Медицинская иммунология
2023, Т. 25, № 5,
стр. 1247-1252

Краткие сообщения
Short communications

Medical Immunology (Russia)/
Meditsinskaya Immunologiya
2023, Vol. 25, №5, pp. 1247-1252

РОЛЬ ПРОВОСПАЛИТЕЛЬНЫХ ЦИТОКИНОВ ПРИ ТИРЕОИДИТЕ ХАШИМОТО, АССОЦИИРОВАННОМ С ПСИХИЧЕСКИМИ РАССТРОЙСТВАМИ

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Резюме. Психические нарушения часто сопровождают аутоиммунные заболевания, например, с 1949 года известно о «микседематозном безумии» – это психоз, причиной которого является гипотиреоз. Самая частая причина гипотиреоза – аутоиммунный тиреоидит Хашимото. Известно также и о другом психоневрологическом расстройстве, ассоциированном с аутоиммунным тиреоидитом – это энцефалопатия Хашимото. Энцефалопатия Хашимото – это тяжелое нарушение функций центральной нервной системы, патогенез которого не связан с гормональными нарушениями. Известно, что цитокины являются регуляторами и участниками воспаления, в том числе и аутоиммунного. Разумеется, когда речь идет о высоких концентрациях провоспалительных цитокинов, мы можем говорить о системном воспалении. Однако минимальные или незначительные колебания цитокинов в пределах диапазонов, характерных для здоровых или для нормергического острофазового ответа при болезни, не могут быть интерпретированы с точки зрения бинарной эндокринологической логики. Известно, что в центральной нервной системе цитокины способны влиять на нейроэндокринный контроль системно регулируемых функций. Нельзя забывать и о том, что глиальные клетки (астроглия, микроглия) способны к продукции ряда цитокинов и могут оказывать таким путем влияние на нейроны и развитие поведенческих изменений. Кроме того, доказана способность ряда цитокинов вне самой ЦНС действовать на вагальные афференты и через них доносить информацию в ЦНС, влияя на ее состояние и функции. Разумно предположить, что минимальные колебания уровней провоспалительных цитокинов могут оказывать влияние на состояние и функции ЦНС. Целью исследования было изучить уровни провоспалительных цитокинов у пациентов с аутоиммунным тиреоидитом; у пациентов с аутоиммунным тиреоидитом, ассоциированным с психическими нарушениями; у группы здоровых лиц; и оценить влияние уровней цитокинов на клинические проявления. В группе пациентов с тиреоидитом и психическими расстройствами уровни CCL20/MIP3α, IL-13, IL-2, IL-27, IL-5 были

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П.А. Соболевская, А.Н. Гвоздецкий, И.В. Кудрявцев, В.А. Черешнев, Л.П. Чурилов «Роль провоспалительных цитокинов при тиреоидите Хашимото, ассоциированном с психическими расстройствами» // Медицинская иммунология, 2023. Т. 25, № 5. С. 1247-1252.
doi: 10.15789/1563-0625-ROP-2812

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For citation:

P.A. Sobolevskaya, A.N. Gvozdetskiy, I.V. Kudryavtsev, V.A. Chereshnev, L.P. Churilov "Role of proinflammatory cytokines in Hashimoto's thyroiditis associated with psychiatric disorders", Medical Immunology (Russia)/Meditsinskaya Immunologiya, 2023, Vol. 25, no. 5, pp. 1247-1252.
doi: 10.15789/1563-0625-ROP-2812

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DOI: 10.15789/1563-0625-ROP-2812

достоверно выше, чем в других группах. При этом между клиническими проявлениями психических расстройств и уровнями цитокинов положительной корреляции установлено не было. Но была выявлена положительная корреляция между уровнями некоторых цитокинов и свободным трийодтиронином, а также уровнем антитиреоидных антител. Психические расстройств, ассоциированные с аутоиммунным тиреоидитом могут быть связаны с изменениями в цитокиновом профиле и являться результатом нейровоспаления.

Ключевые слова: цитокины, тиреоидит, нейровоспаление, психические расстройства, энцефалопатия Хашимото, шизофрения

ROLE OF PROINFLAMMATORY CYTOKINES IN HASHIMOTO'S THYROIDITIS ASSOCIATED WITH PSYCHIATRIC DISORDERS

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Abstract. Mental disorders often accompany autoimmune diseases, for example, since 1949 it has been known about "myxedematous madness", a psychosis caused by hypothyroidism. The most common cause of hypothyroidism is Hashimoto's autoimmune thyroiditis. It is also known about another neuropsychiatric disorder associated with autoimmune thyroiditis, Hashimoto's encephalopathy. It is a severe dysfunction of the central nervous system, the pathogenesis of which is not associated with hormonal disorders. Cytokines are regulators and participants of inflammation, including autoimmune. Certainly, when we are talking about high concentrations cytokines, we mean systemic inflammation. The minimal or mediocre fluctuations in cytokines within the ranges that are characteristic of healthy status or normergic acute phase response in disease cannot be interpreted from the point of view of binary endocrinological logic. In the CNS, cytokines are able to influence on the neuroendocrine control of systemically regulated functions. It is also important that glial cells (astroglia, microglia) are capable of producing a number of cytokines and can affect neurons and develop behavioral changes. In addition, the ability of a number of cytokines outside the CNS itself to act on vagal afferents and through them to convey information to the CNS, affecting its state and functions, has been proven. It is reasonable to assume that minimal fluctuations in cytokine levels may also affect the state and function of the CNS. The aim of the study was to investigate the levels of cytokines in patients with thyroiditis; in patients with thyroiditis associated with mental disorders; in a group of healthy individuals; and evaluate the effect of cytokine levels on clinical manifestations. In the group of patients with thyroiditis and mental disorders, the levels of CCL20/MIP3α, IL-13, IL-2, IL-27, IL-5 were significantly higher than in other groups. At the same time, no positive correlation was found between the clinical manifestations of mental disorders and the levels of cytokines. A positive correlation was found between the levels of some cytokines and free triiodothyronine, as well as the level of antithyroid antibodies. Mental disorders associated with autoimmune thyroiditis may be associated with changes in the cytokine profile and result from neuroinflammation.

Keywords: cytokines, thyroiditis, neuroinflammation, psychiatric manifestations, Hashimoto's encephalopathy, schizophrenia

The study was supported by a grant of the Russian Science Foundation RSF No. 22-15-00113.

Introduction

Mental disorders often accompany autoimmune diseases. In 1949, "myxedematous madness" was described, a psychosis associated with hypothyroidism. The main cause of hypothyroidism in areas without iodine deficiency is Hashimoto's autoimmune thyroiditis (AIT), affecting up to 15% of the female and 1-5% of the male population in some regions [1]. The focus of modern thyroidology is Hashimoto's encephalopathy (HE), a severe dysfunction of the central nervous system (CNS) against the background of AIT, manifested by various psychoneurological and behavioral disorders, the pathogenesis of which is not associated with hormonal disorders, since HE is observed in euthyrosis [15].

When evaluating data regarding the systemic concentrations of cytokines in mental disorders, it is worth to notice that cytokines are not hormones, but chemical bioregulators of short-distance focal, contact and zonal action (paracrine, juxtacrine, and autocrine modes of signaling). The minimal or mediocre fluctuations in concentrations within the ranges that are characteristic of healthy status or normergic acute phase response in disease cannot be interpreted from the point of view of binary endocrinological logic. The direction of a particular cytokine effect on various cells differs in paracrine versus systemic modes of action, depending on the contextual permissive background of other bioregulators acting locally or systemically at the moment [8, 14].

However, the central nervous system (CNS), in particular, its hypothalamic area, undoubtedly is accessible to the effects of cytokines through the systemic circulation and from local glial/neuronal interactions. Both may alter the neuroendocrine control of systemically regulated functions [11]. The elements of the intra-barrier and extra-barrier immune systems of the brain, in particular, glial cells are capable of producing a number of cytokines and can thus influence neurons and induce behavioral changes [9, 11]. In addition, it has been proven that cytokines outside the CNS itself are able to affect vagal afferents thus conveying information to the brain [6].

Aim: to study the cytokine profile in Hashimoto's autoimmune thyroiditis (AIT), both in mentally intact patients and in those having psychiatric disorders (PD), and to evaluate the relationships of cytokine levels with clinical manifestations

Materials and methods

We have studied three groups of patients: Three groups of patients were involved: 1) AIT+PD, 27 patients (mean age 53.7±16.0 years), having various psychiatric diagnoses verified at specialized hospital (among them: schizophrenia (n = 15), obsessive compulsive disorder (n = 1), Alzheimer disease (n = 1), dementia (n = 4), bipolar affective disorder (n = 4), organic delusional disorder (n = 1), depression (n = 1)). 2) AIT, 30 mentally healthy patients with Hashimoto's thyroiditis (mean age 48.1±12.0 years) 3) HC – 30 mentally and somatically healthy individuals (mean age 40.6±12.4 years). An informed consent was obtained from all participants prior to the study. The study was approved by the Ethics Committee of St Petersburg State University (protocols No. 76 dated 06/30/2017, No. 84 dated 06/20/2018 and No. 10/19 dated 10/17/2019).

The cytokine concentrations in peripheral venous blood serum were measured by multiparametric fluorescent analysis on a Luminex device, MagPix model (Luminex Inc., USA) with a commercial Human Th17 Magnetic Bead Panel kit (Merck, Germany), the study was carried out according to the manufacturer's instructions.

Laboratory studies of autoantibodies and hormones in peripheral venous blood serum were carried out on a BioMark xMark plate spectrophotometer (Bio-Rad, USA). Quantitative assessments of serum concentrations of anti-thyroperoxidase antibodies (anti-TPO), anti-thyroglobulin antibodies (anti-TG), free thyroxine (FT4), free triiodothyronine (FT3), thyroid stimulating hormone (TSH), and prolactin were carried out using commercial kits of reagents from Hema-Medica (Russia). The level of autoantibodies to alpha-enolase were measured using reagent kits from Cusabio Biotech Co., Ltd (PRC). Each study was performed according to the kit manufacturer's instructions.

Common methods of variation statistics were applied. Absolute values and fractions of the whole – n (%) were used to describe categorical variables. Continuous, discrete, and rank variables were described by the median and quartiles: Me ($Q_{0.25}$-$Q_{0.75}$) [12]. Intergroup analysis was performed using the Mann–Whitney test (U-statistics). Spearman's test (r-statistics) was used to perform correlation analysis between quantitative, countable and ordinal characteristics [12]. To assess the association of categorical variables with quantitative ones, a logistic model with an ordered choice was used, where the coefficient of the model (the logarithm of the odds ratio (log (odds)) served as a measure of association [4]. Improvement for multiple testing of hypotheses was carried out by the Benjamini–Hochberg correction [3]. The results were considered statistically significant if the probability of error of the first kind (p) was < 0.05 [13]. The calculations were performed in the programming language R v. 4.1.0.

Results and discussion

The serum concentrations of 12 cytokines in 3 groups of patients were analyzed. The levels of CCL20/MIP-3α (from the English "Macrophage Inflammatory Protein-3") and IL-13 were statistically significantly different in all three groups of patients, the highest levels of these cytokines were in patients from the AIT + PD group, and the lowest in healthy individuals. And the levels of IL-2 and IL-27 were statistically significantly higher in patients from the AIT + PD group than in healthy individuals, while the level of IL-27 was statistically significantly higher in patients with psychiatric disorders, compared with patients only with Hashimoto's. IL-21 and IL-5 levels were statistically significantly higher in the AIT group and in the AIT+PD group compared to the HC group. And the level of IL-15, on the contrary, was statistically significantly higher in the group of heal-

TABLE 1. RESULTS OF ANALYSIS OF THE LEVELS OF VARIOUS CYTOKINES IN THE STUDIED GROUPS, Me ($Q_{0.25}$-$Q_{0.75}$)

Cytokine	Control group of healthy individuals- HC	Group of mentally healthy patients with Hashimoto's thyroiditis – AIT	Group of patients with Hashimoto's thyroiditis, associated with psychiatric disorders – AIT+PD	Group comparison options	Statistical significance (p)
CCL20/MIP3α	7.36 (4.25-12.76)	15.12 (10.06-25.20)	26.04 (13.00-52.75)	HC - AIT	p = 0.006*
				HC - AIT + PD	p < .001*
				AIT - AIT + PD	p = 0.013*
IFNγ	0.82 (0.00-5.02)	1.68 (0.21-6.25)	1.68 (0.41-3.78)	HC - AIT	p > 0.999
				HC - AIT + PD	p > 0.999
				AIT - AIT + PD	p > 0.999
IL-1β	1.08 (0.26-2.00)	1.49 (0.73-3.71)	1.29 (1.08-2.10)	HC - AIT	p = 0.220
				HC - AIT + PD	p = 0.280
				AIT - AIT + PD	p = 0.665
IL-12P70	0.38 (0.00-1.59)	0.99 (0.00-5.32)	2.07 (0.00-5.00)	HC - AIT	p = 0.738
				HC - AIT + PD.	p = 0.306
				AIT - AIT + PD	p = 0.738
IL-13	0.61 (0.00-2.07)	50.84 (17.15-91.30)	102.9 (51.78-172.60)	HC - AIT	p < 0.001*
				HC - AIT + PD	p < 0.001*
				AIT - AIT + PD	p = 0.038*
IL-15	50.84 (32.87-70.60)	0.56 (0.00-3.98)	1.45 (0.15-3.08)	HC - AIT	p < 0.001*
				HC - AIT + PD	p < 0.001*
				AIT - AIT + PD	p = 0.289
IL-17A	0.0 (0.00-1.91)	0.0 (0.00-1.87)	1.44 (0.00-3.37)	HC - AIT	p = 0.625
				HC - AIT + PD	p = 0.138
				AIT - AIT + PD	p = 0.282
IL-2	0.39 (0.00-3.83)	3.25 (0.24-4.50)	4.59 (3.26-6.79)	HC - AIT	p = 0.125
				HC - AIT + PD	p = 0.008*
				AIT - AIT + PD	p = 0.065
IL-21	0.0 (0.0-0.5)	8.30 (0.00-18.77)	7.43 (0.00-13.59)	HC - AIT	p < 0.001*
				HC - AIT + PD	p < 0.001*
				AIT - AIT + PD	p = 0.527
IL-27	0.48 (0.36-0.71)	0.56 (0.47-0.75)	0.78 (0.64-1.05)	HC - AIT	p = 0.310
				HC - AIT + PD	p = 0.003*
				AIT - AIT + PD	p = 0.003*
IL-5	0.0 (0.00-0.03)	1.24 (0.01-4.15)	1.06 (0.05-2.39)	HC - AIT	p < 0.001*
				HC - AIT + PD	p < 0.001*
				AIT - AIT + PD	p = 0.729
TNFα	15.86 (10.28-21.4)	21.32 (15.47-25.75)	19.5 (16.38-24.96)	HC - AIT	p = 0.192
				HC - AIT + PD	p = 0.192
				AIT - AIT + PD	p = 0.804

Note. *, are marked values p < 0.05 (according to the Mann–Whitney U test).

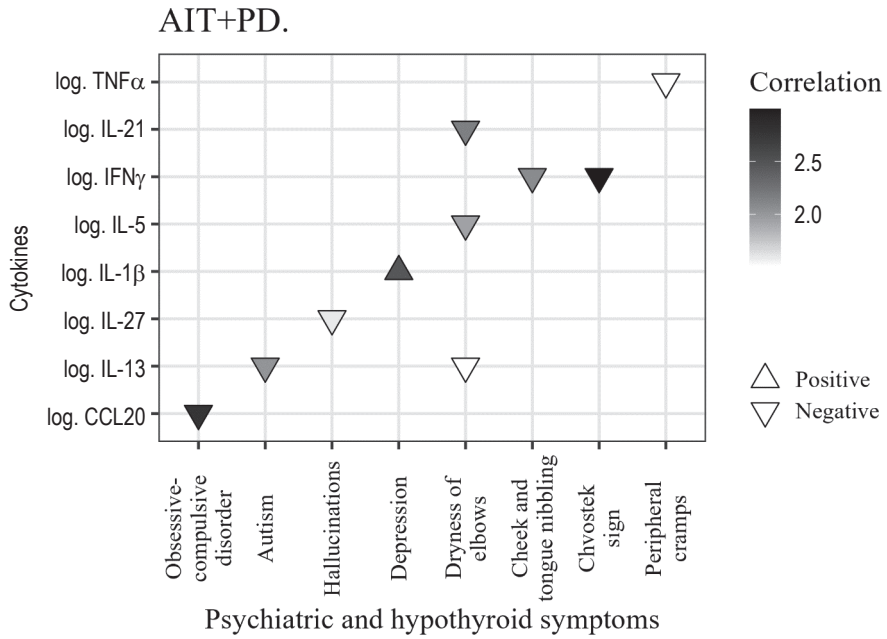

Figure 1. Results of correlation analysis between cytokine levels and various psychiatric and hypothyroid symptoms in patients with Hashimoto's thyroiditis and psychiatric disorders

thy individuals than in other groups. And the levels of IFNγ, IL-1β, IL-12P70, IL-17A and TNFα did not differ significantly in the study groups. The results are presented in Table 1.

Thus, both IL-13 and IL-5 were significantly higher in patients with mental disorders. Both of these cytokines belong to Th2-dependent, and their production is closely related, which probably explains the concordance of their changes in AIT. The increase in their production in AIT was also recorded by other authors. IL-13 is associated with the development of von Basedow-Graves disease, it is expressed not only in lymphocytes, but also in thyrocytes, and its production depends on TSH and its receptor [2].

To assess the mechanistic role of these changes, we evaluated the correlations between cytokines and hormones or autoantibodies. In AIT+ PD group, statistically significant direct correlations were found between the concentrations of FT3 and two cytokines: IL-1β ($r = 0.42$; $p = 0.031$) and IL-15 ($r = 0.51$; $p = 0.015$). This could result from the ability of these cytokines to alter hypothalamic-pituitary regulation of endocrine functions through vagal afferents that bear their receptors [8]. The finding is also quite consistent with the exclusive role of FT3 in the central nervous system: it is this particular hormone that has receptors on microglial cells and controls the processes of their neuroinflammatory activation and phagocytic behavior [10].

While analyzing the relationships between cytokines and various autoantibodies in AIT + PD group, we found significant direct correlations between the concentration of antibodies to TG and some cytokines: IL-15 ($r = 0.55$; $p = 0.008$) and IL-27 ($r = 0.4$; $p = 0.038$). IL-15 is known to be a cytokine stimulating memory T cells, $CD8^+$ lymphocytes and enhancing immune responses against intracellular parasites, but may also promote autoimmune inflammation in some autoimmunopathies. However, it also promotes T regulator differentiation under certain permissive conditions [5] which is in agreement with our results.

AIT patients without mental disorders had statistically significant inverse correlations between antibodies to TPO and IL-12P70 ($r = -0.54$; $p = 0.021$) and IL-17A ($r = -0.72$; $p = 0.003$) During the analysis of the relationship between cytokine levels and various clinical symptoms of mental disorders or hypothyroidism, almost all cytokines were negatively correlated with clinical manifestations, that is, the higher was the cytokine level, the less pronounced was the symptom (Figure 1). However, IL-1β levels were positively correlated with signs of depression (Figure 1). The data obtained in this study can be interpreted taking into account that cytokines can shift tryptophan metabolism in the CNS towards kynurenine pathway, which contributes to neurotransmitter disorders involved in the pathogenesis of schizophrenia [7].

Conclusion

Mental disorders in AIT are related to characteristic changes in cytokine profile, which may result from neuroinflammation and associated with the level of anti-thyroid autoimmunity (anti-TG antibodies) as well as with the level of FT3.

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Поступила 15.04.2023
Отправлена на доработку 24.04.2023
Принята к печати 26.04.2023

Received 15.04.2023
Revision received 24.04.2023
Accepted 26.04.2023