STATE OF CYTOKINES IN PATIENTS WITH AUTOIMMUNE THYROIDITIS

Mihai Sheremet – PhD, candidat în ştiinţe,
Universitatea de Stat de Medicină din Bucovina, Ucraina, Cernăuţi,
Nina Tkachuk – PhD, candidat în ştiinţe,
Universitatea de Stat de Medicină din Bucovina, Ucraina, Cernăuţi,
Yana Girla – magistru în medicină,

Universitatea de Stat de Medicină din Bucovina, Ucraina, Cernăuţi,
Andrei Tibirna – PhD, asistent universitar,
USMF „Nicolae Testemiţanu", Chişinău, Republica Moldova
e-mail: Mihayl71@gmail.com, telefon-+380956064607

Summary

The paper presents some data about cytokine content in blood plasma of patients with autoimmune thyroiditis. A significant increase in production of anti-inflammatory cytokines by peripheral blood cells was observed. It was established that the degree of activation of pro-inflammatory cytokines corresponds to the degree of the thyroid gland enlargement.

Key words: thyroid gland; autoimmune thyroiditis; T cells; cytokines

Rezumat. Starea citokinelor la pacienţii cu tiroidită autoimună

Lucrarea prezintă câteva date despre conţinutul de citokine în plasma sanguină a pacienţilor cu tiroidită autoimună. A fost observată o creştere semnificativă a producţiei de citokine anti - inflamatorii de către celulele sanguine periferice. S-a stabilit că gradul de activare a citokinelor pro -inflamatorii corespunde cu gradul de extindere a glandei tiroide.

Cuvinte-cheie: glanda tiroidă; tiroidită autoimună; T-celule; citokine

Резюме. Состояние цитокинов у больных аутоиммунным тиреоидитом

Приведены некоторые данные о содержании цитокинов в плазме крови больных аутоиммунным тиреоидитом. Выявлено значительное увеличение производства противовоспалительных цитокинов клетками периферической крови. Было установлено, что степень активации провоспалительных цитокинов соответствует степени увеличения размеров щитовидной железы.

Ключевые слова: щитовидная железа; аутоиммунный тиреоидит; Т-клетки; цитокины

Introduction. In recent years, experts around the world express a special interest in the problem of chronic iodine deficiency. More than 2 billion. More than 2 billion people in the world are under the risk of insufficient iodine intake which results in the fact that about 700 million of them have an enlarged thyroid gland and 40 million are mentally retarded [1,2].

Subclinical and clinical forms of hypo- and hyperthyroidism in patients with autoimmune thyroiditis (AIT) generally result from this disease [3]. In maintaining immune homeostasis the cytokine system plays a significant role, and its imbalance significantly contributes to the pathogenesis of autoimmune diseases. Such cytokines as tumor necrosis factor alpha (TNF- α) and interleukins (IL), activate the proliferation of B and T lymphocytes, increase the expression of IL-2 receptor by T-cells and that of immunoglobulins by B-cells [4].

The question of the prevalence of cytokines produced by any class of T helpers (Th) in the development of autoimmune diseases of the thyroid gland is not fully understood. The papers present some data, showing a shift towards Th1 and Th 2, and they can not contradict each other, as they were obtained at different stages of the pathological process [5,6].

The aim was to identify the characteristics of cytokine level, depending on the degree of the thyroid gland enlargement in patients with autoimmune thyroiditis [7,8].

Material and methods. The object of the study were 60 women of reproductive age with a diagnosis of AIT, forming the clinical group. As a control (group 1) 20 healthy women of the same age were examined.

The average age of women in the clinical group was 32,8 ± 4,3 years and in the control group- 35,4 ± 3,6 years. According to the degree of the thyroid gland enlargement, the clinical group of women was divided into 3 subgroups: 10 women (16%) with degree I (group 2), 25 women (42%) - the 2nd degree (group 3) and 25 women (42%) - with the 3rd degree (group 4). The diagnosis of Hashimoto's thyroiditis was made by ultrasonography of the thyroid gland, by determining antibodies in blood plasma to thyroglobulin and thyroid peroxidase by means of enzyme immunoassay (ELISA). Determination of TNF-α, IL-1β, IL-4, IL-6 in plasma was performed by ELISA using an analyzer „Multiskan" with sets produced by a company „Vector-Best" (Russia).

A statistical analysis of the material was performed using the variation statistics by means of computer software packages Statlab and Microsoft Excel. The mean value (M) and an error of the average value (m) were calculated. The difference in mean values were evaluated by Student t-test and the probability P that was recognized as statistically significant at $P < 0.05$.

Table 1

Indices of cytokines in blood plasma of patients with autoimmune thyroiditis

Analysed groups	Statistical indices	Analysed indices			
		TNF- α, pg/ml	IL - 1β, pg/ml	IL-4, pg/ml	IL – 6, pg/ml
1. control, n=20	M±m	2,07 0,104	1,96 1,128	1,794 0,169	2,723 0,231
Clinical: 2. With the 1st degree of the TG enlargement n=10	M±m	5,54 0,24	5,88 1,137	1,736 0,121	6,03 0,399
3. with the 2nd degree of the TG enlargement n=25	M±m	8,487 0,333	8,82 0,359	1,61 0,111	6,63 0,518
4. With the 3rd degree of the TG enlargement n=25	M±m	15,11 2,856	17,199 2,866	0,97 0,118	7,038 1,504

Results and discussions

The table 1 shows that AIT causes activation of the cytokine system. For example, rate of blood TNF-α compared to the control value significantly increases as the degree of the TG enlargement increases. While its concentration increases by 2,67 times in the 1st degree of the TG enlargement, it increases by 4,1 times in the 2nd degree and by 7,3 times in the 3rd.

TNF- α values in the 2nd degree of the thyroid gland enlargement significantly exceeds the value in degree I, and, respectively, in the 3rd degree it is by 2.72 times higher than in group 2 and by 1.78 times than in the 3rd group. A similar dynamic is observed as to the concentration of IL-1β. Less pronounced increase is observed in the dynamics of the content of IL-6, but its value is fairly significant compared with the control one. The value of IL-4 does not tend to increase with increasing degree of thyroid gland enlargement.

As follows from the data, patients with autoimmune thyroiditis experience an activation of proinflammatory cytokines and the greater degree of enlargement of the thyroid, the more pronounced this activation. It should be noted that IL-1β is the only cytokine that can induce the expression of apoptosis receptor or Fas-antigene on the cells of the thyroid gland which confirms the role of this cytokine in the development of autoimmune reactions [9]. TNF- α is Fas-ligand, which means that it has some properties of apoptogenic cytokine [10]. Thus, TNF-α and IL-1β modulate the function and proliferation of thyroid

follicular cells. Together with gamma interferon, proinflammatory cytokines are involved in the regulation of production of autoantibodies, they stimulate the proliferation of antigen specific T- and B-lymphocytes which produce clones to different antigenic epitopes and stimulate the synthesis of glycosaminoglycans in retroorbital fibroblasts and modulate the expression of adhesion molecules and histocompatibility antigens (HCA) of the 2nd class on the surface of the follicular cells, which can lead to a disorder in antigen recognition and to a start of the thyroid autoimmune processes.

Thus, the study of some indices of the cytokine system in AIT onset shows that in addition to dysregulation of proliferative processes and differentiation of immune cells, an activation of thyroid tissue inflammation occurs. Imbalance between pro-inflammatory (TNF-α, IL-1β, IL-6) and anti-inflammatory cytokines (IL-4) leads to an increase of triggers and the development of hypertrophic processes in the thyroid gland. One of the mechanisms of its development is a discrepancy between the inflammation and the ability of the phagocytic system as well as endotoxin tolerance of monocytes [11].

Together with hormones and neurotransmitters, cytokines are the basis of chemical signaling by which, in multicellular organisms, morphogenesis and tissue regeneration are regulated [12]. Significant activation of proinflammatory cytokines in AIT leads to activation of phagocytes, their migration to the thyroid gland to a release of inflammatory mediators - derivatives of lipids, of prostoglandin E2, thromboxanes and platelet activity factor and to the synthesis of glycoproteins adhesion as well as to the activation of T- and B-lymphocytes [13].

Some reduction of IL-4 in the blood of patients with autoimmune thyroiditis shows the tensity in compensatory mechanisms caused by the immune system. Since IL-4 enhances eosinophilia, accumulation of mast cells, secretion of immunoglobulin G, starts the synthesis of immunoglobulin E by activated B-lymphocytes, stimulates the population of cytotoxic T lymphocytes. The activation of IL-4 inhibits the release of inflammatory cytokines and prostaglandins from activated monocytes and interferon-gamma production [12,13].

However, we must take into account that the development of autoimmune processes in the thyroid gland is not only possible as a result of increased cell proliferation, but also due to a disorder in the mechanisms of its programmed death - apoptosis, in which cytokines play an important role. It is quite possible that inhibition of apoptosis occurs as early as at the time of the beginning of the production of antibodies to thyroid tissue and still more in precancerous and cancerous conditions. Derangement of the ratio of proliferation and apoptosis regulating normal cellular homeostasis can lead to uncontrolled cell proliferation in the thyroid gland.

Conclusions

1. In autoimmune thyroid diseases a significantly increased production of proinflammatory cytokines in peripheral blood cells can be observed.

2. The degree of activation of proinflammatory cytokines corresponds to the degree of the thyroid gland enlargement.

References

1. Serum negative autoimmune thyroiditis displays a milder clinical picture compared with classic Hashimoto's thyroiditis / M. Rotondi, L. Martinis, F. Coperchini [et al.] // Eur. Journal of Endocrinology. – 2014. № 17. – P. 135-141.

2. González C. Morbidity following thyroid surgery: does surgeon volume matter? / C. González, G. Franch-Arcas, A. Gómez-Alonso // Langenbeck's Archives of Surgery. – 2013. – Vol. 398, № 3. – P. 419-422.

3. Evidence of a Combined Cytotoxic Thyroglobulin and Thyroperoxidase Epitope-Specific Cellular Immunity in Hashimoto's Thyroiditis / M. Ehlers, A. Thiel, C. Bernecker [et al.] // The Journal of Clinical Endocrinology & Metabolism. – 2012. – Vol. 97, № 4. – P. 1347-1354.

4. Possible Evolution of Autoimmune Thyroiditis in Hypothyroidism: Role of Obesity. Obes Control Ther / G. De Pergola, A. Ciampolillo, L. Tarantino [et al.] // Symbiosis. – 2014. – Vol. 1, № 1. – P. 450-455.

5. Flechas J. Autoimmune Thyroiditis and Iodine Therapy / J. Flechas // Journal of Restorative Medicine. – 2013. – Vol. 2, № 1. – P. 54-59.

6. Nodules in Autoimmune Thyroiditis Are Associated With Increased Risk of Thyroid Cancer in Surgical Series But Not in Cytological Series: Evidence for Selection Bias / M. G. Castagna, V. Belardini, S. Memmo [et al.] // The Journal of Clinical Endocrinology & Metabolism. – 2014. – Vol. 99, № 9. – P. 1304-1310.

7. Increased Dietary Iodine Causes Thyroid Autoimmunity by Exposing a Cryptic Thyroglobulin Epitope / B. Rapoport, S. M. McLachlan, Latrofa F. [et al.] // Clinical Thyroidology. – 2014. – Vol. 26, № 3. – P. 60-64.

8. Plasmacytoid dendritic cells in patients with autoimmune thyroid disease / M.Marazuela, S. Leskela, A. Rodríguez-Muñoz // Journal of Clinical Endocrinology and Metabolism. – 2013. – Vol. 98, № 7. – P. 2822-2833.

9. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules / H. Gharib, E.Papini, R. Paschke [et al.] (AACE/AME/ETA Task Force on Thyroid Nodules) // Endocr. Pract. – 2010. – Vol. 16 (1). – P. 1–43.

10. Ali S.Z. The Bethesda System for Reporting Thyroid Cytopathology: Definitions, Criteria and Explana-

tory Notes / S.Z. Ali, E.S.Cibas. – New York: Springer, 2010. – 174 p.

11. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management / E. Horvath, S. Malilis, R. Rossi [et al.] // J Clin Endocrinol Metab. – 2014. – Vol. 116. – P. 1748-1751.

12. Cost-Effectiveness of a Novel Molecular Test for Cytologically Indeterminate Thyroid Nodules / H. Li, K.A. Robinson, B. Anton [et al.] // J Clin Endocrinol Metab. – 2011. – Vol. 96. – P. 1719–1726.

13. Cytopathologic Diagnosis of Thyroid Nodules Varies Considerably / E.S.Cibas, Z.W. Baloch, G. Fellegara [et al.] // Clinical Thyroidology. – 2013. – Vol. 25. – P. 261-263.