Evaluation of Hypothalamic Pituitary-Adrenal Axis and its Diurnal Variation in Chronic Fatigue Syndrome Patients without any Pschiatric Disorders

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Abstract

Chronic Fatigue Syndrome (CFS) is a condition of unknown etiology. It is characterized by persistent or relapsing debilitating fatigue for at least six months in the absence of a medical diagnosis that would explain the clinical presentation. Recently, it has been reported that patients with CFS might have impaired hypothalamic-pituitary-adrenal (HPA) axis function, and it has been suggested that a part of the pathogenesis of the disease might be associated with abnormalities of the endocrine system and that the illness is not simply a manifestation of an underlying psychiatric disorder. To clarify this impairment the present study included 20 patients with CFS, but without concurrent depressive disorder, and 20 normal volunteers matching in weight, age, and sex as control subjects. All subjects were evaluated by semi structured psychiatric interview, guided by ICD-10 symptom checklist for mental disorders by Beck Depressive Inventory scale to exclude patients with any psychiatric disorders, and by Multidimensional Fatigue Inventory scale to evaluate the severity of fatigue in its five subscales. Basal activity of the HPA axis was estimated by measuring baseline morning and evening serum cortisol and adrenocorticotrophic hormone (ACTH) concentrations and the diurnal changes in hormonal levels were assessed. Semi-structural psychiatric interview excluded any psychiatric disorders, while Beck Depressive Inventory scale excluded depression and showed that minor depressive symptoms were significantly increased ($P<0.05$) in CFS patients than in normal controls. Multidimensional Fatigue Inventory scale showed that general fatigue, mental fatigue, physical fatigue, reduced activity, and reduced motivation were all significantly increased ($P<0.05$ for each) in CFS patients compared to normal controls. Meanwhile, total fatigue showed significant increase ($P<0.01$) in CFS patients. Morning cortisol levels were significantly lower ($P<0.01$) in CFS patients while evening levels were significantly higher ($P<0.01$). The diurnal change in cortisol level was significantly impaired in CFS than in controls ($P<0.01$). ACTH concentrations were significantly higher in both morning ($P<0.01$) and evening ($P<0.01$) compared to control subjects. A significant negative correlation between cortisol and ACTH levels was encountered in CFS patients only in the morning, while control subjects showed this significant negative correlation in both morning and evening samples.

A reduced diurnal variation in cortisol level was observed in CFS and this showed negative significance with the five subscales of the Multidimensional Fatigue Inventory ($P<0.01$ in each) suggesting that the diurnal cortisol variation was related to fatigue in its five subscales. Conclusion: The pattern of adrenocortical function in CFS patients is different from that in health suggesting a hormonal basis for this syndrome beside its psychological element.

Introduction

Chronic Fatigue syndrome (CFS) is a controversial condition of uncertain etiology. It has no established cause or proven treatment ***(Straus S.E., 1994)***. It is a symptom complex that has attracted considerable attention in recent years. Several reports suggested that it might be under-diagnosed because of lack of absolute clinical signs and laboratory indicators. In 1988, the Centers for Disease Control and Prevention (CDC) proposed the term chronic fatigue syndrome, and a case definition requiring debilitating fatigue in addition to other signs and symptoms for a period of at least 6 months ***(Holmes et al., 1988)***. This definition was refined and simplified in 1994 by an international group ***(Fukudo et al., 1994)*** that defined the disease as being characterized by debilitating fatigue and associated with myalgia, sleep disturbance, cognitive impairment, anxiety, and low mood ***(Schluederberg et al., 1992)***. Recently, diagnosis of CFS requires severe unexplained fatigue for more than 6 months that is of a new or definite onset, not due to continuing exertion, not resolved by rest, functionally impairing, and accompanied by 4 or more of the following 8 new symptoms

1- Memory or concentration complaint, 2- Sore throat, 3- Tender lymph nodes, 4- Muscle pain, 5- Multijoint pain, 6- A new pattern of headaches, 7- Unrefreshing sleep, 8- Post exertional malaise lasting more than 24 hours ***(Schluederberg et al., 1992)***. Although CFS has been reported in patients as young as 5 years and as old as 65 years, most patients are from 25 to 40 years. Early studies appear to indicate a female predominance ***(Buchwald and Komaroff, 1991)***, but a more recent report indicated that this might not be the case ***(Lloyd et al., 1991)***.

For several years there was a hypothesis, which stated that CFS arised or was maintained by derangement of the HPA axis. This possibility was considered because depression was a prominent feature of the disease and patients with major depression were reported to demonstrate central nervous system-mediated activation of the HPA axis ***(Taerk et al., 1987)***. But it was surprising to find that the symptoms of CFS can also be associated with a primary glucocorticoid deficiency ***(Demitrack et al., 1991)***. The results from both evening and morning samples could reflect a general hypo-cortisolaemia in CFS or an alteration in the diurnal activity of the HPA axis. Clinically, CFS patients reported a general increase in fatigue. This could reflect an alteration in the normal diurnal variation of the HPA axis hormones ***(McCain et al., 1989)***.

Aim of the work:

The aim in our study is to determine the relationship between hormone levels and clinical manifestations, to emphasize the association of the expected derangement of HPA axis in CFS patients without any psychiatric disorders.

Patients and methods:

Patients were selected from the outpatient clinics of Cairo University hospital. Twenty patients meeting the criteria for CFS ***(Schluederberg et al., 1992)*** were recruited. The age at the onset of the disease ranged between 35-43 years, (mean$\pm$SD = 38.2$\pm$10.1), sex (male/female : 8/11), weight ranged between 68-79kg, (mean$\pm$SD = 76.1$\pm$15.3), and the mean duration of the disease was 18 $\pm$4.2 months.

Twenty matched volunteers with age ranged between 32-40 years, (mean±SD = 35.1±9.7), sex (male/female : 11/9), and weight ranged between 66-77kg, (mean±SD = 74.1±14.4) were recruited as a control group (Table 1). The presence of any significant medical or psychiatric conditions was excluded in all subjects by thorough clinical evaluation. This included physical examination and laboratory screening tests as recommended by the International CFS study group***(Holmes et al., 1988)***. All subjects included in the study had no previous psychiatric disorders and were not taking any medications at the time of assessment.

The following scales were used to evaluate all patients

1. Current psychiatric disorders, particularly depression was excluded by performing a semi structured psychiatric interview guided by ICD-10 Symptom Checklist for Mental Disorders ***(Janca et al., 1994)*** and ICD-10 diagnostic criteria for research ***(WHO, 1992)***.
2. Beck Depression Inventory (BDI), which is a self-report scale, used to assess the degree of depression.
3. The Arabic version of Multidimensional Fatigue Inventory ***(Wafaa and Hanna S., 1997)*** was used to assess the degree of total fatigue and its five subscales. High scores indicate a higher degree of fatigue. The Multidimensional Fatigue Inventory (MFI-20) ***(Snets et al., 1995)*** is a multidimensional self-report instrument, which is characterized by being short, doesn't contain any somatic items and designed to provide a complete description of fatigue experience.

Hormonal Assay

Morning blood samples were drawn between 8:30-10:00 h. and other samples were drawn at 20:00 h. of the same day (15 CFS, 16 controls), or at 20:00 h followed by samples drawn at 8:30 h. the next morning (5 CFS, 4 controls). Blood samples were processed, preserved and later on tested according to the methodology of ***Seth and Brown, (1978)*** as described by ***Christie et al., (1986)*** for estimating the cortisol level by radioimmunoassay (RIA) and ***Fink et al., (1988)*** for estimating the ACTH level by double antibody RIA.

Statistical analysis was done using computer package for mean, standard deviation, student t.test, probability for significance, correlation coefficient between variable parameters was estimated, ***(Cohen J., 1988).***

Results:

Assessment of severity of depression of all subjects according to BDI scale ***(Beck et al., 1961)*** showed that CFS patients had a mean ± SE of 10.25± 0.62 while normal controls had a mean ± SE of 6.3 ± 0.49. CFS patients showed significant increase in mild depressive symptoms ($P<0.05$) compared to normal controls (Table 2).

A complete self-description of fatigue in all subjects according to the Arabic version of MFI-20 ***(Wafaa and Hanaa, 1997)*** showed that CFS patients had significantly higher scores ($P<0.05$) than the control group on all subscales of MFI-20, as CFS patients showed means±SE of 15.31± 0.40 in general fatigue, 13.49 ± 0.45 in mental fatigue, 13.98 ± 0.48 in physical fatigue, 16.22 ± 0.30 in reduced activity, 13.52 ± 0.48 in reduced motivation, and 72.53 ±

1.45 in total fatigue, while normal controls showed means±SE of 9.55 ± 0.36 in general fatigue, 9.17 ± 0.32 in mental fatigue, 9.25 ± 0.31 in physical fatigue, 8.80 ± 0.34 in reduced activity, 8.69 ± 0.27 in reduced motivation and 45.31 ± 0.93 in total fatigue. CFS patients showed a highly significant increase (P< 0.01) of total fatigue compared to the normal controls (Table 3, Fig.1).

Patients with CFS had a mean ± SE morning cortisol level of 14.656 ± 0.30 ug/dl and a mean±SE evening level of 7.943± 0.21 ug/dl while normal controls had a mean±SE morning level of 18.473± 0.99 ug/dl and a mean±SE evening level of 6.226± 0.29 ug/dl. CFS patients showed highly significant decrease (P<0.01) in the morning and a highly significant increase (P<0.01) in the evening cortisol levels compared to the normal controls.

Diurnal variation between morning and evening cortisol levels in CFS patients showed a mean±SE of 6.713± 0.20 which indicated a highly significant decrease (P<0.01) than normal controls who showed a mean±SE of 12.246±0.76 (table 4, Fig.3). The diurnal cortisol variation was related to fatigue in its five subscales where it showed high significance (P<0.01) with each of the five fatigue subscales in CFS patients compared to the normal controls who showed no significance (P>0.05) in all fatigue subscales (Table 3, Fig.2).

Patients with CFS had a mean±SE morning ACTH level of 35.343± 1.21 pg/ml and a mean±SE evening level of 20.383± 0.91 pg/ml while normal controls had a mean±SE morning level of 18.453± 1.73 pg/ml and a mean±SE evening level of 12.08± 0.94 pg/ml. CFS patients showed highly significant increase (P<0.01) in both morning and evening ACTH levels compared to the normal controls. Diurnal variation between morning and evening ACTH levels in CFS patients showed a mean±SE of 14.96±0.44 pg/ml which indicated a high significant increase compared to normal controls who showed a mean±SE of 6.373± 0.85 pg/ml (Table5, Fig.4). There was a significant negative correlation between morning ACTH and cortisol levels in CFS patients (-0.381) and a highly significant negative correlation in normal controls (-0.944), while correlation between evening ACTH and cortisol levels was non-significant in CFS patients (-0.118), but was negatively significant in normal controls (-0.630). Correlation between the diurnal variation in both ACTH and cortisol showed high negative significance in both CFS patients (-0.538) as well as in normal controls (-0.941) (Table 5).

Table (1) : Clinical characteristics of CFS patients and control subjects.

		Control	CFS
Sex (male / female)		**11/9**	**8/11**
Age (Years)	**Range**	**32 – 40**	**35 – 43**
	Mean ± SD	**35.1 ± 9.7**	**38.2 ± 10.1**
Weight (kg)	**Range**	**66 – 77**	**68 – 79**
	Mean ± SD	**74.1 ± 14.4**	**76.1 ± 15.3**

Table (2) : Beck Depressive Inventory scale for psychiatric assessment.

		Control	CFS
Beck Depressive Inventory (BDI)	**Range**	**2-10**	**5-16**
	Mean ± SE	**6.3±0.49**	**10.25±0.62**
	$p^{Control}<$		**<0.05**

Table (3) : Multidimentional Fatigue Inventory (MFI-20) Scale.

		General Fatigue	Mental Fatigue	Physical Fatigue	Reduced Activity	Reduced Motivation	Total Fatigue
Control	Range	6.5-12.3	6.4-12.3	6.7-12.1	6.2-12.1	6.4-10.5	38-54.5
	Mean ± SE	9.55±0.36	9.17±0.32	9.25±0.31	8.80±0.34	8.69±0.27	45.31±0.93
	$p^{Cortisol\ diur.\ var.}<$	>0.05	>0.05	>0.05	>0.05	>0.05	
CFS	Range	12.4-18.3	10.1-16.4	10.8-17.5	14.1-18.6	10.4-16.7	63.6-84.7
	Mean ± SE	15.31±0.40	13.49±0.45	13.98±0.48	16.22±0.30	13.52±0.48	72.53±1.45
	$p^{Control}<$	<0.05	<0.05	<0.05	<0.05	<0.05	<0.01
	$p^{Cortisol\ diur.\ var.}<$	<0.01	<0.01	<0.01	<0.01	<0.01	

Table (4): Mean cortisol level (ug/dl), and correlation between morning and evening results in CFS patients and normal controls.

Group		Cortisol		
		Morning	Evening	Diurnal Variation
Control	Range	13.1-25.2	3.7-7.4	9.1-17.9
	Mean±SE	18.473±0.99	6.226±0.29	12.246±0.76
CFS	Range	11.1-17.6	5.1-10.1	4.7-9.1
	Mean±SE	14.656±0.30	7.943±0.21	6.713±0.20
	$p^{Control}<$	<0.01	<0.01	<0.01

Table (5) : Mean ACTH level (pg/ml), correlation between morning and evening results, and correlation to cortisol level in both CFS patients and normal controls.

Group		ACTH		
		Morning	Evening	Diurnal variation
Control	Range	6.8-25.9	5.1-15.4	0.1-10.5
	Mean±SE	18.453±1.73	12.08±0.94	6.373±0.85
	Corr. to Cortisol	-0.944 (<0.01)	-0.630 (<0.05)	-0.941(<0.01)
CFS	Range	17.2-42.7	5.1-24.3	10.5-19.5
	Mean±SE	35.343±1.21	20.383±0.91	14.96±0.44
	$P^{Control}$ <	<0.01	<0.01	<0.01
	Corr. to Cortisol	-0.381 (<0.05)	-0.118 (>0.05)	-0.538 (<0.01)

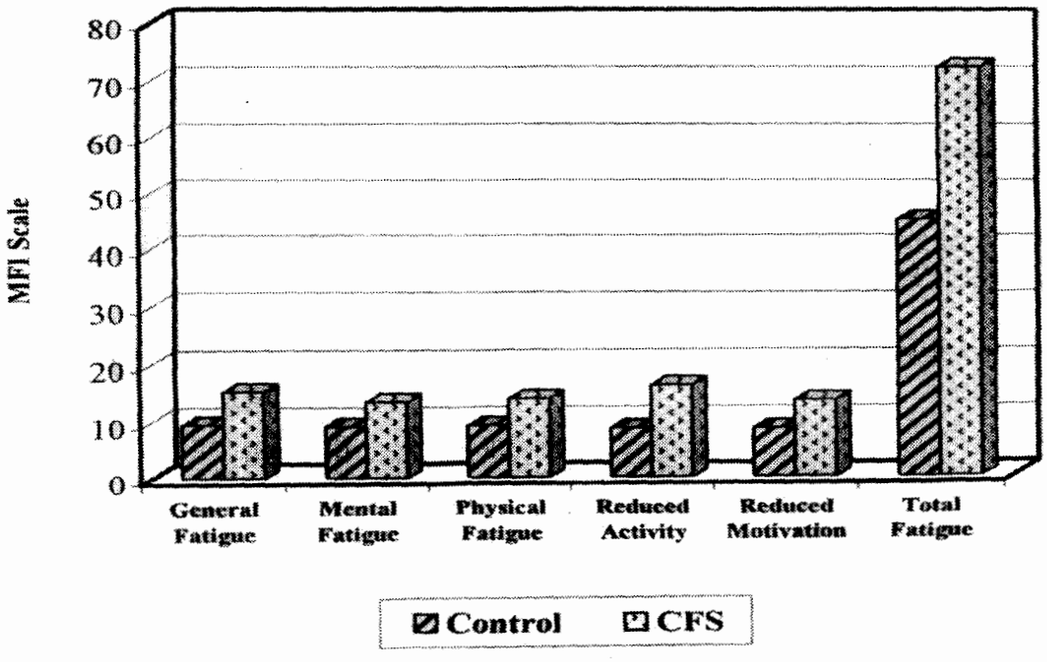

Fig. (1) : MFI-20 Scale in CFS and Controls.

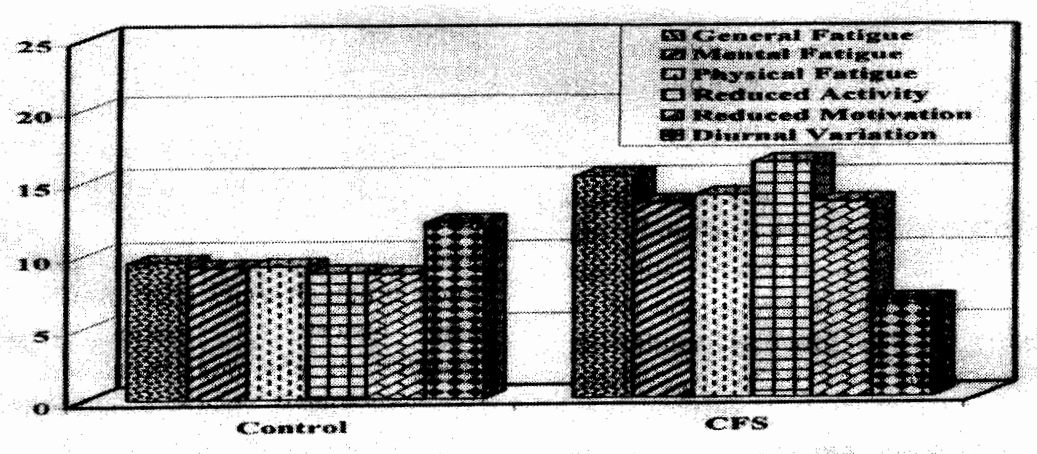

Fig. (2) : MFI-20 Scale Correlation with Cortisol diurnal variation in CFS and Controls.

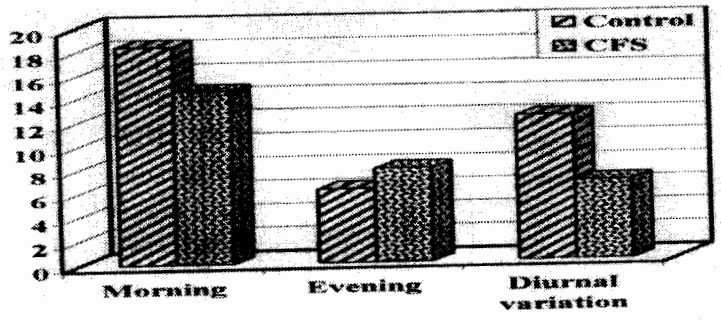

Fig. (3) : Serum Cortisol morning, evening and diurnal variation in CFS and Controls.

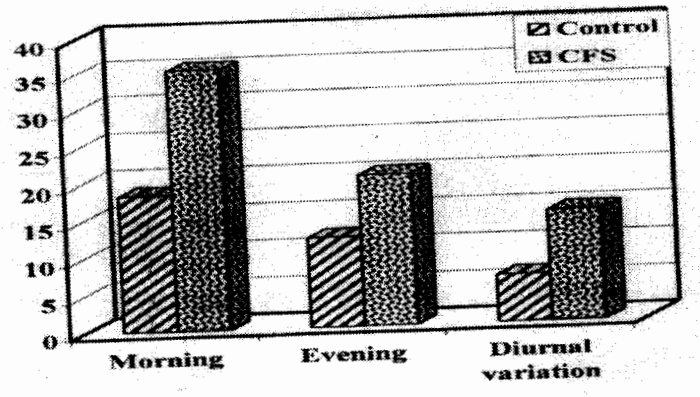

Fig. (4) : Serum ACTH morning, evening and diurnal variation in CFS and Controls.

Discussion :

Altered hypothalamic-pituitary adrenal (HPA) axis is a well-recognized feature of several unrelated, apparently non-endocrine, disorders including ; depression, obesity, and starvation. However, the changes are commonly mild and their basis are uncertain, and they highlight how little is understood of the complexity of the processes controlling cortisol secretion. Nevertheless, evidence is accumulating that HPA function may be altered in some people with CFS. On the other hand, ***McKenzie and colleagues (1998)*** found no correlation between changes in HPA function and illness severity in CFS, and ***Leese and colleagues (1996)*** have suggested that any changes that occur may be attributable to sleep deprivation. The interrelationship between CFS and various psychological disorders, particularly depression was also the subject of much controversy. Some clinicians assumed that CFS patients had a higher prevalence of past depression and/or a family history of affective disorder which might predispose to CFS ***(Manu et al., 1990)***. However, other reports assumed that the incidence of past psychiatric or affective disorders among CFS patients was not greater than the general population ***(Hickie et al., 1990)***.

In the present study we examined the HPA axis function and psychiatric condition of the Egyptian CFS patients. Our study included twenty patients with CFS, but without concurrent depressive disorder, meeting the criteria for CFS ***(Schluederberg et al., 1992)*** who were recruited from Cairo university hospital. The selection of the normal control subjects was based on normal individuals matching the age, sex, and body weight of the patient group to avoid the effect of these three variants on HPA axis ***(Raber J., 1998, Meaney et al., 1993 , Roesnfeld et al., 1992)***. Medical and psychiatric disorders were totally excluded by thorough clinical evaluation and laboratory screening tests as recommended by the International CFS study group ***(Holmes et al., 1988)***. Patients with history of previous psychiatric disorders or any medications at the time of the assessments were excluded to avoid their effect on HPA axis ***(Musselman et al., 1993, Pizza et al., 1996)*** for the same purpose, depression as well as other psychiatric disorders were totally excluded by performing a semi structured psychiatric interview guided by ICD-10 Symptom Check list for mental disorders ***(Janca et al., 1994)*** as well as by Beck Depressive Inventory (BDI) scale ***(Beck et al., 1961)***. According to BDI scale, CFS patients showed significant increase of mild depressive symptoms ($P<0.05$). These symptoms as explained by ***Goldstein (1991)*** may be due to both primary biological CNS factors and secondary psychological reactions. The presence of primary CNS factors is suggested by the presence of concurrent appearance of cognitive and sleep symptoms with the presumed biologically based symptoms of irritability, lability, panic disorders, and dysphoria. Secondary reactions may include exacerbation of a pre-existing affective disorders or maladaptive coping style. In the present study, psychological symptoms of depression can be considered as a psychological reaction which arises as a result of fear and frustration in reaction to a seemingly endless and untreatable multisystem illness, as there was no history of any pre-existing psychiatric disorders. The complete description of fatigue

reported by all subjects according to the Arabic Version of MFI-20 (Table 3) clarified that CFS patients showed significantly higher degrees of the five aspects of fatigue ($P<0.05$ in each) compared to the control group. The profile of fatigue showed that patients gave much concern to their functioning, feeling of exhaustion, cognitive impairment, reduced motivation, and productivity as was previously mentioned by several studies as ***Grafman et al., (1991) and Fukudu et al., (1994)***.

The significant decrease ($P<0.01$) in morning cortisol level, increase ($P<0.01$) in evening cortisol level, and decrease ($P<0.01$) in diurnal variation in cortisol level in our CFS patients are compatible with previous reports of low morning cortisol levels in fatigue ***(Potaliakhoff, 1981)*** and in CFS patients ***(Demitrack et al., 1991)***, but are not compatible with results of ***Yatham et al., (1995)*** who found a non-significant reduction in base line morning cortisol level or with ***Young et al., (1998)*** and ***Wood et al., (1998)*** who recently reported non-significant elevations in morning cortisol level in CFS patients.

Although ***Demitrack et al., (1991)*** reported a similar low morning cortisol levels in CFS patients, they reported significantly lower evening cortisol level. Thus, our study reported a disturbance in the HPA axis in CFS patients in the form of mild hypocortisolaemia which matched with ***Demitrack et al., (1991)*** who reported that pure CFS i.e without psychiatric comorbidity and depression, seemed to be characterized by disturbances in the HPA axis. Also, ***McKenzie and Straus (1995)*** reported that CFS patients had a slight deficiency of the stress hormone cortisol which is opposite to the hypercortisolaemia reported in major affective disorders.

Estimation of ACTH levels clarified that CFS patients showed highly significant increase ($P<0.01$) in both morning and evening levels that is compatible with ***Taerk et al., (1987)*** who reported elevated evening ACTH levels in this category of patients.

The significant increase in the evening cortisol level in our CFS patients may explain the lack of significant correlation between evening cortisol and ACTH levels. This significant increase in the evening cortisol level and its significant decrease in the morning are responsible for the observed significant impairment in diurnal variation of cortisol in our patients. This finding was reported by ***McCain et al., (1989)*** in fibromyalgia, and by ***Lascalles et al., (1974)*** in pain syndrome, and by ***Carroll et al., (1976)*** in depressive illness. However in all these studies, the lack of diurnal cortisol level variation was accompanied by elevated plasma cortisol levels rather than mild hypocortisolaemia which we reported in our study of CFS patients. These similarities and variations may account for the partial overlap in symptoms of CFS and these syndromes. The impaired diurnal variation in cortisol level, as reported in our study showed high significance ($P<0.01$) with the five subscales of the MFI-20 clarifying that fatigue with all its aspects (Table 3) is related to the diurnal cortisol variation. These findings highly suggest the presence of a cause or effect relation to the symptoms reported in CFS patients.

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تقيم محور ما تحت المهاد-الغدة النخامية- الغدة الجار كلوية و تغيره النهارى فى مرضى زملة الإجهاد المزمن الذين لايعانوا من اضطرابات نفسية

إن زملة الإجهاد المزمن هى حالة غير معروفة السبب ، تتميز بحالة متكررة أو مستمرة من الإجهاد و الوهن لمدة لا تقل عن ستة شهور رغم عدم وجود سبب عضوى يفسرها. هناك تقارير حديثة تقول أن هؤلاء المرضى ربما يعانوا من اختلال فى وظيفة محور ما تحت المهاد-الغدة النخامية-الجار كلوية ، و أن جزء من أسباب المرض ترجع إلى اختلال فى وظائف الغدد الصماء ، و أن المرض ليس ببساطة نتيجة اضطراب نفسى . و لتوضيح هذه المقولة ، أجرى البحث على عينة من عشرين مريض يعانوا من زملة الإجهاد المزمن و لا يعانوا من الاكتئاب النفسى .و قورنوا بعينة ضابطة تتكون من عشرين متطوع لا يعانوا من هذا المرض و أصحاء جسمانيا و متماثلين معهم من حيث الوزن و العمر و الجنس . و تم الفحص النفسى لكل العينة باستخدام الفحص النفسى الاكلينيكى المدعم بالمقياس العالمى للصحة النفسية العاشر ، و مقياس بيك للاكتئاب لاستبعاد أى اضطراب نفسى ن و بمقياس الإجهاد متعدد الاتجاهات لتقييم شدة الإجهاد . النشاط الأساسى لمحور ما تحت المهاد-الغدة النخامية-الجاركلوية قد تم فحصه بحساب المستوى القاعدى لكمية هرمون الكورتيزول و ACTH فى الصباح و المساء و تغير كميته النهارى . الفحص النفسى الإكلينيكي أوضح عدم وجود اضطرابات نفسية و مقياس بيك للاكتئاب أوضح عدم وجود اكتئاب نفسى ، بينما دل على وجود أعراض اكتئاب بسيطة بدلالة إحصائية دالة فى مجموعة المرضى مقارنة بالعينة الضابطة . مقياس الإجهاد متعدد الأبعاد أوضح بقيمة إحصائية دالة أن الإجهاد العام و الذهنى و البدنى و انخفاض النشاط و الحافز أكثر فى مجموعة المرضى مقارنة بالمجموعة الضابطة . و فى نفس الوقت القيمة الكلية لمقياس الإجهاد كانت مرتفعة فى عينة المرضى . مستوى هرمون الكورتيزول كان منخفضا فى الصباح مرتفعا فى المساء بقيمة إحصائية دالة فى عينة المرضى ، و أيضا ظهر اضطراب إحصائي دال فى مستوى هرمون الكورتيزول بالنهار فى عينة المرضى مقابلة بالعينة الضابطة . هرمون ACTH كان مرتفعا بدلالة إحصائية فى الصباح و المساء فى عينة المرضى مقابلة بالعينة الضابطة .كان هناك ارتباط إحصائي عكسى دال بين مستوى هرمون الكورتيزول و ACTH فى عينة المرضى فقط فى الصباح ، بينما المجموعة الضابطة ظهر فيها هذا الارتباط العكسى الدال فى الصباح و المساء . إن انخفاض التغير فى مستوى هرمون الكورتيزول فى النهار قد ظهر فى عينة المرضى و قد وضح ذلك بقيمة إحصائية عكسية دالة مع الأبعاد الخمسة لمقياس الإجهاد متعدد الأبعاد ، و يدل ذلك على أن التغير النهارى لمستوى الكورتيزول له علاقة بالأبعاد الخمسة للإجهاد .الخلاصة : إن النموذج الوظيفي للغدة الجار كلوية فى مرضى زملة الإجهاد المزمن يختلف عنه فى الأصحاء مما يوحى بوجود عنصر هرمونى لهذه الزملة بالإضافة إلى عنصر نفسى .