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NEUROENDOCRINE AND IMMUNE INTERACTION IN AUTOIMMUNE THYROIDITIS

Rana Rahimova ✉, ***Gulnara Dashdamirova***, ***Ilaha Shahverdiyeva***, ***Vafa Yagubova,*** ***Narmin Bayramova***

Azerbaijan Medical University, Baku, Azerbaijan

✉ ***r.rahimova10@yahoo.com***

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ABSTRACT

The purpose of the study is to elucidate the interrelationships and notable correlations among the indicators of hormonal regulation, immune status, and markers of neurodegeneration in patients diagnosed with autoimmune thyroiditis. The study enrolled a total of 170 patients with autoimmune thyroiditis (divided subclinical and manifest form). Control group consist of 65 people without thyroid pathologies or other autoimmune diseases. The examination of cytokine profiles in patients with autoimmune thyroiditis revealed a significant increase in cytokine levels in groups of patients with subclinical and manifest forms of the disease compared to the control group. The analysis of antibody levels in patients with different clinical forms of hypothyroidism revealed that the median concentration of Ab-nDNA was significantly higher in patients with a manifest form of the disease compared to those with a subclinical group. According to an assessment of neuron-spesific enolase levels in the blood plasma of patients with autoimmune thyroiditis significantly compared to control group. Furthermore, a study examining the concentration of neuron-spesific enolase in patients with different clinical forms of autoimmune thyroiditis revealed that individuals with a subclinical form of the disease had statistically significant increase (p=0.042) in the value of this parameter. Our study results revealed significant changes in immunological parameters and markers of neurodegeneration in patients with autoimmune thyroiditis alongside hormonal imbalance.

Keywords: autoimmune thyroiditis, neuron-specific enolase, IgA, IgM, IgG, antibodies

INTRODUCTION

Hashimoto's thyroiditis (HT) is a prevalent form of autoimmune thyroiditis (AIT) that is believed to result from a combination of genetic and environmental factors, which lead to immunological changes and subsequent neuroendocrine disorders [7, 9, 12]. Approximately 25–30 % of patients with thyroid disease exhibit indications of thyroid dysfunction, which can vary in severity from subclinical hypothyroidism (defined by elevated TSH levels but with thyroid hormones still within the normal range) to overt clinical hypothyroidism [4].

The symptoms of primary hypothyroidism are varied and nonspecific, owing to the broad spectrum of actions of thyroid hormones on different tissues and organs. These nonspecific symptoms may stem from dysfunction in the cardiovascular, digestive, urinary, reproductive, and nervous systems, as well as skin and its appendages [7, 13]. Recent scientific research has elucidated the close interconnection between the central nervous system (CNS), immune system, and endocrine system, which operate as an integrated triad. [8, 13].

It is widely acknowledged that a person's mental state, endocrine function, and immune status are closely linked, although these relationships are not direct, but are mediated by the hypothalamic-pituitary-adrenal (HPA), sympathetic, and neurovegetative regulation systems [11].

The relationship between the immune and nervous systems has been substantiated through empirical investigation, which has demonstrated the involvement of immune cells in the regulation of homeostasis via specialized mechanisms that express receptors for a diverse array of signaling molecules, thereby eliciting a neuroendocrine response [10, 13].

As key mediators in intercellular signaling, cytokines transmit signals over a considerable spatial range from the site of production, eliciting their effects at a distance. Cytokine receptors on lymphoid cells facilitate communication between the CNS and the immune system. Moreover, cytokines have been shown to penetrate the brain, inducing the secretion of similar substances within the CNS under the influence of various brain structures, such as the hypothalamus, thalamus, hippocampus, pituitary gland, and caudate body. These interactions endow a unified network of neuroimmune-endocrine interactions [11,14].

The aforementioned discourse establishes the requisite foundation for exploring pathogenetically validated methodologies for the diagnosis and management of thyroid pathologies. The exploration of neuroimmune-endocrine mechanisms implicated in the pathogenesis of autoimmune disorders necessitates a critical reassessment of the therapeutic efficacy of various drugs currently employed in clinical practice. Although a comprehensive investigation of the impact of diverse regulatory systems and their role in chronic AIT is still lacking, the urgency and importance of an interdisciplinary approach to studying this condition are apparent. This highlights the significance of probing the association between hormonal and immune status markers and the state of the central nervous system in patients with autoimmune thyroid diseases.

The purpose of the study is to elucidate the interrelationships and notable correlations among the indicators of hormonal regulation, immune status, and markers of neurodegeneration in patients diagnosed with autoimmune thyroiditis.

MATERIAL AND METHODS

The diagnosis of AIT was established based on the medical history, thyroid status, and positive antibodies to the thyroid-stimulating hormone (TSH) receptor in the patients' blood. The study enrolled a total of 170 patients with AIT, 64 men, and 106 women aged between 18 and 64 years. Control group consist of 65 people aged 20 to 65 years, without thyroid pathologies or other autoimmune diseases. The university ethics committee approved the present study (Ref.no: AMU/IEC/No12/07.02.2020).

The patients were classified into two groups: group 1 included 74 patients with a manifest form of the disease, characterized by symptoms such as decreased body temperature, myxedematous edema, difficulty breathing, hair loss, drowsiness, and constipation. The diagnosis of the manifest form of AIT was made based on the clinical presentation of the disease. The laboratory studies revealed elevated levels of thyroid-stimulating hormone (TSH), reduced levels of free triiodothyronine (fT3) and free thyroxine (fT4) hormones, and increased titers of anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) antibodies.

Group 2 included 96 patients with a subclinical form of the disease, characterized by an increase in TSH and normal levels of T3 and T4, with an erased clinical picture. The concentration of thyroid hormones – T3, T4, and TSH – was determined using the immunochemiluminescent method on the IMMULITE 2000 Xpi apparatus (USA). The concentration of cytokines IFN-γ and IL-8 in blood serum was determined using enzyme-linked immunosorbent assay (ELISA), while the levels of immunoglobulins A, M, and G in the blood serum were determined using an automatic analyzer "EL 808 Bio-Tek Instruments, Inc." (USA). The levels of antibodies to native DNA (Ab-nDNA) and denatured DNA (Ab-dDNA) in the blood serum were also determined using ELISA, the concentration of neuron-specific enolase (NSE) in blood plasma using solid-phase ELISA.

The study results were subjected to statistical analysis using the StatSoft software package. To represent quantitative parameters, medians, upper and lower quartiles were calculated. Intergroup comparisons in terms of quantitative indicators were conducted using the Mann-Whitney rank nonparametric test. To investigate potential relationships between the levels of studied biochemical and immunological parameters, a correlation analysis was performed, and the Spearman correlation coefficient was calculated. This analysis was conducted in order to determine whether a significant correlation existed between the levels of these parameters.

RESULTS OF THE STUDY AND THEIR DISCUSSION

Our research results demonstrated that individuals with AIT exhibit altered concentrations of thyroid hormones compared to control group. Specifically, patients with overt hypothyroidism in manifest forms displayed significantly lower levels ($p<0.05$) of fT3 and fT4 in comparison to the corresponding levels in the

control and subclinical group (Table 1). In contrast, the level of thyroid-stimulating hormone (TSH) was markedly elevated ($p<0.05$) in both subclinical and manifest groups relative to the corresponding concentration of this hormone in the control group.

Table 1. Concentrations of thyroid hormones and TSH in patients with autoimmune thyroiditis in a state of hypothyroidism, Me (Q25; Q75)

Indicators	Control group (n=65)	Sublinical form (n=96)	Manifest form (n=74)
Free T3, pg/ml	2.4 (2.1; 2.6)	2.4 (1.9; 2.7)	1.2 *# (1.1; 1.2)
Free T4, pg/dl	1.9 (1.5; 2.3)	1.9 (1.8; 2.1)	0.8 *# (0.7; 0.8)
TSH, mlU/ml	2,1 (1.3; 2.3)	4,2* (3.5; 4.6)	19.0*# (16.1; 24.3)

Note:
** – Statistically significant difference compared to the control group at p<0.05 level;*
 # – Statistically significant difference compared to the subclinical group at p<0.05 level;

According to an assessment of NSE levels in the blood plasma of patients with AIT, the median of this indicator was found to be 16.0 (13.5; 20.0) ng/ml, which is significantly compared to the corresponding level in the control group, which was 5.0 (4.3; 6.0) ng/ml. Furthermore, a study examining the concentration of NSE in patients with different clinical forms of AIT revealed that individuals with a subclinical form of the disease had a NSE level of 10.5 (7.8; 12.5) ng/ml, while those with the manifest form of AIT group showed a statistically significant increase ($p=0.042$) in the value of this parameter, which was 25.0 (23.0; 26.0) ng/ml.

The examination of cytokine profiles in patients with AIT revealed a significant increase in cytokine levels in groups of patients with subclinical and manifest forms of the disease compared to the control group. Among cases of subclinical hypothyroidism, the median concentration of IL-8 was 26.7 (18.6; 34.6) pg/ml, while the median concentration of INF-γ was 2.5 (1.8; 3.7) pg/ml. The concentrations of these markers were significantly higher ($p=0.022$) than those in the control group. In patients with the manifest form of hypothyroidism, the median plasma levels of IFN-γ and IL-8 were 13.2 pg/ml (10.8; 17.5) and 52.4 pg/ml (38.7; 70.2), respectively, which was statistically significantly higher ($p=0.004$) than the similar indicators in the control group. In the control group, the median levels of IFN-γ and IL-8 were 0.34 (0.31; 0.38) and 21.7 (18.5; 24.0), respectively.

In the group of patients with subclinical hypothyroidism, the levels of anti-TG and anti-TPO antibodies were found to be elevated, with a median range of 456 (395; 544) IU/ml and 523 (464; 568) IU/ml, respectively. These levels were significantly higher compared to the control group, which had median values of 16 (13; 30) IU/ml and 20 (13; 25) IU/ml, respectively ($p<0.001$). Furthermore, in patients with manifest form the presence and levels of autoantibodies were also found to be significantly elevated, with median values of 470 (381; 527) IU/ml and 531 (458; 566) IU/ml for anti-TG and anti-TPO, respectively, compared to the control group.

The present study aimed to investigate the levels of antibodies to DNA in patients with different clinical forms of hypothyroidism. The analysis of antibody levels in patients with different clinical forms of hypothyroidism revealed that the median concentration of Ab-nDNA was significantly higher in patients with a manifest form of the disease compared to those with a subclinical course of hypothyroidism (8.6 (5.4; 16.4) U/ml vs. 6.8 (2.1; 13.8) U/ml, respectively; $p<0.05$) and the control group (2.6 (1.45; 3.55) U/ml; $p< 0.001$).

The median concentration of Ab-dDNA was higher in patients with a manifest form of hypothyroidism compared to subclinical form of the disease (4.9 (3.37; 10.1) U/ml vs. 4.0 (1.6; 6.0) U/ml, respectively; $p<0.05$) and the control group (4.6 (1.3; 5.9) U/ml). There were no statistically significant differences in the levels of Ab-dDNA between the indicated groups.

The investigation into the relationship between thyroid hormones and NSE activity levels with humoral immunity characteristics in AIT patients revealed several statistically significant correlations in various directions. As shown in Table 2, moderate positive correlations were found between fT3 and the concentration of immunoglobulin A in AIT patients. However, negative significant associations of moderate strength were observed between this fT3 and the concentrations of IgG, interferon-γ, as well as anti-TG and anti-TPO.

Furthermore, moderate positive correlations were found between the concentration of fT4 and the level of IgA. Conversely, negative statistically significant relationships were established between the value of fT4 and the levels of IgG, IFN-γ, IL-8, and anti-TG, anti-TPO, and Ab-nDNA. Reverse correlations (compared to T3 and T4) were found for TSH levels in patients with AIT.

The level of NSE enzyme activity was also found to be statistically significantly associated with humoral immunity factors in patients with AIT. Negative correlations were observed between NSE enzyme activity and IgA concentrations. However, positive correlations were found between NSE enzyme activity and the levels of IgG, IL-8, and anti-TG, anti-TPO, and Ab-nDNA.

Table 2. Correlation between humoral immunity parameters, concentrations of thyroid hormones (fT3, fT4), thyroid-stimulating hormone (TSH) and neurospecific enolase (NSE) in patients with AIT.
(Spearman correlation coefficients, r)

Indicators	Free T3	Free T4	TSH	NSE
Ig A	0.391 (p=0.031)	0.313 (p=0.008)	-0.425 (p<0.001)	-0.342 (p=0.042)
Ig M	-0.195 (p=0.079)	0.224 (p=0.208)	0.239 (p=0.093)	0.152 (p=0.126)
Ig G	-0.442 (p=0.011)	-0.379 (p=0.014)	0.289 (p=0.115)	0.394 (p=0.040)
INF-γ	-0.403 (p<0.001)	-0.361 (p=0.002)	0.439 (p=0.023)	0.305 (p=0.059)
IL-8	-0.180 (p=0.134)	-0.438 (p<0.001)	0.541 (p=0.006)	0.419 (p<0.001)
Anti-TG	-0.456 (p=0.015)	-0.388 (p=0.004)	0.430 (p=0.009)	0.342 (p=0.034)
Anti-TPO	-0.375 (p=0.045)	-0.605 (p<0.001)	0.429 (p<0.001)	0.328 (p=0.032)
Ab-nDNA	-0.267 (p=0.092)	-0.464 (p<0.001)	0.385 (p=0.019)	0.415 (p=0.003)
Ab-dDNA	0.096 (p=0.103)	-0.233 (p=0.304)	0.195 (p=0.094)	0.283 (p=0.167)

The current data suggests notable advancements in comprehending the fundamental principles of neuroimmunology concerning the emergence of autoimmune disorders. Simultaneously, numerous authors highlight indications of a tight interconnection between the nervous, endocrine, and immune systems as constituents of the overall adaptation system. Incorporating this perspective enables the investigation of the pathogenetic mechanisms of endocrine anomalies in autoimmune processes and the development of a therapeutically justified multifaceted approach that accounts for the identified aberrations [3, 12].

There have been numerous confirmations of the participation of neuroimmunomodulation in various structures of the brain, including the brain stem, cerebral cortex, septum, basal ganglia, and limbic structures. Notably, it has been demonstrated that humoral immunity factors, particularly interleukins IL-1 and tumor necrosis factor, can stimulate the expression and release of corticotropin-releasing factor and arginine-vasopressin in neurons of the paraventricular nucleus of the hypothalamus. This, in turn, leads to the stimulation of adrenocorticotropic hormone secretion, resulting in an increase in the secretion of glucocorticoids [3, 5, 6].

Human body’s defenses strategy is based on the presence of a two-stage protection: non-specific (innate immune system) and specific (adaptive immune system). It is widely recognized that cellular and humoral immunity disorders play a significant role in the development of autoimmune diseases affecting the thyroid gland, including HT. A vast amount of data has been accumulated on the involvement of various biologically active substances in the disease's manifestations. These substances participate in dysregulation and pathogenetic signaling cascades and may act simultaneously as different markers and prognostic factors for

HT [1, 2].

CONCLUSIONS

Our study results revealed significant changes in immunological parameters and markers of neurodegeneration in patients with HT, alongside hormonal imbalance. Notably, we observed significant associations of moderate strength among the studied parameters, indicating the existence of neuroimmunoendocrine interactions that play a critical role in the pathogenesis of thyroid lesions and the development of clinical manifestations of HT.

Despite the considerable advances made in comprehending the mechanisms underlying the development of HT, the links between the pathogenesis that give rise to disruptions of neuroendocrine regulatory influences, culminating in subsequent autoimmune reactions in the gland tissue, continue to elude understanding. Further research must be directed towards exploring the trigger mechanisms responsible for neuroendocrine imbalance that instigate autoimmune reactions and delineating the precise role of individual signaling pathways in the pathogenesis of HT. The outcomes of such investigations would facilitate the identification of molecules and markers that can be targeted for the diagnosis and management of this pervasive ailment.

REFERENCES

1. Chaker L, Cappola AR, Mooijaart SP, Peeters RP. Clinical aspects of thyroid function during ageing. The lancet Diabetes & endocrinology. 2018;6(9):733-742. DOI: 10.1016/S2213-8587(18)30028-7
2. Efendiyev A.M., Azizova G.I., & Dadashova A.R. (2018). Investigation of some endogenous antimicrobial peptides in thalassemia. Thalassemia Reports, 8(2). DOI:10.4081/thal.2018.7744
3. Hamadi GM. Article Review: Immunological Markers Related with Thyroidisum. Int. j. res. appl. sci. biotechnol. [Internet]. 2022;9(2):19-32.
4. Hamous J, Dvořák J, Bušovský I, Šnajdr M. Hashimotos thyroiditis. Rozhl Chir. 2021;100(3):110-112. DOI: 10.33699/PIS.2021.100.3.110-112
5. Kishitani T, Matsunaga A, Ikawa M. Limbic encephalitis associated with anti-NH2-terminal of alpha-enolase antibodies: A clinical subtype of Hashimoto encephalopathy. Medicine (Baltimore). 2017;96(10):e6181. DOI: 10.1097/MD.0000000000006181
6. Lu Y, Qin J, Xiang Y. Experimental evidence for alpha enolase as one potential autoantigen in the pathogenesis of both autoimmune thyroiditis and its related encephalopathy. Int. Immunopharmacol. 2020;85:e106563. DOI: 10.1016/j.intimp.2020.106563
7. Ragusa F, Fallahi P, Elia G. Hashimotos' thyroiditis: Epidemiology, pathogenesis, clinic and therapy. Best Pract. Res. Clin. Endocrinol. Metab. 2019;33(6):e. 101367. https://doi.org/10.1016/j.beem.2019.101367
8. Rahimova R. Determination of neurodegenative markers in the blood serum of patients with autoimmune thyroiditis. Azerbaijan Medical Journal. 2022; 1:75–80. https://doi.org/10.34921/amj.2022.1.012 [in Russian]
9. Rahimova R. Relationship between CTLA4, TNF-α and PTPN22 gene polymorphism and the serum levels of antithyroglobulin and antiperoxidase antibodies in autoimmune thyroiditis. AIMS Medical Science. 2023; 10(1): 14-23. doi: 10.3934/medsci.2023002
10. Ralli M, Angeletti D, Fiore M, D'Aguanno V, Lambiase A, et al. Hashimoto's thyroiditis: An update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation. Autoimmun Rev. 2020 Oct;19(10):102649. DOI: 10.1016/j.autrev.2020.102649
11. Valencia-Sanchez C, Pittock SJ, Mead-Harvey C, Dubey D, Flanagan EP, et al. Brain dysfunction and thyroid antibodies: autoimmune diagnosis and misdiagnosis. Brain Commun. 2021;3(2):fcaa233. DOI: 10.1093/braincomms/fcaa233
12. Weaver LK, Behrens EM. Weathering the storm: Improving therapeutic interventions for cytokine storm syndromes by targeting disease pathogenesis. Curr Treatm Opt Rheumatol. 2017;(1):33-48. DOI: 10.1007/s40674-017-0059-x
13. Yoneda M. Hashimoto's Encephalopathy and Autoantibodies. Brain Nerve. 2018; 70(4):305-314. DOI: 10.11477/mf.1416201004
14. Zdor VV, Geltser BI, Eliseikina MG, Markelova EV, Tikhonov YN, et al. Roles of Thyroid Hormones, Mast Cells, and Inflammatory Mediators in the Initiation and Progression of Autoimmune Thyroid Diseases. Int Arch Allergy Immunol. 2020;181:715-726. DOI: 10.1159/000508937

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