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THE CONTENT OF CYTOKINES IN THE BLOOD SERUM OF PATIENTS WITH EARLY LATENT SYPHILIS IN PROCESS OF TREATMENT

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Ключевые слова: *сифилис скрытый ранний, цитокины, лечение, прогноз*

Abstract. The content of cytokines in the blood serum of patients with early latent syphilis in process of treatment. Zakharov S.V., Zakharov V.K., Gorbuntsov V.V. *Objective – to study the concentration of pro- and anti-inflammatory cytokines in patients with early latent syphilis before and after treatment. The study was conducted in 112 patients with early latent syphilis (52 men and 60 women) and 15 healthy persons of the control group – all aged 18-43. Serological tests were used: the classical complex of serological reactions (CSR), ELISA, the reaction of passive hemagglutination (RPGA), immunofluorescence reaction with absorption (RIF-abs) and RIF-200. Using ELISA, the levels of cytokines IL-2, IL-6, IL-10, TNFα, and INFγ were determined in serum (in patients with latent syphilis, before and after treatment). The analysis of the received data was carried out with application of the program package Statistics 6.0. To identify the relationships between the indices, Friedman's nonparametric variance analysis with the*

definition of χ^2 was used. The concentration of IL-10 before treatment in patients with early latent syphilis was significantly increased by 3.7 (14.9±0.9 pg/ml compared to the control group 4.11±0.5 pg/ml). The dependence of the content of this cytokine on the period of infection was established. It was found that one year after treatment concentration of IL-10 remained 1.8 times higher. The concentration of IL-6 was increased by 6.5 times in patients with latent early syphilis and was also dependent on the period of the infection, and also even 1.5-2 years after treatment the IL-6 content remained elevated. It was also found that in patients with latent early syphilis the concentration of IL-2 was increased by 2.3 times and it did not normalize in 24.5% of patients even two years after treatment. In patients with latent early syphilis, the concentration of TNFα was increased by 3.6 times. After treatment, the concentration of TNFα decreased, but exceeded the control values by 1.55 times. Further analysis of the concentration of TNFα revealed that, with a disease period of up to one year, the concentration of this cytokine was normal during ten months after treatment, and in patients with the disease period of more than one year, after treatment normalization of the TNFα level was absent in 64.5% even after 18 months. It was found that the concentration of INFγ in patients with early latent syphilis before treatment was increased by 3.8 times in comparison with the control group. After treatment, almost 25 % of patients with the duration of the infection more than one year revealed no normalization of INFγ and it was increased by 1.5 times. In patients with latent early syphilis there was a significant increase in the concentration of cytokines TNFα and INFγ, an imbalance of IL-2, IL-6, IL-10 as well as. The dependence of the cytokine concentration on the period of infection is noted. Based on the study of the cytokine status in patients with early latent syphilis with periods of infection of more than one year, the use of immunomodulatory therapy may be recommended. Increasing the concentration of such cytokines as TNFα, IL-6, IL-10 after treatment can be used as prognostic tests of serological resistance.

Реферат. Вміст цитокінів у сироватці крові хворих на ранній прихований сифіліс у процесі лікування. Захаров С.В., Захаров В.К., Горбунцов В.В. *Мета роботи - вивчити концентрацію про- і протизапальних цитокінів у пацієнтів з раннім прихованим сифілісом до і після лікування. Дослідження проводилося у 112 пацієнтів з раннім прихованим сифілісом (жінок - 60, чоловіків - 52) і 15 здорових пацієнтів групи контролю віком 18-43 роки. Застосовували серологічні методи дослідження: РЗК, ІФА, РПГА, РІФ. Методом ІФА визначали в сироватці крові (у пацієнтів з прихованим сифілісом - до і після лікування) рівні цитокінів IL-2, IL-6, IL-10, TNFα, і INFγ. Аналіз отриманих даних проводився із застосуванням пакета програм Статистика 6.0. Для виявлення зв'язків між показниками застосовували непараметричний дисперсійний аналіз Фрідмана з визначенням χ2. Концентрація IL-10 до лікування в пацієнтів з раннім прихованим сифілісом була достовірно підвищена в 3,7 раза (14,9±0,9 пг/мл порівняно з групою контролю 4,11±0,5 пг/мл). Було встановлено залежність вмісту цього цитокіну від термінів інфекції. Було встановлено, що через один рік після лікування концентрація IL-10 залишалася підвищеною в 1,8 раза. Концентрація IL-6 була підвищена в пацієнтів з прихованим раннім сифілісом у 6,5 раза і також була залежна від термінів інфекції, і навіть через 1,5-2 роки після лікування вміст IL-6 залишався підвищеним. Було також встановлено, що в пацієнтів з прихованим раннім сифілісом концентрація IL-2 була підвищена в 2,3 раза і вона не нормалізувалася в 24,5% пацієнтів навіть через два роки після лікування. У пацієнтів з прихованим раннім сифілісом концентрація TNFα була підвищена в 3,6 раза. Після проведеного лікування концентрація TNFα у них зменшувалася, але перевищувала показники контролю в 1,55 раза. При подальшому аналізі концентрації TNFα було встановлено, що при термінах захворювання до одного року через десять місяців після лікування була нормалізація концентрації цього цитокіну, а в пацієнтів з термінами захворювання більше одного року після лікування нормалізації рівня TNFα не було в 64,5% навіть через 18 місяців. Було встановлено, що концентрація INFγ у пацієнтів з раннім прихованим сифілісом до лікування була підвищена в 3,8 раза порівняно з контрольною групою. Після лікування майже в 25% пацієнтів з термінами інфекції більше одного року нормалізації INFγ не було і він був підвищеним в 1,5 рази. У пацієнтів з прихованим раннім сифілісом спостерігається значне підвищення концентрації цитокінів TNFα і INFγ, а також дисбаланс IL-2, IL-6, IL-10. Відзначається залежність концентрації цитокінів від термінів інфікування. На підставі вивчення цитокінового статусу в пацієнтів з раннім прихованим сифілісом з термінами інфікування більше одного року можна рекомендувати застосування імуномодулюючої терапії. Підвищення концентрації таких цитокінів, як TNFα, IL-6, IL-10, після лікування може бути використано в якості прогностичних тестів серологічної резистентності.*

The urgency of the latent syphilis problem is caused by the fact that in the structure of syphilis incidence its part amounts more than 50 %, the mechanisms of its pathogenesis remain unstudied completely, and after the treatment of such patients the serological resistance arises [1, 3, 4, 7, 9].

Among numerous factors contributing to the increase of the number of cases of the early latent syphilis, a significant part is belongs to [1, 2, 4, 11]:

- the significant spread of antibiotics using, both for the treatment of syphilis and for the treatment of other STIs;
- expansion and introduction into practice of a number of highly sensitive methods of examination (immunoenzyme method, immune blotting, the reaction of passive hemagglutination (RPGA));
- the reduction of the virulent properties of the pale treponema itself and its resistance to therapy.

In addition, some researchers believe that *L*- and cyst-forms of the pale treponema itself can be one of the reasons of the latent course of syphilis [4, 18]. At the same time, none of the researchers studying the mechanisms of the syphilitic infection pathogenesis has doubts as to the fact that the prognosis of the disease depends on the state of the immune system [7, 12, 15, 16, 17]. Until now, there is no consensus among specialists on understanding the mechanism of immunity disorders under the latent syphilis [2, 4, 5].

The above data indicate that the issue of the classification and mechanisms of the immune system disorders initiation under this form of syphilis remains unresolved [2, 16, 17]. Studies of the content of anti-inflammatory cytokines in patients with early latent syphilis, which have been conducted earlier, are highly contradictory and incomplete [4, 5, 8-13].

Under the chronic inflammation peculiar to syphilitic infection in particular, the normal cytokine profile changes, and that is manifested by increased secretion of pro-inflammatory cytokines [3, 5, 6].

However there is another view on the role of interleukins created in the cells of a sick person under the influence of pale treponema due to the activation of *Th*1 cells [12, 13].

To this day almost no studies have been conducted on the content of *IL*-2 in the blood serum of patients with latent syphilis, while *IL*-2 plays a significant role in the activation of the immune system through the stimulation of the synthesis of *INF*γ, *IL*-6. Unlike *IL*-2, *IL*-6 is produced by different types of cells by activation of *CD*4 + and *CD*8 + and belongs to the proinflammatory cytokines. One of the most important cytokines determining the immune response is *IL*-10. Under its influence, cellular immunity (*Th*1) is inhibited and humoral immunity (*Th*2) is stimulated, the secretion of *INF*γ, *TNF*α, *IL*-1, *IL*-8 decreases. TNFα is a polypotent immunomodulatory cytokine, namely a mediator of a specific and non-specific immune response that depends on its concentration. TNFα is capable of activating *EK*-cells, increasing the secretion of *IL*-6. TNFα is synthesized mainly by *Th*1-lymphocytes and *EK*-cells and has a significant antibacterial and immunomodulatory effect [5, 6].

A comprehensive study of the cytokine profile in patients with early latent syphilis before and after treatment can give a more detailed idea of the mechanism of the immune response and allow further prognosis of the disease [10, 19-22].

Objective – to study the concentration of pro- and anti-inflammatory cytokines in patients with latent early syphilis before and after treatment.

MATERIALS AND METHODS OF RESEARCH

The study was conducted in 112 patients (52 men and 60 women) aged 18-43 (mean age 31.1±0.7 years) with early latent syphilis who were on treatment at the skin and venereal disease clinic of the State Establishment "Dnipropetrovsk Medical Academy of Health Ministry of Ukraine". The comparison group consisted of 15 practically healthy persons with similar sex and age distribution.

The criteria for inclusion in the study were: age up to 45 years, diagnosis of early latent syphilis. The criteria for exclusion from the study were: age over 45, pregnancy, presence of tuberculosis, viral hepatitis, HIV / AIDS, other infectious diseases; diabetes, as well as antibiotic treatment in the last three months before the study.

For the diagnosis of syphilis serological tests were used: the classical complex of serological reactions (CSR), ELISA (*IgM*, *IgG*), the reaction of passive hemagglutination (RPGA), immunofluorescence reaction with absorption (RIF-abs) and RIF-200. The serum levels of *IL*-2-, *IL*-6-, *IL*-10-cytokone, TNFα, and INFγ were measured by the method of enzyme immunoassay [11]. The analysis of the data received was carried out with application of the program package Statistics 6.0. The difference in indices with $p<0.05$ considered as probable one. To identify the relationships between the indices, Friedman's nonparametric variance analysis with the definition of χ^2 was used. The coupling between indices was considered significant if χ^2 value exceeded the critical one ($\chi^2=3.84$) [3, 4].

RESULTS AND DISCUSSION

The concentration of *IL*-10 in the blood serum of patients with latent early syphilis before treatment was probably ($p<0.05$) increased to 14.9±0.9 pg/ml in comparison with the control group (4.11±0.5 pg/ml), that is by 3.7 times. When analyzing this anti-inflammatory interleukin in patients with an infection period of more than one year, its concentration was 5.7 times higher than in healthy persons (23.5±0.6 and 4.11±0.5; $p<0.05$). If before treatment the concentration of *IL*-10 was increased by 3.7 times, after treatment the content of this interleukin significantly decreased to 10.1±0.2 pg/ml and exceeded the normal values by 2.4 ($p<0.05$). On further observation after treatment, the further decrease in *IL*-10 concentration to 7.5±0.1 pg/ml was marked only after 12.3±1.2 months. That is, even one year after treatment there was no normalization of the *IL*-10 concentration (it remained 1.8 times higher than one in the control group).

In patients with early latent syphilis before treatment, the concentration of *IL*-6 was 31.3±1.2 pg/ml,

that is it was increased by 6.5 times in comparison with the control group.

When analyzing the concentration of *IL*-6, it was found that in patients with a period of infection up to one year it exceeded the norm by almost 10 times (48.3±1.5 compared to 4.8±0.2, $p<0.05$). Under the longer duration of the disease, the concentration of *IL*-6 was almost three times less (15.6±0.5 pg/ml).

After treatment the serum concentration of *IL*-6 remained elevated (7.4±0.8 pg/ml, $p<0.05$) even 1.5-2.0 years after.

The concentration of *IL*-2 in the blood serum of patients with latent early syphilis before treatment was 37.8±4.1 pg/ml while a control group score was 16.5±3.2 pg/ml, that is, it was increased by 2.3 ($p<0.05$) times. When analyzing the concentration of this cytokine depending on the duration of the disease to one year and more than one year, the difference was unreliable. After treatment the normalization of *IL*-2 secretion was lacking in 24.5% of patients even two years after.

When analyzing the secretion of tumor necrosis factor (TNFα), we obtained such results: in patients with latent early syphilis the concentration of TNFα was 18.8±0.6 pg/ml (in the control group 5.2±0.5 pg/ml, $p<0.05$), that is, it was increased by 3.6 times. After treatment, the concentration of TNFα decreased to 8.1±0.3 pg/ml ($p<0.05$) and exceeded the control values by 1.55 times.

Further analysis of the concentration of TNFα revealed that, under the disease period of up to one year, the concentration of this cytokine was normal during ten months after treatment, and in patients with a disease period of more than one year normalization of the TNFα level after treatment was lacking in 64.5% even 18 months after.

The concentration of INFγ in patients with early latent syphilis before treatment was increased by 3.8 times in comparison with the control group (53.7±3.1 pg/ml *vs*. 16.1±1.3, $p<0.05$). After treatment almost 75% of patients revealed normalization of this cytokine and only 25% of patients with period of infection more than one year, revealed no normalization of INFγ and it was increased by 1.5 times.

CONCLUSIONS

1. Under the early latent syphilis there is a significant increase in the concentration of cytokines that are synthesized Th1 type of the (TNFα, INFγ), as well as the imbalance of IL-2, IL-6, IL-10.
2. The dependence of the cytokines concentration on the terms of infection was established; so under duration of the infection of more than one year the imbalance of pro- and anti-inflammatory cytokines was more pronounced.
3. Based on the study of the cytokine status, patients with early latent syphilis with terms of infection of more than one year should be treated with medications causing a positive effect on the immune system.
4. An increase in the concentration of such cytokines as TNFα, IL-6, IL-10 after treatment can be used as prognostic tests of serological resistance.

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