ПОКАЗАТЕЛИ СИСТЕМЫ ЦИТОКИНОВ У ПРАКТИЧЕСКИ ЗДОРОВЫХ ЖЕНЩИН РАЗНОГО ВОЗРАСТА И ВЗАИМОСВЯЗЬ С ЭМОЦИОНАЛЬНЫМ СОСТОЯНИЕМ

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Резюме. Многочисленные исследования показывают роль цитокиновой сети в патогенезе тревожности, депрессии. Однако в настоящее время исследования сопряженности уровней провоспалительных и противовоспалительных цитокинов с уровнем эмоциональной нагрузки достаточно немногочисленны. Целью исследования был анализ сывороточных уровней провоспалительных и противовоспалительных цитокинов и эмоционального состояния у практически здоровых женщин в зависимости от возраста. В сыворотке крови были исследованы уровни IL-1β, IL-6, IL-17, IFNγ, IL-10 и IL-4 у 100 практически здоровых женщин, которые были распределены на 3 группы в зависимости от возраста (ВОЗ): 18-44 (молодой возраст) 30 человек, 45-59 (средний возраст) 40 человек, 60-74 (пожилой возраст) 30 человек (методом сендвич-варианта твердофазного иммуноферментного анализа, пг/мл). Для оценки эмоционального компонента здоровья все обследуемые проходили опросник SF-36 «Оценка качества жизни», где из 8 шкал оценивалась только шкала ролевого функционирования (эмоциональное состояние), значения выражали в баллах. Статистическую обработку полученных данных проводили с помощью аналитического программного обеспечения IBM SPSS Statistics, 22.0. У практически здоровых женщин обнаружено повышение значений IL-1β и IL-6 в группе пожилого возраста ($p < 0,05$), при этом между группами молодого и среднего возраста различий выявлено не было. Уровень IFNγ во всех возрастных группах женщин статистически значимо не отличался. При этом в группе пожилого возраста уровни IFNγ у 40% варьировались от 1,04 до 8,76 пг/мл, а у 60% женщин – от 24,85 до 28,5 пг/мл. IL-17 также был высоким ($p < 0,05$-$0,01$) в группе женщин 60-74 лет. В противовоспалительном звене наблюдалась противоположная картина, так женщин молодого и среднего возраста уровни IL-10 и IL-4 были выше показателей группы пожилого возраста. Таким образом, проведенный анализ позволил констатировать, что показатели цитокинового профиля

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у женщин сопряжены с возрастом. При оценке степени, в которой эмоциональное состояние мешает выполнению работы или другой обычной повседневной деятельности в группе женщин среднего возраста прослеживалось снижение ее уровня (50,6 баллов, $p < 0,01$), а в группах молодого и пожилого возраста значения шкалы приближались к 90 баллам (89,6 и 85,9, баллов соответственно).

Ключевые слова: цитокины, возраст, женщины, стресс, интерлейкины, качество жизни

INDICATORS OF THE CYTOKINE SYSTEM IN PRACTICALLY HEALTHY WOMEN OF DIFFERENT AGES AND INTERRELATION WITH THE EMOTIONAL STATE

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Abstract. Numerous studies show the role of the cytokine network in the pathogenesis of anxiety and depression. However, at present, studies of the correlation between the levels of pro-inflammatory and anti-inflammatory cytokines and the level of emotional stress are rather few. The aim of the study was to analyze the serum levels of pro-inflammatory and anti-inflammatory cytokines and the emotional state in apparently healthy women depending on age. Serum levels were tested IL-1β, IL-6, IL-17, IFNγ, IL-10 and IL-4 in 100 apparently healthy women, who were divided into 3 groups depending on age (WHO): 18-44 (young age) 30 people, 45-59 (middle age) 40 people, 60-74 (old age) 30 people (sandwich variant of enzyme-linked immunosorbent assay, pg/mL). To assess the emotional component of health, all the subjects passed the questionnaire SF-36 "Assessment of the quality of life". Statistical processing of the obtained data was carried out using the analytical software IBM SPSS Statistics, 22.0. In practically healthy women, an increase in the values of IL-1β and IL-6 was found in the elderly group ($p < 0.05$), while no differences were found between the groups of young and middle age. The level of IFNγ in all age groups of women did not differ significantly. At the same time, in the elderly group, the levels of IFNγ in 40% ranged from 1.04 to 8.76 pg/mL, and in 60% of women – from 24.85 to 28.5 pg/mL. IL-17 was also high ($p < 0.05$-0.01) in the group of women aged 60-74. In the anti-inflammatory link, the opposite picture was observed, for example, in young and middle-aged women, the levels of IL-10 and IL-4 were higher than in the elderly group. Thus, the analysis made it possible to state that the parameters of the cytokine profile and emotional state in women are associated with age.

Keywords: cytokines, age, women, stress, interleukins, quality of life

Introduction

Currently, an active lifestyle and work make up 80% of our lives. Such employment inevitably leads to an increase in emotional stress. This is also due to the fact that among able-bodied people, especially women, there is high competition and the need to strengthen the stability of their position. At the same time, emerging stress can stimulate the development of cognitive impairment, which leads to depletion of the pituitary-hypothalamic-adrenal axis, manifested by a decrease in cortisol release and pro-inflammatory activity. At the same time, elevated levels of IL-1β, IL-6 and TNFα can be detected not only in the bloodstream, but also in various organs and tissues [1, 2]. An important role is played by stress resistance, which depends on the psychological portrait of the individual; in this regard, the nature of human life is also an important aspect in the relationship between stress and the immune system. The aim of the study was to analyze the serum levels of the cytokine system and the emotional state in practically healthy women depending on age.

Materials and methods

One hundred practically healthy women were examined, who were divided into 3 groups depending

on age (WHO): 18-44 (young age) 30 people, 45-59 (middle age) 40 people, 60-74 (old age) 30 people. The levels of IL-1β, IL-6, IL-17, IFNγ, IL-10 and IL-4 in blood serum were studied by the sandwich variant of enzyme-linked immunosorbent assay, pg/mL. To assess the emotional component of health, all the subjects took the SF-36 questionnaire "Assessment of the quality of life", where out of 8 scales (physical functioning, role-based physical functioning, pain scale, general health, vitality scale, scale of social functioning, role emotional functioning, psychological health), only the scale of role functioning (emotional state) was assessed; the values were expressed in points. For all scales, the maximum value was 100, the higher the score, the better the quality of life on the scale. Before calculating the indicators, the responses were recoded. Statistical processing of the obtained data was carried out using the analytical software IBM SPSS Statistics, 22.0. For comparative analysis, the chi-square test (χ^2) was used. Spearman's rank correlation coefficient was used to identify the relationship between variables. The scope of the studies performed made it possible to evaluate the results with a reliability of 95-99% of statistical methods.

Results and discussion

It should be noted that the examined women had low values of the studied cytokines in all age groups – from 0.1 to 30 pg/mL. When studying the level of pro-inflammatory cytokines in practically healthy women, an increase in the values of IL-1β and IL-6 was found in the elderly group ($p < 0.05$, Table 1), while there were no differences in the level of the above cytokines between the groups of young and middle age. The level of IFNγ in all age groups of women did not differ significantly. At the same time, in the elderly group, IFNγ levels in 40% ranged from 1.04 to 8.76 pg/mL, and in 60% of women – from 24.85 to 28.5 pg/mL (Table 1).

IL-17 was also high ($p < 0.05$-0.01) in the group of women aged 60-74. In the anti-inflammatory link, the opposite picture was observed, for example, in young and middle-aged women, the levels of IL-10 and IL-4 were higher than in the elderly group. Thus, the analysis made it possible to state that the parameters of the cytokine profile in women are associated with age.

Analysis of the results of the cytokine profile of the blood serum of the examined patients in comparison with the data of other scientists showed that the level of IL-1β in the group of young and middle age is comparable with the data obtained by Markelova E.V. et al. (1.09 pg/mL, 2016), Turmovoy E.P. et al. (1.2 pg/mL, 2017) and Slepovoy A.S. et al. (0.65±0.5, 2016, in the older age group), but lower than the values of patients Slepovoy A.S. et al. (2016) at the age of 26.6±5 years. The level of IL-6 was higher than the values established by Turmovoy E.P. et al. (1.6 pg/mL, 2017, $p < 0.05$) and Slepovoy A.S. et al. (2016), exceeding them by an average of 2 times (7.2±2.3, $p < 0.05$. The levels of IFNγ were comparable to the data obtained in the course of studies by Saibel A.V. (12.52 pg/mL, 2013), but turned out to be higher compared to the results of Turmovoy E.P. et al. (5.5 pg/mL, 2017, $p < 0.05$). IL-17 corresponded to the values of all researchers, except for the values obtained by Seibel A.V. et al. (2013), which, on the contrary, were slightly higher (10.96 pg/mL, $p < 0.05$). There were no significant differences in the level of IL-4 compared with the literature data. The values of IL-10 in the groups of this study were 6 times lower than those of Turmova E.P. et al. (36.7 pg/mL, 2017, $p < 0.01$) and 1.5 times lower than those presented by Seibel A.V. et al. (11.77 pg/mL, 2013, $p < 0.05$), but did not differ from the results of Slepovoy A.S. et al. (2.6 pg/mL, 2016).

When assessing the degree to which the emotional state interferes with the performance of work or other normal daily activities, including spending a lot of time on them, reducing the amount of work done, reducing its quality, a decrease in its level was observed in the group of middle-aged women (50.6 points, $p < 0.01$), and in the young and old age groups, the scale values approached 90 points (89.6 and 85.9 points, respectively). When assessing the degree to which the emotional state interferes with the performance of work or other normal daily activities, including spending a lot of time on them, reducing the amount of work done, reducing its quality, a decrease in its level was observed in the group of middle-aged women (50.6 points, $p < 0.01$), and in the young and old age groups, the scale values approached 90 points (89.6 and 85.9 points, respectively).

It is known that acute stress is associated with the intensification of immune responses, while chronic stress is associated with a limitation of their effectiveness. Currently, a third component has been added to this two-component model, which is characterized by simultaneous activation and suppression of the immune response by changing the secretion pattern during chronic stress [2]. At the early stage of prolonged stress, the production of pro-inflammatory (IL-1β, IL-6, TNFα and IFNγ) is inhibited and the synthesis of anti-inflammatory cytokines (IL-4, IL-10 and IL-13, TGF-β) is enhanced. The next stage of prolonged stress is

TABLE 1. CONTENT OF PRO-INFLAMMATORY AND ANTI-INFLAMMATORY CYTOKINES IN THE BLOOD SERUM OF PRACTICALLY HEALTHY WOMEN, DEPENDING ON AGE, Me ($Q_{0.25}$-$Q_{0.75}$)

No.	Indicator, pg/mL	Practically healthy women, n = 30 (18-44 years old)	Practically healthy women, n = 40 (45-59 years old)	Practically healthy women, n = 30 (60-74 years old)
		1	2	3
1	IL-1β	1.1 (0.7-3.0) $p_{1-3} < 0.05$	1.22 (0.79-4.38) $p_{2-3} < 0.05$	3.29 (0.77-7.25)
2	IL-6	6.8 (0.96-11.4) $p_{1-3} < 0.05$	7.96 (1.38-19.42) $p_{2-3} < 0.05$	13.92 (3.0-22.1)
3	IFNγ	13.36 (4.06-19.80)	15.24 (5.62-19.84)	16.20 (1.46-28.50)
4	IL-17	3.22 (1.3-10.0) $p_{1-3} < 0.01$	3.80 (1.20-19.40) $p_{2-3} < 0.05$	11.30 (1.34-58.60)
5	IL-10	6.3 (1.86-10.83) $p_{1-3} < 0.05$	7.4 (2.02-19.00) $p_{2-3} < 0.001$	2.37 (0.89-4.01)
6	IL-4	11.00 (3.64-14.50) $p_{1-3} < 0.05$	14.85 (4.00-18.86) $p_{2-3} < 0.05$	9.60 (1.80-12.00)

Note. $p_{1, 2, 3}$ compared groups (only statistically significant differences are indicated).

characterized by "saturation" (or tolerance) of catecholamines and glucocorticoids, the effects of which lead to a weakening of influences on further stress reactions due to changes in the content of the nuclear protein "kappa-B" in immunocytes, a key pro-inflammatory factor. Activators of the nuclear protein blocker are IL-1, TNFα, IFNγ, which turn off this inhibitory connection. In turn, being activated, kappa-B stimulates the expression of IL-1, IL-6, IL-8, TNFα, IFNγ, chemokines and other molecular substances involved in the inflammatory response. In the third stage of chronic stress, pro-inflammatory cytokines and inflammatory mediators are activated again, at a certain level of which the inflammatory process is triggered [3].

Under conditions of chronic stress of moderate intensity, the level of pro-inflammatory cytokines, including IL-6, increases both in the blood and in the brain [1]. Chronic psychosocial stress in humans causes a decrease in the production of cortisol, which regulates the immune response, leading to increased synthesis pro-inflammatory cytokines, as well as a decrease in the concentration of serotonin, norepinephrine and dopamine [4, 5]. In addition, stress stimulates the secretion of norepinephrine in the brain tissues, which, acting through β-adrenergic receptors, induces the release of IL-1β from intracellular depots, and also activates the rapid production of this cytokine de novo. It should be noted that in response to stress, anti-inflammatory mechanisms are also activated in the brain, which provide protection against an excessive inflammatory response [1].

Cytokines IL-1 and IL-6 act in both directions, playing the role of modulators, and their receptors are dispersed in many structures of the central nervous system, powerfully stimulating the production of corticosteroids through the effect on corticoliberin. All this testifies to the important role of IL-1 and IL-6 as mediators of neuroimmune interaction in the body's response to stress. The anti-inflammatory effect of interleukins weakens, and the pro-inflammatory effect increases [3, 4], which was shown in the study, namely in the group of older women, apparently in the third phase of chronic stress.

We support the point of view of Lisitsyna T.A. et al. (2019), this study shows that hyperproduction of IL-6 in women aged 60-74 years can lead to a decrease in the level of serotonin and dopamine, which play an important role in the development of anxiety, chronic fatigue, and sleep disturbance. According to researchers, in healthy people who have experienced

stress, low levels of IL-6 in the blood are an indicator of a rapid regression of bad mood [2]. Differences in the production of IL-6 in response to stress factors are explained by genetic polymorphisms, for example, polymorphism of the IL-6 gene (SNPrs1800795) increases the risk of inflammation in individuals exposed to adverse socioeconomic factors, another polymorphism in the IL-6 receptor gene (rs8192284) leads to functional changes in amino acids, disrupting proteolytic reactions [3].

Conclusion

1. In practically healthy women aged 60-74 years, activation of the pro-inflammatory cytokine profile is observed.

2. When assessing the degree of the emotional component that affects the performance of daily duties, it was in the middle-aged group (45-59 years) that the depletion of the hypothalamic-pituitary-adrenal axis was observed, however, normal IL-6 values indicate a rapid regression of bad mood.

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