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Original Article

Dysfunction of anterior pituitary gland in women patients with recent fibromyalgia: A cross-sectional observational study

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ABSTRACT
Objective: To assess the basal levels of circulating anterior pituitary gland hormones in women presented with a recent diagnosis of fibromyalgia (FM).
Methods: This cross-sectional study was included 130 women presented with a clinical signs and symptoms of FM women and 35 age-matched healthy subjects served as controls. The plasma levels of growth hormone (GH) and adrenocorticotrophic hormone (ACTH), and the serum levels of prolactin (PRL) and thyroid stimulating hormone (TSH) were measured. The scores of the Revised Fibromyalgia Impact Questionnaire (FIQR), the number of tender points (TPs), Fatigue Severity Scale (FSS), Insomnia Severity Index (ISI), and the Hamilton's scale for depression (HSD) were measured.
Results: Significantly higher levels of PRL, TSH, and ACTH and lower levels of GH were observed in FM patients. The ACTH level was inversely and significantly correlated with the number of the TPs (r =-0.173, R^2= 0.31, F=4.110, p=0.045). The positive predictive values of GH, THS, PRL and ACTH were 92.3, 63.8, 90.8, and 86.1%, respectively.
Conclusions: Our results indicate that dysfunction of the anterior pituitary gland is a feature of FM.

Keywords: fibromyalgia, hormones, pain, fatigue, depression

INTRODUCTION

Fibromyalgia is a chronic disease of unknown etiology characterized by pain, fatigue, depression and sleep disturbances that linked to several endogenous neurotransmitters and hormones (1-3). Fibromyalgia is a member of centralized pain syndromes by which the pain perception occurred in absence of noxious stimuli (4). Centralized pain disorderar are more common in women (5), and generally associated with fatigue, insomnia, impaired memory, anxiety, and depression (6, 7). Dysregulation of the hypothamic-pituitary adrenal axis is commonly observed in centralized pain disorders (4).

In fibromyalgia, serum levels of adrenocorticotrophic hormone (ACTH) are within normal levels, but any increment in the ACTH levels induced improvement of the clinical symptoms (8). Moreover, when the cortisol production increased, the pain is reduced and the sleep quality is improved (9). Previous studies demonstrated an alteration in the nocturnal ACTH-adrenal signaling and inhibitory feedback mechanism were and linked the changes to the somatic symptoms (9).

Abnormal serum levels of thyroid stimulating hormone (TSH) were observed in FM patients, and a 3.5% had higher TSH levels while 1.4% of patients had a lower serum TSH level (10). However, there is evidence that autoimmune thyroid disease is co-existed with FM as thyroid gland autoimmune antibodies were detected in FM patients (11, 12). There are no cumulative data about the serum levels of prolactin (PRL) and growth hormone (GH) in FM patients. As early as 2001, Gruel et al reported a significant low GH and a significant higher PRL level in a small sample of 20 patients (13). A recent study showed that the serum levels of insulin-like growth factor hormone do not show a significant difference between the women with FM and healthy subjects (14). Moreover, small doses of gamma hydroxybutyrate, a growth hormone enhancing medicine, failed to increase the level of GH and to improve the clinical symptoms (15). Women with FM

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Electronic Journal of General Medicine

showed non-significant changes in the plasma PRL levels when the patients treated with tryptaphan (a precursor of serotonin), while upregulation of the plasma PRL level observed in women with chronic fatigue syndrome (16).

The rationale of this study is the clinical symptoms of fibromyalgia are related to the disturbances of the endocrine system, and to link these disturbances to each clinical feature of FM is a worth trial in understanding the pathogenesis of FM. Literature survey did not disclose any research that measured the anterior pituitary gland hormones at the time of the diagnosis of FM. Therefore, we test the hypothesis that central sensitization of pain pathways is the hallmark of pathogenesis of FM and may cause fatigue, sleep disturbances and mood flactuation leading to the pituitary gland dysfunction. The aim of this study is to assess the basal levels of circulating anterior pituitary hormones in women with a newly diagnosed FM, and to relate these levels to the cardinal features of FM including pain, fatigue, insomnia, and depression.

PATIENTS AND METHODS

This cross-sectional study was conducted in the Department of Pharmacology and Toxicology - Clinical Pharmacy, College of Pharmacy at Hawler Medical University in Erbil- Iraq from Jan 2017 to Dec. 2017. A consent form was obtained from each patient prior to the admission to the study. The study was conducted according to the ethical guidelines constructed by the Institutional Scientific Committee in which the treatment or using device should not be harmful to the patient and the patient is free to decline from the study or to refuse for study admission.

The patients were recruited from the Public Clinics and Private Clinics of Rheumatology in Baghdad-Iraq, and from the Razgary Teaching Hospital in Erbil-Iraq. The eligible patients are women aged less than 60 years old. The criteria for inclusion are new cases of fibromyalgia with signs and symptoms suggestive of fibromyalgia of at least three months of duration. The specialists in the Rheumatology and the researchers examined each patient thoroughly. The diagnosis of fibromyalgia was confirmed by the consultants of Rheumatology using the American College of Rheumatology (ACR) - 10 diagnostic criteria and the Arabic version (17-19) with negative laboratory tests of rheumatic profile including erythrocyte sedimentation rate, C-reactive protein and latex rheumatoid factor. Conditions that influenced the levels of pituitary hormones were excluded. Therefore, patients with a history of hypertension, diabetes mellitus, chronic liver diseases, renal disorders, autoimmune diseases and drug intake e.g. non-steroidal anti-inflammatory drugs were excluded. The sample size of FM patients was calculated by using margin of errors (α = 0.05, β = 0.2), two tails and 95% confidence interval.

The authors examined, interviewed each participant and completed a health questionnaire included Fibromyalgia Impact Questionnaire Revised (FIQR) (20), Insomnia Severity index (ISI) (21, 22), the Hamilton's Depression Rating Scale for depression (HDRS-21) (23) and the Fatigue Severity Scale (FSS) (24). The ISI is a seven-item questionnaire and the items are scored on a five point scale with 0=no problem and 4= severe. Insomnia was defined as a total score of the SIS ≥ 10. The FSS is a nine-item questionnaire and the items are scored on a 7 point scale with 1 = strongly disagree and 7= strongly agree. The mean value of all the scores was determined. The authors assessed the pain that fulfills the following criteria: distributed in all of the body's four quadrants plus axial pain; and at minimum 11 out of 18 predefined tender points that triggered by a pressure of a maximum of 4 kg/cm^2 by using algometry.

Peripheral venous blood samples were drawn immediately into the tubes that containing anticoagulant (EDTA), and the others without anticoagulant. The blood samples were centrifuged at 2500 rpm for 10 min, and the sera and plasma were separated for determination of ACTH, TSH, PRL and GH using the technique of enzyme linked immunosorbent antibody (ELISA) test.

Statistical Analysis

Data are expressed as number, percent; mean ± SD. Independent samples –t- test was used to evaluate differences between the two groups. For all tests, a two-tailed $p \leq 0.05$ was considered statistically significant. The area under the curve of the serum/plasma levels of anterior pituitary hormones of Group II in respect to Group I were estimated using receiving operating characteristics as discriminating factors of FM. Simple (rho) correlation and multi-linear regression tests were used to predict the circulating levels of the hormone in reference to the clinical features and accordingly. The cutoff value, sensitivity, specificity, positive predictive value, and negative predictive value of the serum hormone level as a discriminator of FM were determined. All calculations were made using Excel 2003 and SPSS -20 programs for Windows.

Table 1: *Background data of the participants*

Variables	Group I (n=35)	Group II (n=130)	P
Age (year)	42.7±7.7	41.5±7.6	0.410
Current moking	8 (22.9)	17(13.1)	0.152
Residency			
Rural	8 (22.9)	9 (6.9)	0.006
Urban	27 (77.1)	91(93.1)	0.006
Body mass index (kg/m^2)	25.2±1.2	25.9±2.5	0.111
Total symptoms score of FIQR (0-100)	24.8±3.5	64.2±4.8	< 0.001
Tender points (0-18)	4.9±1.4	14.3±1.7	< 0.001
Mean score of fatigue severity scale (0-90)	2.25±0.21	4.4±0.3	< 0.001
Total Insomnia score	5.6±1.3	19.0±2.0	< 0.001
Total Hamilton Depression score	11.0±2.9	25.9±5.0	< 0.001

The results are expressed as number (percentage), mean ±SD. *P* value is calculated by using unpaired two tailed Student 't' test and the difference between percentage test between Group I (healthy subjects) and Group II (fibromyalgia patients). FIQR: fibromyalgia impact questionnaire revised.

Table 2: *Baseline levels of morning anterior pituitary hormones*

Variables	Group I (n=35)	Group II (n=130)	P
Serum thyroid stimulating hormone (mU/L)	2.84±0.59	3.33±0.42	< 0.001
Serum prolactin (ng/ml)	8.64±2.14	14.11±2.49	< 0.001
Plasma adrenocorticotrophic hormone (pg/ml)	14.3±2.75	16.78±3.21	< 0.001
Plasma growth hormone (pmol/L)	398.6±30.9	309.3±44.5	< 0.001

The results are expressed as mean ±SD. *P* value is calculated by using unpaired two tailed Student 't' test between Group I (healthy subjects) and Group II (fibromyalgia patients).

Table 3: *Correlations between the serum/plasma levels of pituitary hormones with the clinical features of fibromyalgia*
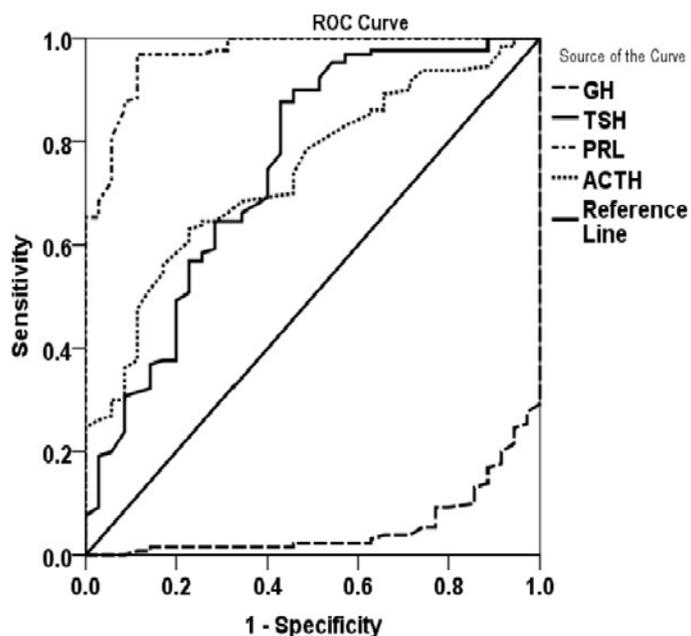
Pituitary hormones	Tender points number		Fatigue severity scale		Insomnia severity index		Hamilton's depression rating scale	
	r	P	r	P	r	P	r	P
Serum thyroid stimulating hormone (mU/L)	-0.153	0.082	-0.063	0.473	0.171	0.052	0.052	0.574
Serum prolactin (ng/ml)	-0.014	0.872	-0.022	0.802	-0.077	0.386	-0.084	0.344
Plasma adrenocorticotrophic hormone (pg/ml)	-0.176	0.045	-0.094	0.287	-0.141	0.109	0.126	0.153
Plasma growth hormone (pmol/L)	0.065	0.461	0.033	0.709	0.111	0.209	0.068	0.444

The results are expressed as correlation factor (r) and probability (*P*) value

RESULTS

A total number of 35 age-matched healthy women served as a control (Group I) and 130 women patients (Group II) diagnosed as recent onset fibromyalgia were included in this study.

Baseline characteristic features of the Group II did not differ significantly from corresponding characteristics of Group I (**Table 1**). The clinical symptoms that associated with fibromyalgia showed significantly higher scores including the total symptoms of FIQR, tender points, fatigue insomnia and depression related symptoms (**Table 1**). Significant higher levels of TSH, PRL, and ACTH hormones were observed in Group II, which reached to 17.3%, 6.3%, and 20% of the Group I levels (**Table 2**). Plasma GH level was decreased significantly to 309.3±44.5 pmol/L compared to 398.6±30.6 pmol/L in the Group I (**Table 2**). Group II patients showed that the area under the curve of the plasma GH was significantly lower than 0.5 whereas the area under the curve of the TSH, PRL, ACTH were significantly higher than 0.5 (**Figure 1**). There were no significant correlations between GH or TSH or PRL with FIQR, TPs, FSS, ISI, HSD, while the ACTH was inversely and significantly correlated with the number of the TPs (**Table 3**). **Figure 2** showed that the significant correlation between tender points number and the plasma ACT level can be predicted in 31% of patients (R^2= 0.31, F=4.110, p=0.045). The cutoff value, sensitivity, specificity, positive predictive value, and negative predictive value of each hormone are presented in **Figure 1**.

Homones	Cutoff value	sensitivity	specificity	PPV	NPV	Area under the curve (95% Confidence interval)	Probability
GH (pmol/L)	380	93.8	73.0	92.3	77.1	0.053 (0.200-0.087)	< 0.001
TSH (mU/L)	3.2	89.3	34.7	63.8	71.4	0.750 (0.650-0.850)	< 0.001
PRL (ng/ml)	11.0	96.7	72.1	90.8	88.6	0.968 (0.939-0.996)	< 0.001
ACTH((pg/ml)	13.5	90.4	56.1	86.1	65.7	0.739 (0.654-0.924)	< 0.001

Figure 1: *Area under the curve of the circulating anterior pituitary hormones in women presented with newly diagnosis of fibromyalgia (Group II). GH: growth hormone, TSH: Thyroid stimulating hormone, PRL: Prolactin hormone, ACTH: Adrenocorticotrophic hormone. PPV: positive predictive value, NPV: Negative predictive value*
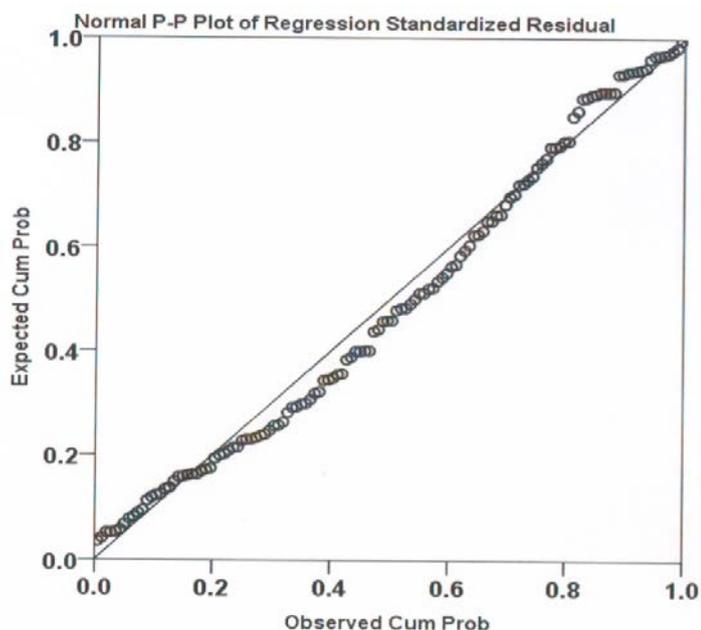

Figure 2: *Regression of the adrenocorticotrophic hormone (as dependent variable) with the tender points number (as independent variable). R=-0.176, R^2=0.031, F=4.11, p=0.045, β-coefficient of ACTH=21.491 and the β-coefficient of the tender points number=0.331*

DISCUSSION

The results of this study show that there are significant changes in the levels of the circulating hormones in patients with fibromyalgia suggestive a dysfunction of an anterior pituitary gland. Although the circulating levels of these hormones are within the normal range, they significantly differ from the corresponding values of healthy subjects (Group I). There is evidence that the pain perception of fibromyalgia is associated with alteration in the circadian rhythm of the GH release and this reflected on its serum level (25). Low levels of GH that observed in this study may be the cause or the outcome of fibromyalgia as there is evidence that using low doses of GH as add-on therapy is effective in reducing the pain (26). Moreover, increasing the serum level of the GH to high normal range could reverse many disorders, including FM (27). Therefore, GH is not a specific factor that linked with fibromyalgia, and this explained the non-significant correlation of the GH levels with clinical features of FM. A significantly higher level of TSH that observed in this study is in agreement with other studies and highlights to measure this hormone as a secondary measure in the diagnosis of FM (10). There is no doubt that stress induced the release of PRL hormone, and this explained the significantly high levels of serum PRL in this study. Prolactin hormone plays a role in the sensitization of the neurons and potentiates the pain response (28). Bote et al. reported that dysregulation or imbalance in the neuroendocrine function is involved in the pathogenesis of FM based on the alterations of the circulating neuroendocrine-stress biomarkers including CRF, ACTH, and insulin growth factor-1 (29). Therefore, a significant high ACTH level that reported in this study is in agreement with other studies. The inverse significant correlation between the number of tender points and the serum ACTH level indicated a physiological body response to pain by increasing the serum cortisol level and thereby a negative feedback mechanism of ACTH secretion. In general, significant high TSH, PRL, and ACTH levels associated with chronic stress which is a manifestation of fibromyalgia (30). The most important finding in this study is the significant inverse correlation between the ACTH hormone level with the number of the tender points, and it can consider as a significant predictor in 31% of FM patients. Previous studies found that there is an association between serum cortisol level and the fatigue symptom as this study confirmed the significant high score of FSS is associated with high ACTH level (31). A low serum cortisol level in FM that reported by other authors and the higher plasma levels of ACTH that found in this study indicates that there is a dysregulation of the hypothalamic pituitary adrenal axis (32). The strength of this study is attributed to the measurements of four hormones simultaneously in women presented with recent onset of fibromyalgia. Fibromyalgia induced changes in the levels of pituitary hormones because our patients did not use any medicine that interferes with the pituitary gland hormones. Therefore, the plasma level of ACTH can serve as a discriminating test of FM (the specificity is 77%), and as a predictor in the assessment of pain in FM. Limitations of the study included that the assessment of diurnal rhythm of the hormones secretion did not carry on as well as the sex hormones levels were not determined.

We conclude that dysfunction of the anterior pituitary gland is a feature of FM and measurement of ACTH is recommended as an aid in the diagnosis of FM and as a predictor of pain severity.

ACKNOWLEDGEMENT

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