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## IMMUNOLOGICAL REACTIVITY AND NATURAL RESISTANCE IN PATIENTS WITH TUBERCULOSIS, TOXOCARIASIS AND TUBERCULOSIS ASSOCIATED WITH TOXOCARIASIS

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### Resume.

**Introduction.** Parasitic diseases continue to affect the population of many countries of the world. About 2 billion people on the planet are infected with helminths, including *Toxocara canis*. Invasion with *Toxocara canis* represents a strong endogenous factor in the formation of the regulatory imbalance of the immune system. The integral evaluation of these indices serves as an important criterion in the diagnosis of toxocarosis and the effectiveness of the applied therapy. In the context of the above, information about research on immune reactivity and natural resistance of tuberculosis patients in association with toxocariasis is of interest.

**Material and methods.** This article is a systematic review of the relevant literature between the year 2001 and 2022. The material for the study was electronic sources published through the web Medline, EMBASE, Global Health, Scopus and Web of science; PubMed; crossref; Google Scholar and others. The following keywords were used “immunological reactivity”, “natural resistance”, “parasitic diseases”, “*Toxocara canis*”, “tuberculosis and toxocariasis”, “immunity”, “helminthiasis”, “toxocariasis”. Bibliographic resources have been systematized by subject and content. The results were grouped and systematized according to the relevant criteria and the level of scientific evidence.

**Results.** Parasites, in particular, *Toxocara canis* and *M. tuberculosis* use different mechanisms to alter the immune response, but these mechanisms can interact with significant consequences for the immunological reactivity of each infection. Chronic helminthic infection causes a wide range of changes in the immune system.

**Conclusion.** The immune reactivity and natural resistance of tuberculosis patients in association with toxocarosis is insufficiently elucidated.

**Keywords:** parasitic diseases, *Toxocara canis*, tuberculosis, immunity.

### Rezumat. Reactivitatea imunologică și rezistența naturală la pacienții cu tuberculoză, toxocaroză și tuberculoză asociată cu toxocaroză

**Introducere.** Bolile parazitare continuă să afecteze populația multor țări ale lumii. Aproximativ 2 miliarde de oameni de pe planetă sunt infectați cu helminți, inclusiv cu *Toxocara canis*. Invazia cu *Toxocara canis* reprezintă un puternic factor endogen în formarea dezechilibrului reglator al sistemului imunitar. Evaluarea integrală a acestor indici servește ca un criteriu important în diagnosticul toxocarozii și eficacitatea terapiei aplicate. În contextul celor de mai sus, sunt de interes informații despre cercetările privind reactivitatea imună și rezistența naturală a bolnavilor de tuberculoză în asociere cu toxocaroză.

**Material și metode.** Acest articol este o revizuire sistematică a literaturii relevante între anii 2001 și 2022. Materialul pentru studiu a fost surse electronice publicate prin web Medline, EMBASE, Global Health, Scopus și Web of science; PubMed; crossref; Google Academic. și alții. Au fost folosite următoarele cuvinte cheie „reactivitate imunologică”, „rezistență naturală”, „boli parazitare”, „*Toxocara canis*”, „tuberculoză și toxocaroză”, „imunitate”, „helmintiază”, „toxocaroză”. Resursele bibliografice au fost sistematizate pe subiect și conținut. Rezultatele au fost grupate și sistematizate în funcție de criteriile relevante și de nivelul de evidență științifică.

**Rezultate.** Paraziții, în special, *Toxocara canis* și *M. tuberculosis* folosesc mecanisme diferite de modificare a răspunsului imun, însă aceste mecanisme pot interacționa cu consecințe semnificative pentru reactivitatea imunologică a fiecărei infecții. Infecția helmintică cronică determină o gamă largă de modificări ale sistemului imunitar.

**Concluzie.** Reactivitatea imună și rezistența naturală a bolnavilor de tuberculoză în asociere cu toxocaroză este insuficient elucidată.

**Cuvinte cheie:** boli parazitare, *Toxocara canis*, tuberculoza, imunitate.

### Резюме. Иммунологическая реактивность и естественная резистентность у больных туберкулезом, токсокарозом и токсокароз ассоциированным с туберкулезом.

**Введение.** Паразитарные заболевания продолжают поражать население многих стран мира. Около 2 миллиардов человек на планете заражены гельминтами, в том числе *Toxocara canis*. Инвазия *Toxocara canis* представляет собой сильный эндогенный фактор формирования регуляторного дисбаланса иммунной системы. Интегральная оценка этих показателей служит важным критерием диагностики токсокароза и эффективности применяемой

терапии. В связи с вышеизложенным представляют интерес сведения об исследованиях иммунной реактивности и естественной резистентности больных туберкулезом в сочетании с токсокарозом.

**Материал и методы.** Данная статья представляет собой систематический обзор соответствующей литературы за период с 2001 по 2022 годы. Материалом для исследования послужили электронные источники, опубликованные через веб-интерфейс Medline, EMBASE, Global Health, Scopus и Web of science; ПабМед; перекрестная ссылка; Google Scholar. и другие. Использовались следующие ключевые слова: «иммунологическая реактивность», «естественная резистентность», «паразитарные заболевания», «токсокары собак», «туберкулез и токсокароз», «иммунитет», «гельминтозы», «токсокароз». Библиографические ресурсы систематизированы по тематике и содержанию. Результаты были сгруппированы и систематизированы по соответствующим критериям и уровню научной доказательности.

Полученные результаты. Паразиты, в частности *Toxocara canis* и *M.tuberculosis*, используют разные механизмы изменения иммунного ответа, но эти механизмы могут взаимодействовать со значительными последствиями для иммунологической реактивности каждой инфекции. Хроническая глистная инфекция вызывает широкий спектр изменений в иммунной системе.

**Заключение.** Иммунная реактивность и естественная резистентность больных туберкулезом в сочетании с токсокарозом изучены недостаточно.

**Ключевые слова:** паразитарные болезни, *Toxocara canis*, туберкулез, иммунитет.

### Introduction.

Parasitic diseases are one of the most common diseases. Expectations that by the end of the XX century. most parasitic diseases will be under control, did not pan out. They continue to affect the population of many countries of the world, and primarily the inhabitants of developing countries located in tropical and subtropical climatic zones. In the US, *Toxocara canis* is considered by the Centers for Disease Control as one of the five neglected parasitic infections and is a public health priority. About 2 billion people of the planet are infected with helminths [1; 2; 3; 4; 5; 6; 7; 8; 9].

Socially significant infections, which are associated with tuberculosis [2], to which toxocarosis and other pathologies are associated, represent a problem of global importance. This group of infections returned in the era of socio-economic and political reforms and achieved a wide spread against the backdrop of socio-economic instability. The combined effects of the interaction between different pathologies of any etiology and tuberculosis leads to increased morbidity and mortality, increased incidence of adverse reactions and epidemiological consequences [1; 2].

In our country there are no statistical data, the infection being reported sporadically. Toxocarosis can occur in the form of small family outbreaks or in groups of children, especially when the socio-economic and hygienic-sanitary conditions are precarious [10; 4; 11; 12; 13; 14].

Tuberculosis remains a global problem. A feature of tuberculosis is an increase in the prevalence of mycobacteria resistant to antimycobacterial drugs, which leads to a decrease in the quality of treatment and, as a result, to an increase in the mortality rate [15; 16; 17].

The invasion by *Toxocara canis* represents a strong endogenous factor in the formation of the

regulatory imbalance of the immune system, which is manifested by the decrease in phagocytosis indices, the increase in the content of circulating immune complexes and total IgE. The integral evaluation of these indices serves as an important criterion in the diagnosis of toxocarosis and the effectiveness of the applied therapy [18].

One of the reasons for the ineffective treatment of tuberculosis and the replenishment of the contingent of patients with relapses of tuberculosis may be concomitant diseases of infectious etiology [19; 20].

In the context of the above, information about research on the immune reactivity and natural resistance of tuberculosis patients in association with toxocarosis is of interest.

### The goal.

To inform about the latest achievements published in studies on immunological reactivity and natural resistance, their violations in patients with tuberculosis, toxocarosis and in the combined form of these diseases.

### Material and methods.

This article is a systematic review of the relevant literature between the year 2001 and 2022. The material for the study was electronic sources published through the web interface Medline, EMBASE, Global Health, Scopus and Web of science; PubMed; crossref; Google Scholar. and others. The following keywords were used “immunological reactivity”, “natural resistance”, “parasitic diseases”, “*toxocara canis*”, “tuberculosis and toxocarosis”, “immunity”, “helminthiasis”, “toxocarosis”. The Universal Decimal Classification (UDC) method was used to search for printed sources. Bibliographic resources have been systematized by subject and content. The results were grouped and systematized according to the rele-

vant criteria and the level of scientific evidence [high, low and very low] [21].

### Results and discussion.

Helminth infections affect more than 1.5 billion people worldwide, while *Mycobacterium tuberculosis* infects a third of the world's population, resulting in 2 million deaths per year. Although tuberculosis and helminth infections coexist in many parts of the world, and it has been shown that the T-helper type 2 helminth response can affect the host's ability to control mycobacterial infection, it is still unclear whether helminth infections actually have an effect on tuberculosis disease. In tuberculosis, the Th 1 response [IL-12, IFN- $\gamma$  and TNF- $\alpha$ ] is of great importance. In addition, *M. tuberculosis* contains well-described Toll-like receptor ligands that are potent stimulators of many proinflammatory cytokines in vitro [22; 23; 24; 25; 26; 27].

Helminth infections are chronic in nature and can lead to significant morbidity. Chronic helminth infection induces a wide range of immune changes characterized mainly by a predominance of T-helper [Th] type 2 immune response and interleukins IL-4, IL-5, IL-13, which cause B cells to turn on the production of IgE antibodies. Also, helminths can alter the adaptive immune response of the host by the induction of T-regulatory cells [Treg] or the secretion of anti-inflammatory cytokines [IL-10 and transforming growth factor - TGF- $\beta$ ]. These factors could have a significant inhibitory effect on the protective, mycobacterial-induced immune response and/or control of mycobacterial infection. Since the immune response is an important condition for helminth and tuberculosis infections, it is important to know the main mechanisms by which co-helminth infections affect host control of *M. tuberculosis* infection [28; 23; 29].

Parasites, particularly *Toxocara canis*, and *M. tuberculosis* use different mechanisms to alter the immune response, and these mechanisms can interact with significant implications for the immunology of each infection. The literature shows that helminth-infected volunteers exhibit a very low Th1 response and IFN- $\gamma$  production to *M. tuberculosis* antigens. Helminth infections can alter the Th1 response through stimulation of Th2 and/or Treg cells. Increased Treg function associated with helminth infections may suppress the Th1 response against unrelated antigens. This fact was confirmed by a publication demonstrating that helminthic intestinal coinfection is associated with a decrease in the Th1 response in active tuberculosis. In this regard, it has been shown in a mouse model that subsequent co-infection with *Schistosoma mansoni* results in reduced Th1 in response to *My-*

*cobacterium avium*, influencing the production of Th1 cytokines. Helminth infection with *M. tuberculosis* has been shown to significantly reduce the *M. tuberculosis*-specific Th1 [IL-12/IFN- $\gamma$ ] response in latent tuberculosis, and that the poor immunogenicity of BCG vaccination in helminth-infected populations has been associated with increased production of TGF- $\beta$  [30; 31; 32; 33; 6; 34; 35; 36; 37; 38].

Some authors have shown that a DNA vaccine encoding the mycobacterial 65-kDa heat shock protein [DNAhsp65] protected mice and guinea pigs from infection with a virulent strain of *Mycobacterium tuberculosis* and cured mice previously infected with naked DNA [naked DNA] as an intramuscular injection [39; 40].

Immunization with helminth antigens has been shown to enhance the Th2 response in mouse and human models, and helminth infections have been reported to induce suppressor T cells that produce inhibitory cytokines [IL-10], which in turn suppress the immune response [41; 30; 42; 43].

Invasion of *Toxocara canis* does not necessarily lead to increased susceptibility to pulmonary tuberculosis. A possible explanation for these discrepancies in the data may be that the effect of helminthiasis on host response to *M. bovis* BCG depends on the helminth species and/or intensity of infection [44].

Helminthic [schistosomal] infection reduces the effect of BCG vaccination due to the action of the Th2 type of response, and this increases susceptibility to *M. bovis* infection [45].

Parasitic infections such as helminths can prevent vaccines from providing optimal protection. In animal studies, the most affected vaccine was BCG. This result indicates that helminth-related disturbances in vaccine response are more severe with direct than with intrauterine exposure to helminths. Further research is needed to find out if deworming people before vaccination can help improve response [46; 47].

Helminths migrate through mucosal sites, causing tissue damage and induction of a type 2 immune response. Antihelminthic defense is based on the mobilization and activation of multiple immune cells, including type 2 innate lymphocytes [ILC2], basophils, mast cells, macrophages, and hematopoietic stem/progenitor cells. In addition, epithelial cells and neurons are recognized as important regulators of type 2 immunity. Together, these pathways stimulate the host's defense responses, which are necessary for the expulsion of worms and the healing of damaged tissues [48; 49].

The gold standard for diagnosing any helminthiasis is the parasitological method. However, intravital

parasitological diagnosis of toxocariasis is practically impossible, since it is difficult to detect migrating larvae, and it is very difficult to identify them by histological sections [50; 51].

It is known that the evolution of the relationship between the parasite and the host has led to the appearance in endoparasites of specific mechanisms for controlling the physiological status of the host, aimed at restructuring its organism in order to create optimal conditions for the development and reproduction of the parasite. A number of researchers believe that the most common pathological effects of all pathogens of parasitic diseases, primarily helminths, are allergization and immunosuppression. The absence of pronounced specific symptoms of helminthiasis and the difficulty in diagnosing them using routine methods lead to low detection and extremely rare identification of helminth infection as an independent disease, which makes this problem relevant for practical healthcare [52; 53].

Toxocariasis is manifested by abdominal, pulmonary syndromes, neurological disorders, eye lesions, eosinophilia, is combined with many lung diseases or occurs under the guise of these diseases. Mediastinal lymphadenopathy can be observed in toxocariasis [56; 55; 56; 57; 58; 59].

The negative impact on human health of toxocar consists of many factors: variability of clinical manifestations, negative impact on the development of post-vaccination immunity, immunopathological reactions of the body, the ability of migrating larvae to transport pathogenic viruses and inhibit spermatogenesis [60].

The antigens of parasites that enter the body cause allergic reactions of an immediate and delayed type. At the same time, there is a phenomenon of molecular [antigenic] mimicry, when the host is „not able to recognize” helminth antigens as „foreign” and does not produce antibodies to them. There is a suppression of the immune response. This is confirmed in studies that show that deworming leads to a decrease in bronchial hyperreactivity, a decrease in allergic inflammation and allergy manifestations [7; 61].

An imbalance of immunological indices develops, reflecting the reduction of the body's resistance and immune deficiency and is in accordance with the opinion regarding the development of immunodepression in most parasitosis [62; 16].

Co-infection with helminths and *Mycobacterium tuberculosis* is common and is thought to influence the risk of developing active tuberculosis. It is known that helminths, unlike tuberculosis, cause a strong Th2 response in the host. However, the direct effect of helminth antigen exposure on host immunity

against tuberculosis is largely unknown. The effect of helminth antigen exposure on early immune control of *Mycobacterium tuberculosis* in monocytes and macrophages was studied. Protein antigens of helminths were used to study the effect of antigens on monocytes, on the differentiation of monocytes into macrophages or mature macrophages in the control of virulent *Mtb H37Rv*. Pre-exposure to peripheral blood mononuclear cells reduced the growth of *Mycobacterium tuberculosis* in monocytes, but neither Th1/Th2 cytokines nor activation markers indicated involvement of T cells. This *in vitro* model shows how helminth infection directly affects the monocyte-macrophage axis at an early stage before the development of cell-mediated immunity [63].

It is well known that, by modulating various immune functions, host infection can alter the course of associated inflammatory diseases of both infectious and autoimmune etiologies. In addition to the main influence of the commensal microbiota on immune status, exposure of the host to viral, bacterial and/or parasitic microorganisms also has a strong influence on inflammatory diseases in the host, in both beneficial and detrimental ways. Moreover, by altering pathogen control and host tolerance to tissue damage, coinfection can strongly influence the development of concomitant infectious disease [64].

Parasitogenic immunosuppression, acting inhibitory on metabolic processes, enzymatic activity, makes it difficult to absorb chemotherapeutic antiparasitic, antibacterial and other drugs [65; 59; 20].

Diagnosis of toxocariasis today is based on laboratory research methods. One of the constant manifestations of the visceral form of toxocariasis is leukocytosis and persistent long-term eosinophilia up to 30–90%. There is also moderate anemia, hyperproteinemia, hypergammaglobulinemia, high IgE levels. The most informative in the diagnosis of toxocariasis are immunological methods, namely the determination of the titer of specific antibodies of the IgG class to *Toxocara canis* by enzyme immunoassay, which has high sensitivity and sufficient specificity for visceral localization of the helminth - 93.7% and 89.3%, respectively. A correlation has been established between clinical manifestations, the severity of the process, and antibody titers. A titer of specific antibodies of 1:800 and above with a high degree of probability indicates a disease, and titers of 1:200–1:400 indicate the carriage of toxocar in visceral toxocariasis and the pathological process in toxocarosis of the eye. Dispensary observation is established for persons with low titers of antitoxocariasis antibodies, and if clinical signs of the disease appear, specific therapy is recommended. However, it must be remembered that



there is not always a direct correlation between the antibody titer and the severity of the disease, since toxocarosis occurs cyclically with relapses and remissions, and therefore there may be significant fluctuations in clinical, hematological and immunological parameters in the same patient. In addition, false results of the study are also possible: false-positive ones can be observed in patients with echinococcosis, opisthorchiasis [in the acute phase of the disease], the migratory phase of ascariasis; false-negative - with toxocarosis of the eyes, primary immunodeficiency, prolonged course of helminthiasis [66; 67; 68; 69].

Quite often, an excessive number of eosinophils is recorded in the peripheral blood of patients with pulmonary tuberculosis. However, the role of these unique cells in the pathogenesis of tuberculosis infection remains unclear to date. Preferential activation of T-lymphocytes-helpers type 2 [Th2] can cause the formation of eosinophilia, since cytokines responsible for the humoral immune response are involved in the regulation of the processes of proliferation, differentiation and activation of eosinophilic leukocytes. In turn, eosinophils, which have not only cytotoxic, but also pronounced immunoregulatory properties, due to the secretion of a wide range of factors, are able to activate [or deactivate] lymphocytes and cause a polarization of the immune response, directing it along one of the development options - cellular or humoral. Tuberculosis infection in combination with an eosinophilic blood reaction is accompanied by a more pronounced imbalance of cytokines mediating the formation of the Th1- and Th2-immune response. Deficiency of IFN- $\gamma$ , a key anti-tuberculosis cytokine in patients with pulmonary tuberculosis accompanied by eosinophilia, on the one hand, may be a consequence of the dominance of humoral immune response cytokines, and on the other hand, act as a factor contributing to the development of an eosinophilic blood reaction in pulmonary tuberculosis. The predominance of the activity of humoral mechanisms in tuberculosis associated with eosinophilia, apparently, can be considered as one of the prognostically unfavorable factors in the immunopathogenesis of the underlying disease [68; 69; 70; 71].

The main role in the mechanism of antiparasitic immunity is played by eosinophils. These cells protect the human body in collaboration with IgE, the level of which invariably increases with toxocarosis, as well as with tissue basophils and macrophages. As is known, the proliferation of eosinophils is regulated by T-lymphocytes.

The intravital parasitological diagnosis of toxocarosis is impossible, because the detection of migrating larvae is very difficult, and their identification

after histological sections is very complicated. Not to mention this, the final parasitological diagnosis of toxocarosis is, undoubtedly, only when larvae are detected in tissue biopsies [72].

In connection with this, an important role in the parasitological diagnosis of toxocarosis belongs to indirect laboratory indicators: long-lasting persistent blood eosinophilia, increased IgE concentration in the blood [73].

Toxocara invasion leads both to the activation of the cellular chain and to the activation of the humoral chain of immunity in the patients' body, which is expressed by increasing the cytokine profile of both types, noting that in the pregnant women in the study with low titers, the expression of the clinical manifestations is weaker, and the level of expressiveness of the immune response stronger, than in seropositive people with high titers [74].

The most permanent signs of visceral toxocarosis - high eosinophilia up to leukemoid reactions of the eosinophilic type. The relative level of eosinophilia in some cases can reach 90%. The absolute number of eosinophils can increase to  $100 \times 10^9/l$ . The total number of leukocytes increases to  $15-100 \times 10^9/l$ . [75; 76; 9; 77; 64; 72].

Hypereosinophilia as a pathological phenomenon was established at the value of 6% and higher in the blood formula of 13.2% of the 1670 patients with lung lesions, hospitalized at the Institute of Phthisio-pneumology in the Republic of Moldova during 2005 and in the first 6 months of in 2006, considering that in some of them, the lung pathology could be determined by the S2 *Toxocara canis* larva. This category of patients was re-examined for the presence of antibodies to the S2 *Toxocara canis* larva in the blood. 221 [13.2%] patients were selected for analysis, of which - 97 [43.9%] men and 124 [56.1%] women. Of these, 76.0% were from villages and 24.0% from cities, the percentage of eosinophils was from 6 to 30%, on average - 9.9%. Of the 221 patients with blood hypereosinophilia - pulmonary tuberculosis - 20 [9.0%]. This category of patients requires mandatory testing as early as possible for the presence of various parasites and especially for the presence of S2 *Toxocara canis* larvae - one of the most widespread helminthiasis with extraintestinal manifestations in our country. It remains to be determined, in which pulmonary pathologies the frequency of detection of antibodies to the S2 *Toxocara canis* larva is higher, to what extent the presence of detected antibodies reflects the parasitological and pathogenic activity, responsible for the pulmonary manifestations, as well as to determine the criteria for prescribing antilarval therapy, duration and its efficiency [12; 13].

Part of the problems in the clinic of parasitic pathologies can be solved by means of immunological methods [59]. Evaluating the performance of chemoprophylactic treatment, comparing the data of the specific response to the pathogen with other indicators of the immune status will allow to forecast the effectiveness of the treatment, because cellular immunity is affected in case of infections, the pathogen of which develops intracellularly in macrophages [tuberculosis and others].

Most frequently, in case of toxocarosis, the lungs are affected. In experimental conditions, it was demonstrated that in mice infected with toxocara, an increased permeability of the pulmonary capillaries is determined in the lungs, inflammatory infiltrates with a predominant content of eosinophils that determine the reactivity of the trachea and IL-5 dependent and CD4+ lymphocytes [78].

In patients admitted to the hospital with suspicion of pseudotuberculosis, in the presence of uncharacteristic symptoms [high eosinophilia, lung damage], it is necessary to carry out a serological examination for toxocarosis [79].

Regression analysis [80] shows a high correlation between tuberculosis and helminthiasis infections [OR . 4.2, 95% CI 2.7–5.9,  $P < 0.001$ ]. The chance of developing tuberculosis increases with the number of types of helminths in a person: in patients infected with one type of helminths it was 4.7 [95% CI 2.5–8.7], and in patients with three or more helminthiasis - 12.2 [95% CI 3.9– 52.6]. The authors concluded that helminthiasis infections can be one of the risk factors for the development of pulmonary tuberculosis. These results may have a major importance in the control of tuberculosis in endemic regions with the prevalence of helminths.

Other authors [81] believe that *Mycobacterium tuberculosis* infection and helminth invasions correspond to the geographical region. They decided to investigate how co-invasion can change the immune response to mycobacterial infection. To investigate this task, mice were simultaneously infected with *Toxocara canis* and *M. tuberculosis*. In mice infected with *Mycobacterium tuberculosis*, a large number of neutrophils and mononuclear cells were detected in the alveolar space with a high parenchymal IFN- $\gamma$  level. At the same time, in the bronchioalveolar lavage of mice infected with *Toxocara canis*, an increase in the number of eosinophils and an increase in the parenchymal IL-5 level were appreciated. In mice with co-infection, the bronchoalveolar lavage is characterized by an increase in the content of eosinophils and a decrease in the accumulation of neutrophils and mononuclear cells. In this way, coinvasion in mice

leads to proliferation in the lungs analogous to the mycobacterial one and is accompanied by similar histopathological changes.

It was established that infiltrative tuberculosis without concomitant parasitic infections occurred with a significant decrease in CD3+, CD4+, CD8+ lymphocytes compared to healthy individuals, which coincides with the data of other authors [82]. The influence of concomitant parasites on the subpopulation composition of T lymphocytes depended on the parasite. In ascariasis and giardiasis, the content of CD3+, CD4+, CD8+ lymphocytes was significantly reduced, in blastocystosis, the content of only CD3+, CD4+ lymphocytes was reduced compared to tuberculosis without concomitant parasites. Concomitant parasites significantly increased the content of CD20+ lymphocytes in all patients compared to healthy ones and the tendency to increase compared to tuberculosis without concomitant parasites. The content of IgE in patients with tuberculosis without concomitant parasites was significantly higher than in healthy people. Concomitant ascariasis, giardiasis and blastocystosis increased Th2-response activation, the level of IgE in them was higher than in tuberculosis patients without concomitant parasites.

In patients with serologically and clinically confirmed visceral toxemia, the content of vitamin C in the blood serum is significantly reduced by 58.6%, vitamin A by 23.3% and vitamin E by 8.76% compared to blood donor data. Against the background of the decrease of these vitamins, it has been established that the invasion of toxocariasis larvae leads to genotoxic and cytotoxic effects in humans, which are characterized by an increase in single-stranded DNA breaks and apoptotic cells by 4.6 and 7.8 times, respectively, in the peripheral blood of patients with visceral toxocarosis compared to the data of donors blood [55].

### Conclusions

Summing up the review of the literature on the analyzed problem, it is possible to conclude: parasites [in particular, *Toxocara canis*] and *M. tuberculosis* use different mechanisms for changing the immune response, and these mechanisms can interact with significant consequences for the immunological reactivity of each infection; chronic helminthic infection causes a wide range of immune changes, characterized mainly by the predominance of T-helper [Th] 2 types of immune response and interleukins IL-4, IL-5, IL-13, which cause B-cells to turn on production of IgE antibodies; in tuberculosis, Th response 1 type [IL-12, IFN- $\gamma$  and TNF- $\alpha$ ] is of great importance. In addition, *M. tuberculosis* contains well-described Toll-like receptor ligands, which in vitro are powerful stimulators of many

pro-inflammatory cytokines; this fact was confirmed by a publication demonstrating that helminthic intestinal co-infection is associated with a decrease in Th1 response in active tuberculosis, it was also shown that helminthic infection occurring with M. tuberculosis significantly reduces M. tuberculosis-specific Th1 [IL-12/ IFN- $\gamma$ ] response to latent tuberculosis; eosinophilia is a characteristic sign both for tuberculosis and for toxocarosis, however, the role of these unique cells in the pathogenesis of tuberculosis infection remains unclear to this day; with toxocarosis infection, eosinophilia is a sign of the main role in the mechanism of antiparasitic immunity, as these cells protect the human body in conjunction with IgE, the level of which invariably increases with toxocarosis; invasion with toxocara leads both to the activation of the cellular chain and to the activation of the humoral chain of immunity in the patients' body, which is expressed by increasing the cytokine profile of both types.

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