAS and MIDAS results were compared between patients.

Then, E, P, FSH, LH, and PRL levels of migraine patients and controls were analyzed if there was a difference between groups and if there was a significant relationship between any hormone level and depression; anxiety; results of MIDAS, BDI, BAI, and FSFI; and FSD and its domains such as desire, arousal, lubrication, orgasm, satisfaction, and pain. Relationship between phase differences in menstrual cycle and FSD was detected in both patients and controls. And further analysis was done to identify the independent factors which affect FSD.

Ethics

The protocol was approved by the local ethics committee of Bakirkoy Research and Training Hospital. Informed consent was obtained from all migraine patients and healthy individuals in the control group before the study.

Statistical analysis

SPSS (Statistical package for the social sciences) version 22 analysis program was used for data analysis. Variables of normal distribution were evaluated by chi-square test. Analysis of homogeneity of variance was done by Levene's test. Variables between two independent groups were compared to each other by the Mann-Whitney *U* and Students' *t* tests. The nonparametric Spearman correlation analysis was used to evaluate the correlation between two variables. Multivariate linear and stepwise logistic regression analysis was used to evaluate the functional relationships between variables and to identify the independent factors which affect FSD in migraine. Relative sensitivity, specificity, positive and negative predictive ratio between the classification, and the actual classification of the cut-off values calculated according to the variables of the patient groups were evaluated by ROC (Receiver Operating Curve) analysis. *p* value <0.05 was determined to be statistically significant and *p* value <0.001 was determined to be statistically very significant.

Results

Eighty female patients with migraine and 62 age-similar female healthy individuals as controls were admitted to our study. Premenstrual or menstrual relationship with migraine was detected in 30 (37.5%) of the patients. Frequency of attacks (Fa), which is described as number of days with migraine per month, was ≤3 days/month in 51 (63.8%) patients whereas ≥4 days/month in 29 (36.2%) patients. 30 (37.5%) patients had 0–12 h duration of attack of migraine (Pa), 32 (40%) patients had 13–24 h Pa, 18 (22.5%) patients had ≥24 h Pa. Distribution of patients according to VAS is given in (Fig. 1). Eleven (13.8%) patients were in grade 1, 26 (32.5%) patients were in grade 2, 25 (31.2%) patients were in grade 3, and 18 (22.5%) patients were in grade 4 according to MIDAS. Mean level of MIDAS score was 15.8 ± 11.7.

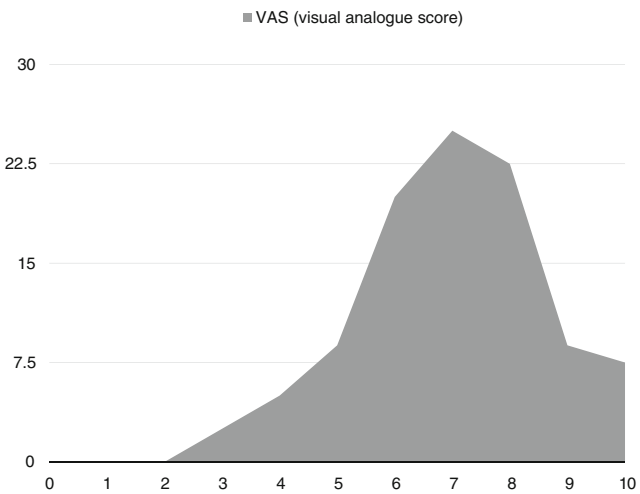

Fig. 1 Distribution of patients according to VAS

Distribution of numbers of patients and controls according to education level, menstrual cycle phases, number of children, depression, anxiety, and FSD are given in (Table 1). Mean levels of age; cigarette packet-year; BDI, BAI, FSFI, and FSD domains; and E, P, FSH, LH, PRL levels in patients and controls are given in (Table 2). Depression (*p* 0.77) and anxiety (*p* 0.31) were not different whereas FSFI score, FSD, arousal, lubrication, orgasm, and satisfaction were very significantly different ($p < 0.001$); P (*p* 0.004) and PRL (*p* 0.02) were significantly different between patients and controls.

VAS was not correlated to any other parameters that were analyzed ($p > 0.05$). Fa was positively correlated to MIDAS grade (*p* 0.028, *r* +0.245), MIDAS score (*p* 0.036, *r* +0.235), depression (*p* 0.041, *r* +0.029), and BDI score (*p* 0.026, *r* +0.250). Pa was correlated to MIDAS score (*p* 0.031, *r* +0.242).

Premenstrual or menstrual relationship of migraine was negatively correlated to depression (*p* 0.045, *r* −0.255). No relationship between phase differences in menstrual cycle and FSD was detected in both patients and controls by one-way ANOVA test.

Correlation analysis among MIDAS, depression, anxiety, FSFI, FSD domains, and hormone levels are given in (Table 3). Age of patients was not correlated to any domains of FSD. Depression and anxiety were very significantly positively correlated to each other. Anxiety and FSFI and FSD had no correlation although anxiety was negatively correlated to arousal (*p* 0.014) and lubrication (*p* 0.034). Depression had no correlation with FSD although it was negatively correlated to arousal (*p* 0.014), lubrication (*p* 0.000), orgasm (*p* 0.018), and FSFI (*p* 0.012).

P and PRL were significantly different between patients and controls ($p < 0.05$). When hormonal levels and FSD correlation was examined in patient group, we found that E and P were not related to depression, anxiety, and FSD domains. PRL was negatively correlated to depression (*p* 0.003), anxiety (*p* 0.046), whereas it was positively correlated to desire (*p* 0.023) and lubrication (*p* 0.057). FSH was positively correlated to orgasm (*p* 0.025). LH was negatively correlated to pain (*p* 0.027).

FSH-LH combination and PRL were found as independent factors which can affect FSD in females with migraine by multivariate linear and stepwise regression analysis. Cut-off values were found as 11.1 mcLU/ml for PRL, 5.6 mLU/ml for LH, and 5.8 mLU/ml for FSH.

Discussion

FSD is a very important public health problem which disturbs patients' relationships with their partners and also impairs quality of life [4, 20]. Migraine patients more oftenly complain from FSD as compared with general population [4, 10]. Desire and arousal disorders were reported as the most

Table 1 Distribution of numbers of patients and controls according to education level, menstrual cycle phases, number of children, depression, anxiety, and FSD

	Patients (total *N*: 80)		Controls (total *N*: 62)		*p* value
	N	%	*N*	%	
Ps	43	53.7	36	58.0	>0. 05
Hs-university	37	46.3	26	42.0	>0. 05
Follicular phase	46	57.5	23	37.1	*p* 0.027 (2-sided significance)
Ovulation	14	17.5	11	17.7	
Luteal phase	20	25.0	28	45.2	
Nc 0	10	12.5	11	17.7	*p* 0.564 (2-sided significance)
Nc 1–2	50	62.5	39	62.9	
Nc >2	20	25.0	12	19.4	
Depression	27	33.8	18	29.0	0.771
Anxiety	59	73.8	46	74.2	0.309
FSD	61	76.3	23	37.1	0.000

Ps primary school, *Hs* high school, *Nc* number of children, *FSD* female sexual dysfunction, *N* number

common sub-scales of sexual dysfunction in migraine patients with prevalence of 73.7 and 64.9%, respectively [10, 21]. In our study, we approved 4 days as a cut-off value for Fa to study FSD in migraine patients to avoid false positivity of chronic frequent headache. We found that all domains except pain were worse in patients with migraine. Pain was not different and high in both groups. In addition, arousal, lubrication, orgasm, and satisfaction were affected much more than desire in our study.

There are a few studies which report different results about relationship between FSD and Fa or Pa [4, 22]. In our study, neither Fa nor Pa was found as correlated to FSD. Also, MIDAS and VAS were not correlated to FSD. The comorbid disorders especially depression and anxiety are common in migraine sufferers [14]. Depression was significantly correlated to increasing Fa in our study. We found that both depression and anxiety increased with higher scores and grades of MIDAS. Depression can disturb neuroendocrine balance, which has some roll in sexual desire and satisfaction [15]. Many studies revealed a relationship between FSD and depression and/or

Table 2 Mean levels of age, cigarette packet-year, BDI, BAI, FSFI, FSD domains, and hormone levels in patients and controls

Mean	Patients (*N*: 80)	Controls (*N*: 62)	*p* value
Age	33.9 ± 6.7	34.2 ± 7.9	0.807
Cigarette py	1.9 ± 4.0	2.48 ± 5.6	0.508
BDI score	13.7 ± 9.0	13.3 ± 9.8	0.771
BAI score	17.4 ± 12.3	15.4 ± 10.7	0.309
FSFI score	22.9 ± 4.7	27.2 ± 4.7	0. 000
Desire	3.3 ± 0.8	3.7 ± 1.1	0. 004
Arousal	3.4 ± 1.0	4.2 ± 0.9	0.000
Lubrication	4.1 ± 1.0	5.1 ± 0.9	0.000
Orgasm	3.8 ± 1.1	4.5 ± 0.9	0.000
Satisfaction	3.9 ± 1.1	4.8 ± 0.9	0.000
Pain	4.4 ± 1.3	4.8 ± 1.3	0.06
E	118.5 ± 130.4	144.8 ± 142.7	0.256
P	2.6 ± 4.3	5.5 ± 6.4	0.004
FSH	6.6 ± 3.8	5.9 ± 3.9	0.249
LH	9.3 ± 10.8	8.7 ± 7.4	0.693
PRL	13.2 ± 7.3	19.0 ± 19.9	0.016

py packet-year, *BDI* Beck Depression Inventory, *BAI* Beck Anxiety Inventory, *FSFI* Female Sexual Dysfunction Index, *E* estrogen, *P* progesterone, *FSH* follicular stimulating hormone, *LH* luteinizing hormone, *PRL* prolactin, *N* number

Table 3 Correlation analysis among MIDAS, depression, anxiety, FSFI, FSD domains, and hormone levels

		r	*p*
MIDAS grade	Depression	+0.263	0.018
MIDAS grade	Anxiety	+0.259	0.020
MIDAS score	Satisfaction	−0.227	0.043
Depression	Anxiety	+0.528	0.000
Depression	FSFI	−0.280	0.012
Depression	PRL	−0.329	0.003
Depression	Menstrual cycle relationship	−0.225	0.031
Anxiety	PRL	−0.224	0.046
Desire	PRL	+0.255	0.023
Arousal	Depression	−0.274	0.014
Arousal	Anxiety	−0.274	0.014
Lubrication	Depression	−0.419	0.000
Lubrication	Anxiety	−0.238	0.034
Lubrication	PRL	+0.214	0.057
Orgasm	Depression	−0.264	0.018
Orgasm	FSH	+0.251	0.025
Satisfaction	Attack frequency	−0.232	0.038
Pain	LH	−0.247	0.027

MIDAS Migraine Disability Assessment Test, *FSFI* Female Sexual Dysfunction Index, *FSD* female sexual dysfunction, *FSH* follicular stimulating hormone, *LH* luteinizing hormone, *PRL* prolactin

anxiety. In our study, FSD in total was not found as related to neither depression nor anxiety interestingly. But we found that sub-scales of FSD such as arousal and lubrication were affected from both of them and orgasm was affected from depression. Our findings suggested that sexual dysfunction occurring in migraine was not related to disease frequency or severity. Also, relationship with comorbid disorders such as depression and anxiety was related to some sub-scales such as arousal and lubrication; they had limited effect in total FSD. It indicated that not just only natural course of disease itself and comorbidities such as depression and anxiety but also hormonal factors should be important in occurrence of FSD in migraine patients. We found that PRL was positively correlated to desire and lubrication, although it had negative correlation with depression and anxiety; FSH was positively correlated to orgasm and LH was negatively correlated to pain in patient group. Also, FSH-LH combination and PRL levels were found as independent factors which had an effect on FSD in our study. Cut-off values were found as 11.1 mcLU/ml for PRL, 5.6 mLU/ml for LH, and 5.8 mLU/ml for FSH. We thought that number of patients may be a limitation in measuring the cut-off levels of hormones, and it should be studied in larger groups.

These findings suggested that FSH-LH combination and PRL were the hormones which are the contributors in FSD in migraine.

In conclusion, FSD was seen more oftenly in female with migraine as compared with healthy ones. Although there were some relationships reported for FSD sub-scales, FSD in total was not directly related to frequency and severity of migraine and comorbid disorders such as depression and anxiety. We found positive correlations between PRL-desire, PRL-lubrication, and FSH-orgasm. Also, there was a negative correlation between LH-pain. FSH-LH combination and PRL levels were found as independent factors which had an effect on FSD.

Our study is important because it is a precursor study as there is no such a study about the relationship between hormones which are related to sexual function and FSD in migrainous females. We think that the relationship between FSD in migrainous females and related hormones will become clearer with future studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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