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Assessment of Serum ACTH, Melatonin, and Cortisol Levels in Patients with Hormone Imbalance and Multiple Sclerosis.

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ABSTRACT

Introduction: Multiple sclerosis (MS) is a long-term inflammatory disease that affects the central nervous system due to an abnormal immune response. Hormonal and enzyme changes in these patients can influence the progression and prognosis of the disease. In this research, the levels of cortisol, adrenocorticotropic hormone (ACTH), melatonin, and lactate dehydrogenase (LDH) in the blood of MS patients were studied.

Methods: This study involved 50 MS patients and 50 healthy individuals. The levels of ACTH, melatonin, and cortisol in the blood were measured using specific ELISA kits. The data obtained were then analyzed statistically using SPSS software.

Results: The findings revealed a significant increase in the levels of cortisol and LDH in MS patients ($P<0.05$), while the levels of melatonin and ACTH showed a significant decrease ($P<0.05$). The elevated cortisol levels may be attributed to chronic stress and inflammation associated with MS. An increase in LDH levels can indicate tissue damage caused by myelin destruction. On the other hand, decreased melatonin levels may lead to sleep disturbances and increased stress in these patients, while decreased ACTH levels may be linked to disruptions in the hypothalamic-pituitary-adrenal (HPA) axis.

Conclusion: The hormonal and enzyme changes observed in MS patients illustrate the wide-ranging impact of the disease on various body systems. The increase in cortisol and LDH as well as the decrease in melatonin and ACTH could serve as useful biomarkers for predicting disease progression and managing the condition. These findings align with previous studies and contribute to a deeper understanding of the pathological mechanisms of MS.

KEYWORDS

Multiple sclerosis, cortisol, ACTH, melatonin, inflammation, hypothalamic-pituitary-adrenal axis

INTRODUCTION

Currently, it is generally accepted that autoimmune diseases contain various groups of immune disturbances that cause aberrant B cell and T cell reactivity to normal constituents of the host [1]. Multiple sclerosis (MS) is a chronic, common autoimmune disease that affects young adults. The body's immune system attacks the protective covering of the nerve cells in the brain, optic nerve, and spinal cord, called the myelin sheath [2, 3]. Thus, MS can cause a numerous range of symptoms, such as fatigue, weakness, cognitive impairment, memory loss, and paralysis, depending on the specific area of the body affected and the extent of nerve damage.

MS is a complex inflammatory heterogeneous disease influenced by various gene effects and environmental factors. Factors such as vitamin D or ultraviolet B light (UVB) exposure, Epstein-Barr virus (EBV) infection, stress, obesity, and smoking modestly increase disease susceptibility [4]. This leads to increased activity of T and B lymphocytes and macrophage infiltration, resulting in progressive demyelination, axonal damage with neuronal loss, and gliosis in both the white and grey matter of the central nervous system (CNS) [5, 6]. Molecular research has indicated MS is influenced by a series of biochemical changes in neuronal functions, which are common and significant factors in other neurodegenerative diseases such as Alzheimer's and Parkinson's diseases [7, 8].

Currently, magnetic resonance imaging (MRI) is used for evaluating disease progression, determining prognosis, monitoring disease activity, and responding to treatment; however, this tool is expensive, lacks sensitivity, is time-consuming, and is a semi-quantitative imaging marker [9, 10]. Therefore, a better understanding of biomarkers can be effective in prognosis, definitive diagnosis, and opening up new therapeutic methods for the treatment of MS, but to our best knowledge, there are no effective serum biomarkers for the diagnosis of MS [11].

Various studies have indicated the possible role of the neuroendocrine system in the diagnosis and prognosis of MS. Recent studies have shown interaction and communication between immune system factors and neuroendocrine activity, as well as endocrine disorders related to dysregulation hormone secretion, can contribute to the expansion of diseases and exacerbate their course. Moreover, it has been demonstrated that the neuroendocrine system has immune-modulatory potential, and the advantageous effects of important hormones, including thyroid and sex hormones, are well-defined in MS experimental models [12, 13]. In this respect, the present study was undertaken to assess specific neuroendocrine hormones and peptides, particularly those that play a crucial role in immune system-related diseases. We addressed on examining the circular concentration of the adrenocorticotropic hormone (ACTH), melatonin, and cortisol hormones in MS.

Many retrospective studies found that physical and psychological stress leads to immune dysregulation and altered or amplified cytokine production, resulting in the development of autoimmune diseases or decreased host defence [14, 15]. Increased cytokine levels during inflammation, an innate immune system response, can effect on glucocorticoid receptors and indirectly upregulate the synthesis of corticotrophin-releasing hormone (CRH), ACTH, and cortisol [2, 16]. In response to stress, CRH binds to a surface protein of corticotrophic cells (pituitary cells) and stimulates their release of ACTH [17]. ACTH is derived from pro-opiomelanocortin (POMC), which undergoes processing by the prohormone convertase PC1 in the anterior pituitary [18]. In the intermediate pituitary lobe and hypothalamus, POMC is further processed by PC2 and other enzymes into more active peptides, such as α-melanocyte-stimulating hormone and β-endorphin [19]. ACTH is one of the first neuropeptides shown to act on receptors on leukocytes and inhibit immune responses. However, certain functions, such as stimulators of glucocorticoid synthesis and secretion in adults, can be enhanced. In addition, ACTH plays a important role in the immune system by acting on the adrenal cortex to regulate the production of cortisol [12].

Cortisol, also known as the primary stress neurohormone, is a steroid hormone that is classified within the glucocorticoid class of hormones [20]. It is ordinarily anti-inflammatory, has a critical impact on regulating the immune system, and helps to keep inflammation within the body under control [14, 21]. Different studies have demonstrated that light conditions can influence cortisol levels, with peaks occurring in the morning. Interestingly, cortisol and melatonin show opposite responses to light: while

cortisol levels rise in response to light, melatonin is synthesised strictly during the night [22]. Melatonin, as a neurohormone, also shows a role in regulating sleep-wake cycles, antioxidant properties, and anti-inflammatory effects [23]. Emerging research indicating that melatonin can inhibit pro-inflammatory Th17 cells (immunosuppression) and stimulate inflammation in people with certain autoimmune disorders [24, 25].

On the other hand, measurements of circular concentration Creatine Phosphokinase (CPK) and liver enzymes such as Serum Glutamic Pyruvic Transaminase (SGPT), Serum Glutamic-Oxaloacetic Transaminase (SGOT), Lactate Dehydrogenase (LDH) in serum blood can be indicative of liver diseases and may provide an early signal for being at risk for other chronic diseases. According to the alteration pattern, liver enzymes in various patients indicated increased SGPT and SGOT in dominant liver injury, increased alkaline phosphatase in cholestatic syndromes, and increased CPK in Systemic lupus erythematosus -related myositis [26, 27]. The main objective of the present study was to measure the serum levels of specific neuroendocrine hormones and peptides, particularly ACTH, melatonin, and cortisol, in patients with MS. Additionally, we aim to explore the relevance of CPK and liver enzymes such as SGPT, SGOT, and LDH with MS.

2. MATERIAL AND METHODS

2.1. Collection of samples and participant

This research aimed to evaluate the ACTH, cortisol, and melatonin concentrations in the serum of patients suffering from MS and healthy people who don't have MS as controls that were referred to the Specialised Center of the Genetic Blood Diseases in Thi-Qar city (Iraq) between 16 March to 30 June 2023. For this purpose, 50 patients with MS disease and 50 healthy people were contained in the study. The inclusion criteria for the patient group included a confirmed diagnosis of MS as defined by the McDonald criteria, with the condition having been present for over a year, and participants had to be at least 18 years old. Informed and written consent is collected from all of the participant. MS cases from other diseases were approved by the patient by employing a combination of clinical evaluation, imaging, and molecular testing. Patients with liver deficiency, kidney disorders, thyroid disorders, acute coronary syndromes, Alzheimer's disease, various cancers, and those with a family history of dementia were excluded from the study. A control group comprised healthy individuals, matched by age and sex, who had not been diagnosed with or suffered from heart disease, thyroid disorders, Alzheimer's disease, or other neurological disorders. Relevant sociodemographic, clinical, and laboratory data, such as age, gender, SGPT, SGOT, LDH, CPK, and BMI (body mass index), were obtained from the patients' medical records and recorded on data sheets. Anthropometric measurements, including weight and height, were also taken. Blood samples (5 ml) were collected from peripheral veins into K-EDTA tubes, plain tubes, and Na-citrated tubes. Serum was separated immediately after clotting by centrifugation at 8000 rpm for 10 minutes. Serum samples were stored at -20°C for biochemical analysis, and the levels of ACTH, cortisol, and melatonin were determined by the ELISA kit.

2.2. Neurohormones and neuropeptide measurement by using ELISA kit

Human ACTH (LS-F39298, LSBio), human cortisol ELISA kit (LS-F10024), melatonin Elisa kit (LS-F39279) was used in this research. Also, a centrifuge instrument (KK, China) and an ELISA reader (Biotek 1800, USA) were used to obtain serum samples.

2.3. Statistical analysis

All experiments were independently replicated at least three times, and the results were presented as the mean ± standard deviation (SD) using Graph Pad in Stat version 10.0.2 (Graph Pad Software, San Diego, CA). Statistical significance was determined using the students t-test with a significance threshold of $p < 0.05$.

3. RESULTS

The clinical and demographic characteristics and biochemical parameters of the whole MS group and the control group are summarized in Table 1. The median age of the subjects was 39.83±7.79 years old, ranging from 25 to 55 years. As shown in this table, 22.7% and 77.3% of patients were female and male, respectively. The median BMI of the MS subjects was 26.38±3.53 kg/m^2 (ranging from 16.85-33.95 kg/m^2). Levels of serum CPK (66.28±15.60 U/L vs. 65.98±14.87 U/L), SGOT (26.00±6.26 U/L vs. 23.72±6.56 U/L), and SGPT (27.49±7.14 U/L vs. 27.30±7.03 U/L) were measured in MS patients and control group. and the results showed

no significant differences between two studied groups. Furthermore, the serum levels of LDH (275.11±98.02 U/L vs. 217.74±74.15 U/L; p=0.001) and cortisol (218.52±34.57 ng/mL vs 137.90±43.46 ng/mL; p=0.0001) were significantly higher in MS patients compared to control group. However, the levels of ACTH (41.43±24.23 pg/mL vs 54.26±27.52 pg/mL; p=0.007) and melatonin (23.11±4.83 pg/mL vs 41.65±6.98 pg/mL; p=0.0001) were significantly lower in MS patients.

Table 1. The clinical and demographic characteristics of subjects.

Parameters	Patients Mean±SD (n=50)	Control Mean±SD (n=50)	P value
Age (years)	39.83±7.79	43.02±5.60	0.009**
BMI (kg/m²)	26.38±3.53	26.32±3.78	0.921
CPK (U/L)	66.28±15.60	65.98±14.87	0.910
LDH (U/L)	275.11±98.02	217.74±74.15	0.001**
SGOT (U/L)	26.00±6.26	23.72±6.56	0.043
SGPT (U/L)	27.49±7.14	27.30±7.03	0.872
ACTH (pg/mL)	41.43±24.23	54.26±27.52	0.006**
Melatonin (pg/mL)	23.11±4.83	41.65±6.98	0.0001**
Cortisol (ng/mL)	218.52±34.57	137.90±43.46	0.0001**

Correlations between different clinical factors were evaluated and the findings are showed in Table 2. As depicted in this table, there was a negative and significant association between serum level of CPK and LDH (*p*=0.036). In addition, serum level of LDH showed a negative and significant association with SGOT and ACTH with *p* values of 0.038 and 0.001, respectively. While a positive and significant correlation was observed between LDH and cortisol levels. Furthermore, a positive and significant association with p=0.050 was detected between serum SGPT and SGOT levels. On the other hand, the correlation between melatonin with cortisol and ACTH was negative and positive with p values of 0.0001 and 0.009, respectively.

Table 2. The correlations between different clinical factors.

Characteristics		EDSS	CPK	LDH	SGOT	SGPT	ACTH	Melatonin	Cortisol
EDSS	R	1	0.221	-0.041	0.034	0.200	0.076	0.096	0.132
	P value	-	0.056	0.724	0.772	0.085	0.516	0.412	0.241
CPK	R	0.221	1	-0.188*	-0.075	0.137	0.125	-0.038	0.132
	P value	0.056	-	0.036	0.404	0.129	0.166	0.671	0.142

LDH	R	-0.041	-0.188*	1	0.186*	-0.040	-0.291**	-0.131	0.231**
	P value	0.724	0.036	-	0.038	0.658	0.001	0.145	0.009
SGOT	R	0.034	-0.075	0.186*	1	0.176*	0.094	-0.156	0.109
	P value	0.772	0.404	0.038	-	0.050	0.295	0.082	0.228
SGPT	R	0.200	0.137	-0.040	0.176*	1	0.161	0.046	0.058
	P value	0.085	0.129	0.658	0.050	-	0.072	0.610	0.519
ACTH	R	0.076	0.125	-0.291**	0.094	0.161	1	0.233**	-0.221*
	P value	0.516	0.166	0.001	0.295	0.072	-	0.009	0.013
Melatonin	R	0.096	-0.038	-0.131	-0.156	0.046	0.233**	1	-0.577**
	P value	0.412	0.671	0.145	0.082	0.610	0.009	-	0.0001
Cortisol	R	0.134	0.132	0.231**	0.109	0.058	-0.221*	-0.577**	1
	P value	0.251	0.142	0.009	0.228	0.519	0.013	0.0001	-

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

4. DISCUSSION

MS is a chronic and inflammatory autoimmune disease that affects the CNS and causes destruction of the myelin sheath. This disease leads to various physical and cognitive disabilities in patients and has extensive effects on various biological systems of the body [28, 29]. In this study, the serum levels of cortisol, ACTH, melatonin, and LDH were investigated in patients with MS. Various studies have investigated the changes in serum levels of cortisol, ACTH, melatonin and LDH in patients with MS. Our study shows that the increase of cortisol and LDH and the decrease of melatonin and ACTH in patients with MS (Table 1), which are in accordance with the results of previous studies.

Cortisol, as a steroid hormone secreted by the adrenal glands in response to stress, plays an important role in regulating the immune system and inflammatory responses [30]. Elevated cortisol levels in MS patients may be due to chronic stress and disease-induced inflammation. Studies have shown that cortisol levels in MS patients are usually higher than normal. This increase can be due to the body trying to control the inflammation and stress associated with the disease. For example, a study by *Fassbender* et al. [31] showed that cortisol levels increased in patients with MS, and this increase can be considered as a compensatory mechanism to reduce inflammation and tissue damage. In patients with MS, serum cortisol levels are increased. This increase can be due to the following reasons: Chronic stress: MS can cause chronic stress in patients, which leads to increased secretion of cortisol. Inflammation: Cortisol has an anti-inflammatory role and its increase can be the body's response to inflammation caused by disease.

ACTH is a peptide hormone secreted by the pituitary gland and stimulates the secretion of cortisol from the adrenal glands [32]. A decrease in ACTH levels in patients with MS can indicate a disturbance in the hypothalamic-pituitary-adrenal (HPA) axis. Previous studies have shown that the HPA axis may be disrupted in patients with MS. For example, research by *Wei and Stafford* [33] has shown that the decrease in ACTH levels in patients with MS could be due to an insufficient response of the pituitary gland to chronic stress and inflammation. This reduction may lead to defects in cortisol regulation and further elevation of cortisol levels. A decrease in ACTH level and disruption of the HPA axis have also been reported in previous studies as a sign of hormonal regulation problems in these patients [34]. The HPA axis may be disrupted in patients with MS, which can lead to

decreased ACTH production. The pituitary may not be able to produce enough ACTH in response to chronic stress and inflammation.

Melatonin is a hormone secreted by the pineal gland and shows a critical role in regulating the sleep-wake cycle [35, 36]. Decreased melatonin levels in patients with MS can lead to sleep problems and severe fatigue, which are common symptoms in these patients. Research has shown that melatonin levels are decreased in patients with MS. For example, *Sandyk* and *Awerbuch* [37] has shown in his studies that a decrease in melatonin can lead to an exacerbation of MS symptoms, including fatigue and sleep problems. Also, melatonin has antioxidant properties and its reduction can lead to increased oxidative stress and aggravation of nerve damage in patients with MS [38]. A decrease in melatonin level has also been reported in previous studies as one of the effective factors in aggravating MS symptoms, including fatigue and sleep problems. MS patients often suffer from sleep problems, which can lead to reduced melatonin production. On the other hand, chronic stress and inflammation can affect melatonin production [39].LDH is an enzyme that is involved in the glycolysis process, and an increase in its level usually indicates tissue damage [40]. The increase in LDH level in patients with MS can be caused by the destruction of nerve tissues and inflammation. Previous studies have also shown that LDH levels in patients with MS are usually higher than normal, and this increase can be used as a biomarker for disease severity. For example, research by Philip G., et al. [41] have shown that increased LDH levels can be related to the severity of nerve tissue destruction and disease progression. An increase in LDH level as a biomarker for MS disease severity has also been reported in previous studies. The increased LDH levels in MS patients can be due to the tissue damage. Destruction of nerve tissues and myelin in MS can lead to an increase in LDH levels. In addition, chronic inflammation in MS can increase LDH production.

The HPA axis plays an important role in regulating stress responses. Disturbance in this axis can lead to changes in cortisol and ACTH levels. Increased cortisol may act as a compensatory mechanism to reduce inflammation, while decreased ACTH may result from an inadequate pituitary response to chronic stress. Melatonin and cortisol act as two important hormones in regulating the sleep-wake cycle and stress responses. Decreased melatonin can lead to sleep problems and increased stress, which in turn can lead to increased cortisol levels. An increase in LDH can indicate tissue damage caused by chronic inflammation. Chronic inflammation in MS can increase cortisol production, which acts as an anti-inflammatory mechanism.

5. CONCLUSION

In our study, the serum levels of ACTH, cortisol, melatonin and LDH were evaluated in MS patients. The results of our study show that cortisol and lactate dehydrogenase levels increased, and melatonin and ACTH levels decreased in MS patients. These changes can be due to chronic inflammation, stress and HPA axis disorders in these patients. The obtain results of our research are consistent with the findings of previous researchs and can contribute to a better understanding of the pathophysiological mechanisms of MS and the development of new therapeutic methods.

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