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Study on the role of tissue-specific and non-specific autoantibodies, matrix metalloproteinase-3 and neuron-specific enolase enzymes in the exacerbation of autoimmune thyroiditis

R. R. Rahimova*[A], A. M. Efendiyev[B], I. J. Shahverdiyeva[C], G. S. Dashdamirova[D], S. R. Guliyeva[E], U. H. Azizova[F]

Azerbaijan Medical University, Baku

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***E-mail:** r.rahimova1008@gmail.com

The aim of the study was to examine the involvement of tissue-specific and non-specific autoantibodies, matrix metalloproteinase-3 and neuron-specific enolase (NSE) enzymes in the development and exacerbation of autoimmune thyroiditis.

Materials and methods. The study enrolled 170 patients with autoimmune thyroiditis (64 males and 106 females aged 18 to 64 years) to comprehensively examine their humoral immune response indicators (IgA, M, G), organ-specific (Ab-TG, Ab-TPO) and organ-non-specific antibodies (Ab-DNA), metalloproteinase-3 and NSE activity. The control group consisted of 65 individuals without thyroid pathologies or other autoimmune diseases, aged 20 to 65 years (26 males and 39 females).

Results. The study has demonstrated changes in the levels of organ-specific and organ-nonspecific antibodies and statistically significantly increased metalloproteinase-3 activity in patients with autoimmune thyroiditis. Positive correlations have been found between elevated levels of IgG, Ab-TG, Ab-TPO, Ab-dsDNA and NSE activity. Negative correlations have been observed between NSE activity and IgA concentrations.

Conclusions. Elevated titers of anti-DNA autoantibodies may indicate an aggravation of the autoimmune process due to cellular structure damage, resulting in gland dysfunction. The findings also suggest that metalloproteinase-3, a marker predicting thyroid tissue damage, may negatively impact the immune response induction, ultimately affecting the activity of neuron-specific enolase. The data have shown that studying biochemical indicators such as antinuclear antibodies (ANA), anti-DNA antibodies, metalloproteinase-3 and neurodegenerative indicators could provide informative markers to determine the nature of the disease development and worsening.

Ключові слова: автоімунний тиреоїдит, нейрон-специфічна енолаза, матриксна металопротеїназа 3 типу, аутоантитіла, Ab-dsDNA.

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Дослідження ролі тканин-специфічних і неспецифічних аутоантитіл, ферментів матриксної металопротеїнази 3 типу та нейрон-специфічної енолази у загостренні аутоімунного тиреоїдиту

Р. Р. Рагімова, А. М. Ефендієв, І. Дж. Шахвердієва, Ґ. С. Дашдамірова, С. Р. Гулієва, У. Г. Азізова

Мета роботи – вивчити внесок тканин-специфічних і неспецифічних аутоантитіл, ферментів матриксної металопротеїнази 3 типу та нейрон-специфічної енолази у розвиток і загострення аутоімунного тиреоїдиту.

Матеріали і методи. Дослідження здійснили за участі 170 пацієнтів з аутоімунним тиреоїдитом (64 чоловіки і 106 жінок віком від 18 до 64 років). Для детального вивчення гуморальної імунної відповіді (IgA, M, G), специфічної для органа (AB-TG, AB-TPO), анти-специфічної для органа (анти-ДНК) аутоантитіл, матриксної металопротеїнази 3 типу, а також активності нейрон-специфічної енолази проаналізували їхні показники. У контрольну групу залучили 65 осіб без патологій щитовидної залози або інших аутоімунних захворювань (26 чоловіків і 39 жінок віком від 20 до 65 років).

Результати. Встановили, що у пацієнтів з аутоімунним тиреоїдитом змінюються рівні органоспецифічних і органонеспецифічних антитіл. Виявили також статистично значуще підвищення активності металопротеїнази 3 типу. Визначили позитивні кореляції між підвищеними рівнями IgG, AB-TG, AB-TPO, AB-dsDNA та активністю ферментів нейрон-специфічної енолази. Негативні кореляції встановили між активністю ферменту нейрон-специфічної енолази та концентраціями IgA.

Висновки. Підвищені титри аутоантитіл до ДНК можуть свідчити про загострення аутоімунного процесу через пошкодження клітинної структури, що призводить до дисфункції залози. Результати показали, що матриксна металопротеїназа 3 типу як маркер, котрий прогнозує пошкодження щитовидної тканини, може негативно впливати на індукцію імунної відповіді; зрештою це впливає на активність нейрон-специфічної енолази. Згідно з одержаними даними, вивчення біохімічних показників: антиядерних антитіл (ANA), анти-ДНК-антитіл, матриксної металопротеїнази 3 типу, – а також нейродегенеративних параметрів дасть змогу визначити інформативні маркери для оцінювання природи розвитку захворювання та його погіршення.

Hashimoto's thyroiditis (HT) is a common form of autoimmune thyroiditis (AIT). The etiopathogenesis of the disease is influenced by genetic and environmental factors, which combine to cause immunological changes in the body. These alterations lead to immune-dependent neuroendocrine disorders [1,2,3]. The severity of thyroid dysfunction in HT ranges from subclinical hypothyroidism, which is characterized by elevated thyroid stimulating hormone (TSH) levels with normal concentrations of thyroid hormones, to overt clinically meaningful hypothyroidism [4].

In cases of primary hypothyroidism, the range of non-specific systemic symptoms is highly diverse due to

the broad spectrum of thyroid hormone effects on various tissues and organs. The regulatory effect of thyroid hormones on the genes that control protein synthesis in multiple types of nerve cells and brain regions has now been described and studied well enough [2,5]. Neuroimmune interactions play a crucial role in tissue defense and organ homeostasis [6].

It has been demonstrated that cytokine receptors on lymphoid cells facilitate communication between the central nervous system (CNS) and the immune system, resulting in a chain of neuroimmune-endocrine interactions [7]. Additionally, matrix metalloproteinases (MMPs), a family of proteolytic enzymes, are involved in the formation of a normal immune response. MMPs play several crucial physiological roles, such as extracellular matrix (ECM) remodeling, cytokine cleavage, and defensin activation [8,9]. Furthermore, they regulate various biological and physiological processes that are mediated by hormones, growth factors, and cytokines [10]. It is important to note that much of the current research on MMP-3 is focused on the CNS development, including axonal guidance and remodeling [11,12].

Numerous studies have confirmed the relationship between the immune and nervous systems. It has been demonstrated that immune system cells regulate homeostasis through specific mechanisms that express receptors for various signaling molecules, ensuring a response from the neuroendocrine system. These molecules include neuropeptides, insulin, proopiomelanocortin, growth hormone, and thyroid hormones [13,14].

Thyroid hormones impact tissue respiration intensity and energy production in nervous tissue cells. In a state of hypothyroidism, the activity of aspartate aminotransferase, gamma-aminobutyric acid aminotransferase, and inositol phosphatase decreases, slowing down the incorporation of amino acids into brain proteins. Moreover, the thyroid controls cerebral stem cells and apoptotic-like processes that ensure the formation of neuronal networks and neuronal plasticity [15,16].

In recent years, there has been a considerably increased interest from researchers in determining the activity of neuron-specific enolase (NSE) as a marker of neurodegeneration [17]. NSE is the neuronal form of the glycolytic enzyme enolase and is found almost exclusively in neurons and cells of neuroendocrine origin. Enolase is expressed in astrocytes and oligodendrocytes and exerts autocrine and paracrine effects on glia, neurons, and microglia. High levels of NSE can be harmful and may trigger the production of pro-inflammatory cytokines, leading to neuronal cell apoptosis.

Enolase can be transported to the cell surface upon receiving stimulatory signals, and this can result in various pathologies, such as injury, autoimmunity, infection, inflammation, and cancer. The expression of enolase on the cell surface is frequently observed in activated monocytes / macrophages, microglia, and astrocytes, which promotes the ECM degradation, the production of pro-inflammatory cytokines / chemokines, and the invasion of inflammatory cells into the sites of injury and inflammation [18,19].

The potential pathological role of enolase in neurodegeneration and how enolase inhibition affects neurodegenerative processes are currently being studied [20]. Autoimmune thyroid diseases are also characterized by the presence of organ non-specific autoantibodies, such as anti-DNA antibodies, the clinical significance of which has not been adequately studied [21].

There is a close interdependence between a person's mental state, the endocrine system function, and the state of immunity, governing the body adaptation to environmental changes. It is important to note that there is an insufficient number of comprehensive studies on various regulatory molecules in chronic autoimmune thyroiditis. The whole preceding arguments assume the possibility of an interdisciplinary study on AIT and highlight the importance of studying the correlation between different biochemical parameters that compose immune responses.

Aim

The aim of the study was to examine the involvement of tissue-specific and non-specific autoantibodies, MMP-3 and NSE enzymes in the development and exacerbation of AIT.

Materials and methods

Comprehensive examinations of 170 patients with AIT (64 males and 106 females, aged 18 to 64 years) have been conducted to determine humoral immune response indicators (IgA, IgM, IgG), organ-specific (Ab-TG, Ab-TPO) and organ-non-specific antibodies (Ab-DNA), MMP-3 and NSE activity. The control group consisted of 65 individuals without thyroid pathologies or other autoimmune diseases aged 20 to 65 years (26 males and 39 females). The diagnosis of AIT was made based on laboratory analysis and ultrasonography.

Criteria for inclusion in the study were patients with a primary diagnosis of AIT and the absence of concomitant allergic or other autoimmune severe somatic diseases.

Criteria for exclusion from the study were any concomitant diseases in a medical history of patients, comorbidity associated with AIT due to the autoimmune process exacerbation, substantial abnormalities in blood test results, pregnancy and lactation, acute or chronic inflammatory processes affecting the immunological status.

The patients were assigned to two groups based on clinical and laboratory examinations, including the measurement of TSH, free thyroxine (T4) and free triiodothyronine (T3) levels.

Group 1 consisted of 74 patients with a manifest form of the disease. Group 2 included 96 patients with a subclinical form.

Patients with the manifest form of AIT may experience a range of symptoms including a decrease in body temperature, myxedematous edema (puffy eyes), obesity, voice changes, drowsiness, mental impairment, dyspnea, chest tightness, slowing of cardiac conduction, constipation or diarrhea, limb numbness, hair thinning or loss, and irregular menstrual periods or amenorrhea. In the group of patients enrolled in the study, TSH levels were increased while T3 and T4 hormone levels were decreased. Moreover, increased titers of organ-specific antibodies, in particular Ab-TG and Ab-TPO were observed. The subclinical form of AIT is characterized by increased TSH and normal T3 and T4 levels with a lack of clinical symptoms.

Table 1. Concentrations of thyroid hormones and thyroid stimulating hormone in patients with autoimmune thyroiditis, Me [25 %; 75 %]

Parameter, units of measurement	Control group, n = 65	Subclinical 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, ng/dl	1.9 [1.5; 2.3]	1.9 [1.8; 2.1]	0.8 [0.7; 0.8]*,#
TSH, mIU/ml	2.1 [1.3; 2.3]	4.2 [3.5; 4.6]*	19.0 [16.1; 24.3]*,#

*: statistically significant difference compared to the control group, p level < 0.05; #: statistically significant difference compared to subclinical group, p level < 0.05.

Table 2. Correlations between humoral immunity parameters and neuron-specific enolase (NSE) activity in patients with AIT (Spearman's correlation coefficients, r)

Parameter	Ig A	Ig M	Ig G	Ab-TG	Ab-TPO	Ab-dsDNA	Ab-ssDNA	MMP-3
NSE	-0.342 p = 0.042	0.152 p = 0.126	0.394 p = 0.040	0.342 p = 0.034	0.328 p = 0.032	0.415 p = 0.003	0.283 p = 0.167	0.044 p = 0.565

The levels of thyroid hormones (T3, T4) and TSH were measured by immunochemiluminescent method using an IMMULITE 2000 Xpi apparatus (USA). Serum levels of immunoglobulins A, M, and G were measured using an automatic analyzer (EL 808 Bio-Tek Instruments, Inc., USA). Serum concentrations of anti-native (double-stranded) DNA antibodies (Ab-dsDNA) and anti-denatured (single-stranded) DNA antibodies (Ab-ssDNA) were determined using an enzyme-linked immunosorbent assay (ELISA). Serum concentrations of NSE and MMP-3 activity were detected using a solid-phase ELISA.

The study results were analyzed statistically using a StatSoft software package. Medians, upper and lower quartiles were calculated to represent quantitative parameters. Groups were compared using the Kruskal–Wallis one-way analysis of variance followed by pairwise comparison using the Mann–Whitney test. A correlation analysis was performed to examine potential associations between the levels of studied parameters, and the Spearman correlation coefficient was calculated.

Ethics approval for research: the present study was approved by the Ethics Committee of Azerbaijan Medical University (Ref. no: AMU / IEC / No. 12 / 07.02.2020).

Results

Values of thyroid status indicators allowed randomization of patients into subclinical and manifest groups *(Table 1)*.

The study results showed a significant decrease in IgA levels in both subclinical (1.9 [1.6; 2.7 g/l] and manifest patient groups (1.6 [1.0; 2.3] g/l) compared to the control group (2.6 [2.4; 2.9] g/l). The reverse was true for IgG concentrations, which were increased in both groups, 12.6 [10.4; 15.1] g/l and 16.9 [12.6; 21.8] g/l, respectively, compared to the control group levels (11.4 [9.5; 13.0] g/l), p < 0.05. Herewith, there were no significant differences in IgM levels between patient groups with different types of hypothyroidism.

In assessing plasma NSE levels in patients with subclinical AIT, the median indicator was found to be 10.5 [7.8; 12.5] ng/ml. It was significantly higher than the corresponding level in the control group, which was 5.0 [4.3; 6.0] ng/ml. Besides, the study analyzed NSE concentrations in patients with various clinical forms of AIT. The results showed that individuals with manifest form of AIT had a statistically significant increase (p = 0.042) in the value of this parameter, with a median of 25.0 [23.0; 26.0] ng/ml.

In the group of patients diagnosed with subclinical hypothyroidism, the levels of Ab-TG and Ab-TPO 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 those in the control group, the median values of which were 16 [13; 30] IU/ml and 20 [13; 25] IU/ml, respectively (p < 0.001). In patients with manifest form, Ab-TG and Ab-TPO were found to be significantly elevated with median values of 470 [381; 527] IU/ml and 531 [458; 566] IU/ml, respectively, compared to those in the control group.

The analysis of anti-DNA antibody levels in patients with various clinical conditions of hypothyroidism revealed that the median concentration of Ab-dsDNA was significantly higher in patients with manifest form of the disease compared to those with subclinical course (8.6 [5.4; 16.4] IU/ml vs 6.8 [2.1; 13.8] IU/ml, respectively (p < 0.05), while it was 2.6 [1.45; 3.55] IU/ml in the control group. The median concentration of Ab-ssDNA was higher in patients with manifest hypothyroidism compared to those with subclinical hypothyroidism (4.9 [3.37; 10.10] IU/ml vs 4.0 [1.6; 6.0] IU/ml, respectively (p < 0.05), and the control value was 4.6 [1.3; 5.9] IU/ml. There were no statistically significant differences in the Ab-ssDNA levels between the patient groups.

The study showed a statistically significant increase in MMP-3 activity in each group of patients examined, both in subclinical and manifest forms of the disease, compared to the control individuals (23.0 [16.0; 26.0], p = 0.015). The study compared the MMP-3 levels in patients with different clinical forms of AIT and found that patients with manifest form of AIT had significantly higher MMP-3 levels (59.0 [56.0; 65.0] ng/ml) compared to patients with subclinical form of the disease (52.1 [48.0; 56.5] ng/ml), p = 0.023.

In this paper, a correlation analysis between biochemical parameters and NSE was carried out *(Table 2)*. The NSE enzyme activity level was statistically significantly associated with humoral immunity factors in AIT patients. 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, Ab-TG, Ab-TPO, and Ab-dsDNA. There was no significant correlation between the MMP-3 serum level and NSE enzyme activity.

Discussion

Thyroid hormones affect almost all organs and system in the body, including the heart, CNS, autonomic nervous system, bone, gastrointestinal tract, and metabolism. Changes in

thyroid hormone levels can lead to disturbances of physiological processes in different directions.

It was interesting to study immunoglobulin concentrations. Amid a significant increase in IgG and decrease in IgA compared to the control, the level of IgM was changed insignificantly. There are data in the literature on findings of Marta Ząbczyńska et al. concerning a higher cytotoxic effect of IgG in patients with HT [22]. Our study has shown changes in the levels of organ-specific and organ-non-specific antibodies in patients with AIT. Elevated titers of anti-dsDNA antibodies may indicate an aggravation of the autoimmune process due to cellular structural damage, leading to thyroid dysfunction. Granito A., Muratori L. et al. have also demonstrated the role of anti-dsDNA antibodies as markers of the autoimmune process [23]. Regarding anti-ssDNA antibody levels, we have not found any significant changes between the studied groups that could be interpreted as disease exacerbating factors. The results have shown an increase in the MMP-3 activity in patients of the studied groups, which could be indirectly associated with progressive organ damage, ulceration or excessive collagen accumulation, persistence of inflammation and fibrosis due to their substrate, ECM.

Numerous studies have shown the immunomodulatory role of MMPs. For example, Irena Ivković et al. have demonstrated that the balance in the regulation of MMPs by hormones and cytokines was shifted towards an increased MMP activity in pathological conditions, resulting in tissue degradation [24]. He Luying et al. have reported that MMP enzymes as well as their inhibitors play an active role in thyroid destruction and may negatively affect the immune response induction [25]. Zipfel P., Rochais C. et al. have suggested that ECM overdegradation caused by excessive MMP activation was associated with multiple diseases, including central nervous system disorders [26].

The study on NSE as an indicator of nervous system damage has shown an increased enzyme activity in AIT patients, which could be explained by gradual neuronal death and release of neuron-specific enzymes into the bloodstream. Thyroid hormones are known to affect the intensity of tissue respiration and energy production in nerve tissue cells, and NSE is a glycolytic enzyme found predominantly in neurons and cells of neuroendocrine origin [27].

Conclusions

1. The activity of matrix metalloproteinase-3 has been found to be higher in patients with autoimmune thyroiditis, especially in manifest form with a value of 59.0 [56.0; 65.0] ng/ml.

2. Titers of anti-double-stranded DNA antibodies have been revealed to be increased in the disease exacerbation, reaching 8.6 [5.4; 16.4] IU/ml in manifest form.

3. The determination of neuron-specific enolase activity and its correlation with the level of anti-double-stranded DNA antibodies at Spearman's correlation coefficient of 0.415 ($p = 0.003$) allows an objective assessment of the depth and intensity of nervous system lesion.

4. In summary, the study on the biochemical parameters described and their cause-and-effect relationships can help in assessing the nature of the disease development and exacerbation as well as the probability of comorbid pathology.

Perspectives for further scientific research include a study on the prognostic value of MMP-3, Ab-dsDNA and NSE in AIT.

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Information about the authors:
Rahimova R. R., PhD, Associate Professor of the Department of Biochemistry, Azerbaijan Medical University, Baku.
ORCID ID: 0000-0001-6080-0622
Efendiyev A. M., PhD, DSc, Professor of the Department of Biochemistry, Azerbaijan Medical University, Baku.
ORCID ID: 0009-0006-9246-7987
Shahverdiyeva I. J., MD, PhD, Senior Researcher of the Scientific Research Laboratory, Department of Biochemistry, Azerbaijan Medical University, Baku.
ORCID ID: 0000-0003-3368-1124
Dashdamirova G. S., PhD, Associate Professor of the Department of Biochemistry, Azerbaijan Medical University, Baku.
ORCID ID: 0000-0003-4051-3559
Guliyeva S. R., PhD, Associate Professor of the Department of Biochemistry, Azerbaijan Medical University, Baku.
ORCID ID: 0000-0002-0878-5688
Azizova U. H., PhD, Assistant of the Department of Biochemistry, Azerbaijan Medical University, Baku.
ORCID ID: 0000-0001-5159-5700

Відомості про авторів:
Рагімова Р. Р., канд. біол. наук, доцент каф. біохімії, Азербайджанський медичний університет, м. Баку.
Ефендієв А. М., д-р біол. наук, професор каф. біохімії, Азербайджанський медичний університет, м. Баку.
Шахвердієва І. Д., канд. мед. наук, старший науковий співробітник науково-дослідної лабораторії, каф. біохімії, Азербайджанський медичний університет, м. Баку.
Дашдамірова Ґ. С., канд. біол. наук, доцент каф. біохімії, Азербайджанський медичний університет, м. Баку.
Гулієва С. Р., канд. біол. наук, доцент каф. біохімії, Азербайджанський медичний університет, м. Баку.
Азізова У. Г., канд. біол. наук, асистент каф. біохімії, Азербайджанський медичний університет, м. Баку.

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