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Poor sleep and high anxiety levels in women with functional hypothalamic amenorrhoea: A wake-up call for physicians?

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ABSTRACT

Objective: To assess sleep disorders (SleD) in women with functional hypothalamic amenorrhoea (FHA) and to identify possible associations with known FHA predisposing factors.
Study design: We conducted a prospective case-control study spanning the period January 2016 to April 2018. We recruited forty-one FHA women and 86 healthy controls. We assessed SleD and other FHA predisposing factors via self-reported questionnaires. The Spearman's correlation coefficient (rho) was used to examine possible correlations among the different variables. Multivariate logistic regression analysis was conducted to identify independent factors associated with SleD.
Results: Women with FHA reported having higher SleD ($p = 0.004$), abnormal eating attitudes ($p < 0.0001$), higher anxiety levels (AL) ($p < 0.0001$), overweight preoccupation ($P < 0.0001$) and increased weekly physical activity ($p = 0.004$). There was a significant positive correlation between SleD and AL (rho = 0.88, $p < 0.0001$). Significant correlation was also found between AL and several Athens insomnia scale constituents, including sleep induction (rho = 0.53, $p = 0.0004$), awakenings during the night (rho = 0.6, $p < 0.0001$), final awakening (rho = 0.42, $p = 0.006$), total sleep duration (rho = 0.64, $p < 0.0001$), quality of sleep (rho = 0.63, $p < 0.0001$), well-being during the day (rho = 0.34, $p = 0.03$) and sleepiness during the day (rho = 0.51, $p = 0.007$). High AL were correlated with 2.83-fold increased SleD risk ($p = 0.04$).
Conclusion: FHA women are seemingly more prone to SleD and those with SleD suffer from higher AL. In view of this evidence, the potential rationale of adding psychological and SleD evaluation to their clinical care is highlighted.

Introduction

Functional hypothalamic amenorrhoea (FHA) is characterised by reversible menses cessation in women without any organic disorders, as a result of gonadotropin-releasing hormone (GnRH) pulsatile secretion suppression below a critical range. There is a complex interplay of excessive exercise, energy deficit, abnormal eating attitudes (AEA) in addition to external and intrapersonal psychological stressors on hypothalamic-pituitary-gonadal (HPG) axis desynchronization [1].

There is cumulative evidence suggesting that FHA is attributable to cognitive, behavioural, emotional and psychological stressors triggering a stress-arousal response [2–4]. Previous studies underscored the psychological FHA correlates; notwithstanding, the pivotal role of SleD has not been elucidated thus far. Given that the anxiety levels (AL) and sleep disorders (SleD) are often interrelated, we hypothesised that FHA women suffer from SleD. We aimed to revisit the AL role on FHA pathophysiology and to identify possible associations with other known FHA predisposing factors.

Materials and methods

Study approval

We conducted a prospective case-controlled study at a tertiary referral clinic for gynaecological endocrinology and paediatric and

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adolescent gynaecology, spanning the period January 2016 to April 2018. The study received approval by the Ethics Committee of the University of Athens prior to enrolment (Protocol No 33/131 2016).

Study participants

We recruited a total of 127 women following written informed consent. Anonymity and confidentiality was secured for all data collected.

Patients with FHA

Forty-one women met the diagnostic criteria of FHA: [1] history of secondary amenorrhoea for at least six months; [2] low serum luteinising hormone (<1 IU/Lit); [3] negative progesterone withdrawal test, where norethisterone was administered at a dose of 5 mg twice a day for five days; [4] a normal prolactin levels; [5] at least one of the following predisposing factors: excessive exercise (> 5 h per week) and more than 15% body weight loss. None of these women met the criteria for anorexia nervosa [5]. All women with headache, nausea, or visual disturbances underwent Magnetic Resonance Imaging (MRI) of the pituitary and brain to rule out central nervous system pathology. They were all high school or university students.

Controls

We recruited 86 High School and University students, who had normal menstrual cycles (27–32 days) for the previous year and normal body-mass index (BMI) for their age. We sought to relatively match the two groups concerning the participants' age.

Sleep disorders (SleD)

SleD were assessed via the Athens Insomnia Scale (AIS-8), an eight-item self-report questionnaire. It assesses factors related to both nocturnal sleep and daytime dysfunction, rated on a zero to three scale. A cut-off of six is used to establish the diagnosis of insomnia. AIS-8 was validated in a Greek adult population with satisfactory internal consistency (Cronbach's a consistency 0.89) [6].

Anxiety levels (AL)

Current anxiety symptoms were assessed via the State-Trait Anxiety Inventory (STAI) [7], a 20-item self-report questionnaire. Each item is scored on four levels of anxiety intensity from 'not at all' to 'very much'. The total score ranges from 20 to 80. Higher scores indicate greater AL. The inventory was translated and validated in the Greek population with satisfactory internal consistency (Cronbach's a 0.96) [8].

Abnormal eating attitudes (AEA)

Eating disorders were assessed via the Eating Attitudes Test (EAT-26)- an abbreviated 26-item of the EAT-40- which measures problematic or maladaptive eating attitudes and behaviours [9]. Each item is rated on a six-point scale from 'never' to 'always'. The total score ranges from zero to 78. A higher score indicates AEA; hence a higher AEA likelihood. A cut-off of 20 is used to determine AEA cases. The EAT-26 was translated and validated for a Greek population of adolescents with a satisfactory internal consistency (Cronbach's a 0.78) [10].

Overweight preoccupation (OP)

The body image attitudes were assessed via the Multidimensional Body-Self-Relations Questionnaire (MBSRQ) [11]. The MBSRQ consists of a five-point scale rated from 'definitely disagree' to 'definitely agree'. High scores indicate higher overweight preoccupation (OP) levels. A cut-off of 2.5 is used to determine OP cases. The MBSRQ was translated and validated in Greek population with satisfactory internal consistency(Cronbach's a 0.77) [12].

Physical activity (PA)

The physical activity (PA) levels were measured through the International Physical Activity Questionnaire (IPAQ) [13]. Results are reported as metabolic equivalents (METs) per week. METs represent the amount of expended energy during PA. One MET is the expended energy at rest. According to the IPAQ MET-scoring method, vigorous PA expenditure is multiplied by eight, moderate by four and mild, such as walking by 3.3 METs respectively. The questionnaire was translated and validated in a Greek population with satisfactory internal consistency (Cronbach's a 0.63 - 0.92) [14].

Statistical analysis

The Kolmogorov-Smirnov test was used to determine the normal sample distribution. Student's test for normal distribution or Wilcoxon rank test for skewed distribution was used for continuous variables. The categorical data were analysed via Fisher's or Chi-squared test. The Spearman's correlation coefficient (rho) was used to examine possible correlations among the different variables. Multivariate logistic regression analysis in a stepwise method (p-value for entry 0.05, p-value for removal 0.1) was conducted to identify independent factors associated with SleD. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were computed from the results of the logistic analyses. All reported p-values were two tailed. Statistical significance was set at < 0.05. MedCalc (MedCalc software, Ostend, Belgium) was used for the statistical analyses.

Results

The mean age of women with FHA was 17.8 years, whilst that of the healthy counterparts was 18.32 years ($p = 0.27$). The mean BMI of the FHA and healthy group was 19.78 kg/m^2, and 21.4 kg/m^2 respectively ($p < 0.0001$). The demographic characteristics and the hormonal profile of both groups are shown in Table 1.

According to the AIS-8, 61% (25/41) of women with FHA and 24.4% (21/86) of healthy controls reported having SleD. The mean AIS-8 score in the FHA and control group was 6.48 and 4.88 respectively ($p = 0.004$) (Table 2). Women with FHA were characterised by significantly higher scores at the subscale of awakenings during the night ($p = 0.003$), final awakening ($p < 0.0001$), total sleep duration ($p = 0.0009$), and quality of sleep ($p < 0.0001$) when compared to healthy controls. Eumenorrheic women reported having higher scores at the subscale of sleepiness during the day ($p < 0.0001$) (Table 2). There were significant differences found in all psychosocial parameters and weekly PA. Women with FHA reported having higher EAT-26 ($p < 0.0001$), STAI ($p < 0.0001$), MBSRQ ($P < 0.0001$) and IPAQ ($p = 0.0035$) scores when compared to eumenorrheic controls (Table 2).

Table 1
Demographic characteristics and hormonal profiles.

	FHA	Controls	p-value
Age	17.8 ± 1.79 (15-22)	18.32 ± 2.73 (14-24)	0.27
BMI	19.78 ± 0.62 (18.5-21.1)	21.4 ± 1.89 (18-25)	<0.0001
Height	168 ± 2.79 (163-175)	164.86 ± 5.46 (150-178)	0.0001
Weight	56.39 ± 2.51 (52-62)	58.23 ± 5.87 (47-70)	0.06
Education	11.8 ± 1.79 (9-16)	13.4 ± 2.74 (8-18)	0.0009
LH	0.75 ± 0.32 (0.3-1.5)	N/P	N/P
FSH	0.98 ± 0.36 (0.3-1.8)	N/P	N/P
Prolactin	13.06 ± 3.01 (6.5-19)	N/P	N/P

Data are summarized as mean ± SD (range).
SD: Standard Deviation; BMI: Body Mass Index; LH: Luteinizing Hormone; FSH: Follicle Stimulating Hormone; FHA: Functional Hypothalamic amenorrhea; N/P: Not Performed.

Correlation analysis

We performed a Spearman's rho correlation analysis to examine a possible association between questionnaire measurements of SleD and other psychosocial and PA parameters. We demonstrated a significant positive correlation between SleD and AL according to the questionnaires used (rho = 0.88, $p < 0.0001$). No other statistically significant correlations were found (Table 3). The correlation between AL and AIS-8 subscales showed that AL were inversely correlated with the subscale of sleep induction (rho = 0.53, $p = 0.0004$), awakenings during the night (rho = 0.6, $p < 0.0001$), final awakening (rho = 0.42, $p = 0.006$), total sleep duration (rho = 0.64, $p < 0.0001$), sleep quality (rho = 0.63, $p < 0.0001$), in addition to well-being (rho = 0.34, $p = 0.03$) and sleepiness during the day (rho = 0.51, $p = 0.007$) (Table 4).

Multivariate logistic regression analysis

We sought to identify possible independent factors exerting negative impact on sleep in FHA women via multivariate logistic regression. We demonstrated that high AL were correlated with a 2.83-fold increased risk for SleD ($p = 0.04$) (Table 5).

Discussion

The neuropsychologic correlates of FHA are well-established. Nonetheless, the evidence concerning the SleD in FHA women is lacking. To the best of our knowledge this is the first study assessing SleD in women with FHA. Our findings suggest a

Table 2
Questionnaire scores in FHA and healthy control groups.

	FHA	Controls	p-value
AIS score < 6	16(39%)	67(75.6%)	
AIS score ≥6	25(61%)	21(24.4%)	<**0.0001**
AIS score	6.48 ± 2.79 (2-13)	4.88 ± 2.93 (1-14)	**0.004**
Sleep induction	0.6 ± 0.54 (0-2)	0.67 ± 0.71 (0-3)	0.6
Awakenings during the night	0.97 ± 0.48 (0-2)	0.53 ± 0.68 (0-3)	**0.003**
Final awakening	1.09 ± 0.49 (0-2)	0.45 ± 0.6 (0-3)	<**0.0001**
Total sleep duration	1.31 ± 0.64 (0-3)	0.89 ± 0.65 (0-3)	**0.0009**
Sleep quality	1.31 ± 0.64 (0-3)	0.38 ± 0.55 (0-2)	<**0.0001**
Well-being during the day	0.46 ± 0.5 (0-1)	0.62 ± 0.57 (0-2)	0.12
Functioning capacity during the day	0.36 ± 0.48 (0-1)	0.44 ± 0.52 (0-2)	0.44
Sleepiness during the day	0.36 ± 0.53 (0-2)	0.87 ± 0.5 (0-2)	<**0.0001**
EAT-26 < 20	21(51.2%)	76(88.4%)	
EAT-26 ≥ 20	20(48.8%)	10(11.6%)	<**0.0001**
EAT-26 score	18.75 ± 5.46 (8-26)	10.86 ± 5.95 (3-29)	<**0.0001**
STAI score < 55	15(36.6%)	35(40.7%)	
STAI score ≥ 55	26(63.4%)	51(59.3%)	0.66
STAI score	65.75 ± 6.09 (55-74)	56.34 ± 9.48 (38-75)	<**0.0001**
IPAQ score <1500	7(17.1%)	48(55.8%)	
IPAQ score ≥ 1500	34(82.9%)	38(44.2%)	<**0.0001**
IPAQ score	2632.2 ± 1036.7 (891-4695)	2024.7 ± 1090.75 (377-4998)	**0.0035**
MBSRQ score <2.5	17(41.5%)	76(88.4%)	
MBSRQ score≥2.5	24(58.5%)	10(11.6%)	<**0.0001**
MBSRQ score	2.68 ± 0.97 (1-3.8)	1.79 ± 0.77 (1-4)	<**0.0001**

Data are given as number with proportion for categorical variables and as mean ± SD (range) for continuous variables. Mann-Whitney *U* test was used to compare continuous variables with skewed distribution. Pearson chi-squared test was used in the comparison of dichotomous variables.
SD: Standard Deviation, STAI: State Trait Anxiety Index; EAT-26: Eating Attitudes Test-26; International Physical activity Questionnaire; MBSRQ: Body-Self-Relations Questionnaire.

Table 3
Correlations between AIS-8 score and test variables.

	rho	p-value
STAI score	0.79	<**0.0001**
EAT-26 score	0.2	0.2
MBSRQ score	0.26	0.1
IPAQ score	0.01	0.95

Spearman's non parametric test was performed to consider possible correlations between AIS-8 and the test variables.

Table 4
Correlations between AIS-8 constituents and STAI score.

	Rho	p-value
Sleep induction	0.53	**0.0004**
Awakenings during the night	0.6	<**0.0001**
Final awakening	0.42	**0.006**
Total sleep duration	0.64	<**0.0001**
Quality of sleep	0.63	<**0.0001**
Well-being during the day	0.34	**0.03**
Functioning capacity during the day	0.23	0.14
Sleepiness during the day	0.51	**0.007**

Spearman's non parametric test was performed to consider possible correlations between AIS-8 subscales and anxiety levels.

Table 5
Multivariate logistic regression for sleep disorders in FHA patients.

	OR	95% CI	p-value
STAI score	2.83	1.0-8.0	**0.04**
EAT-26 score	0.81	0.37-1.77	0.6
IPAQ score	1.0	0.99-1.00	0.98
MBSRQ score	1.17	0.01-95.54	0.94

OR: Odds ratio; 95% CI: 95% Confidence Intervals; STAI: State Trait Anxiety Index; EAT-26: Eating Attitudes Test-26; International Physical activity Questionnaire; MBSRQ: Body-Self-Relations Questionnaire.

significant vulnerability of women with FHA to SleD in addition to a robust association between SleD and high AL.

In this cohort, nearly six out of ten women with FHA reported having SleD, while those with high AL had a nearly 3-fold higher risk of developing SleD. Moreover, in the current study, sleep was conceptualised as a multidimensional construct, and anxiety was seemingly characterised by an array of broader impact to sleep patterns. Interestingly, higher STAI scores were significantly correlated with delayed sleep induction, awakenings during the night, earlier final awakening, insufficient total sleep duration, unsatisfactory sleep quality, as well as decreased sense of well-being and sleepiness during the day. Anxiety has been previously linked to SleD [15] and experimentally induced stress has been shown to exert adverse impact on sleep patterns [16]. Of note, according to the diagnostic SleD classification (ICSD-2), stress is considered as the main insomnia factor [17]. This association appears to be complex and bidirectional. High AL seemingly compromise sleep patterns, which in turn, translates into poor cognitive, behavioural and psychomotor performance; hence creating and perpetuating a vicious cycle [8–20].

Sleep disturbances possibly lower the psychological threshold at which a woman experiences an event as stressful. Babson et al, assessed the impact of sleep deprivation on anxiety, general distress and depression on an adult non-clinical sample, underscoring its deleterious effect in eliciting negative emotions [21]. Whether SleD alone, may interfere with the pulsatile secretion of GnRH, thus leading to menstrual aberrations, is not clear. It is possible, however, that it plays a role in the complex neuroendocrine pathways controlling the HPG axis. A negative correlation between nocturnal serum melatonin and LH levels has been previously demonstrated [22]. Women with FHA have been shown to present higher melatonin peak amplitude, in addition to extended secretion towards the morning [23]. Interestingly, melatonin has been shown to directly downregulate GnRH gene expression in a cyclical manner, over a 24 h interval [24].

From a theoretical standpoint, stress could affect sleep through a variety of mechanisms. It has been hypothesised, that one's coping style and emotional regulation ability, may determine the grade of stress and anxiety influence on sleep quality [23]. Women with FHA are often characterised by inadequate coping responses to stress stimuli and dysfunctional behaviours, including perfectionistic performance pressure, unrealistic goals, concerns about other people's opinion, low self-esteem, negative attributions and high AL [1–4]. They are also characterised by excessive concern about body image, dieting and weight gain [1–4]. Our findings clearly indicate higher AL, AEA and OP levels in women with FHA. These stressors apparently trigger emotional and physiological arousal, which negatively affect the sleep patterns. Subsequently, the sleep disturbances further increase stress levels, creating a vicious cycle of deteriorating sleep patterns [25,26]. As expected, we found higher PA in the FHA group. There is a possible ceiling and floor effect of PA on sleep for those who already enjoy good quality sleep, while others with SleD would benefit most by increasing PA [27]. Furthermore, PA appears to ameliorate self-esteem and cognitive functioning, while it decreases AL and depression [28]. However, there was no significant negative correlation between SleD and PA found.

The aforementioned susceptibility to stressors leads to lower hypothalamic-pituitary-adrenal (HPA) axis activation threshold, and subsequently higher corticotropin-releasing-hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol levels owing to stress response. The adverse stress impact on FHA pathophysiology is also well established. Existing evidence highlighted the FHA neuropsychologic correlates in addition to high serum and cerebrospinal cortisol levels in patients with FHA [2–4,29–33]. Moreover, ovarian function recovery is accompanied by a decrease in cortisol levels [33]. The rapid eye movement (REM) sleep is characterised by elevated serum ACTH levels, whilst SleD lead to an impaired fluctuation of cortisol secretion throughout the day [34]. The HPA axis activity is also increased during REM, and significantly decreased during slow-wave sleep [35]. That being so, this interrelation between sleep and HPA axis explains the impact of AL on sleep patterns to an extent and vice versa.

This study, provides meaningful and practical information regarding SleD, AL and other traits in women with FHA, stressing the importance of investigating underlying psychosocial parameters associated with the pathophysiology of FHA. Clinicians, who frequently care for patients with FHA, should carefully consider the role of anxiety, AEA, in addition to potential cognitive behavioural and emotional stressors leading to GnRH aberration. As shown in this cohort, important screening information could be accurately obtained via appropriately selected inventories. Since a high prevalence of psychological and sleep disturbances was demonstrated in this study, we postulate that all women with FHA merit a psychological and SleD evaluation. A positive screen for AEA and/or psychological symptoms, should prompt referral for detailed nutrition and psychological consultations as well as any necessary interventions. For instance, behavioural therapy has been successfully utilised to restore the neuroendocrine profile and ovarian function of women with FHA [4,36].

One of the main strengths of our study, is its prospective design. Parametric data was collected using widely known inventories, validated for the Greek population, ensuring thus high accuracy levels. Another strength is the use of an age-matched control group to compare our findings. Nonetheless, some study limitations should be acknowledged when interpreting our results. Foremost, our findings should be considered preliminary, owing to the relatively small sample size of both groups. An additional limitation is the subjective assessment of SleD and other psychosocial parameters, using self-reported questionnaires rather than polysomnography. Therefore, aspects of sleep patterns might have been under- or over-estimated. However, the scales used have been well correlated with objective measurement in the past. Hormonal profiles were obtained solely for the FHA group, whilst stress hormonal profiles were not performed. Finally, participants did not undergo psychological evaluation.

Conclusion

The present study demonstrated that, a significant proportion of women with FHA suffers from SleD. In addition, SleD were clearly associated with higher AL. Given that interventions to ameliorate sleep patterns and lower AL could help reverse FHA, further studies are warranted to elucidate optimal screening tools and procedures in gynaecological clinical practice and ultimately establish effective interventions for this challenging group of patients.

Disclosure statement

The authors have no conflict of interest to disclose.

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We certify that no party has a direct interest in the results of the research and that no benefit will be conferred to us or any organisation with which we are associated.

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