CO-INFECTION WITH HERPESVIRUSES AS A NEW ASPECT OF TUBERCULOSIS IN CHILDREN

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Summary. The increase in the incidence of tuberculosis in adults in recent years leads to negative changes in the epidemiological situation among children. Tuberculosis infection is often found against the background of various chronic pathologies. It has been established that the activation of opportunistic, especially herpetic, infections increases the risk of infection with MBT. Tuberculosis, in turn, has a clinically more severe course against the background of secondary immunodeficiency. In childhood, the immaturity of the immune system is added, which in turn can also serve as a prerequisite for the progression of the tuberculosis process. A so-called vicious circle is formed - a persistent, latent herpes infection leads to the appearance of an immunodeficiency state, in turn, mycobacterium tuberculosis – contributes to the further deepening of immunological dysfunction, which leads to the development of the syndrome of violation of anti-infective protection and creates the basis for the progression of the tuberculosis process. Currently, the actual goal of scientific research is to establish the specific weight of herpesvirus infections among tuberculosis patients, their impact on the occurrence, spread and course of various forms of tuberculosis, the study of virological, immunological and clinical-epidemiological aspects of the problem of co-infection of tuberculosis and herpesviruses. The resolution of the issue of combined infection as a new aspect of tuberculosis can play a decisive role in the effective diagnosis and prediction of the severity of the course of tuberculosis in childhood at the current stage and will improve the epidemiological situation with tuberculosis in general.

Keywords. tuberculosis, herpes viruses, co-infection, a new aspect of tuberculosis

In the second half of the 20th century, there was an assumption about the possible complete disappearance of infectious diseases from our planet by the end of the century. These predictions turned out to be wrong, and infectious diseases not only did not disappear from the planet but are leading to an intensive attack on humanity. Infectious diseases, especially in recent years, began to occupy one of the leading places among human diseases. In the conditions of socio-economic changes, and deterioration of the ecological situation, most infectious diseases took a severe course with often fatal consequences. Diphtheria and tuberculosis have returned from previous years. In April 1993, the World Health Organization (WHO) declared tuberculosis a problem of worldwide concern [1].

The last decades were characterized by the deterioration of the epidemiological situation with tuberculosis. Every year in the world, 7 to 10 million
people are diagnosed with tuberculosis for the first time, about 3 million of whom die. As you can see, over a hundred years of studying and fighting tuberculosis infection, humanity has not achieved significant success. The total number of tuberculosis patients reaches 50-60 million. About 95% of TB cases and 98% of TB deaths occur in developing countries. At the same time, 75% of patients are persons from productive population groups (18-55 years old). If the tuberculosis control system does not improve, experts predict that almost 1 billion infected people will be registered in the world, 200 million people will get tuberculosis, and about 40 million will die from this disease [2].

In Ukraine, where a tuberculosis epidemic has been registered since 1995, the tuberculosis incidence rate has increased by 2 times in recent years and was equal to the rate of 75.6 per 100,000 populations; the death rate increased by 2.2 times, which is 20.5 per 100,000 populations. Every hour in Ukraine, 4 people fall ill with tuberculosis, of which one patient dies. The number of severe and neglected forms of tuberculosis has increased, and multi-resistant tuberculosis has appeared. In recent years, the average age of tuberculosis patients in Ukraine has been decreasing, while it is constantly increasing in developed countries. Among the persons who contracted tuberculosis for the first time, 17% are workers, 3.6% are workers in the agricultural sector, 4.3% are civil servants, and almost half of them (2%) are medical workers, 4.1% are students and students 40% of all patients are people of working age who do not work, 15.3% are pensioners. In general, socially unprotected verst is make up more than 60% [3].

The increase in the incidence of tuberculosis in adults in recent years leads to negative changes in the epidemiological situation among children. Tuberculosis infection is often found against the background of various chronic pathologies. After the decline of the endemicity, the main role in the incidence of tuberculosis is not exogenous, but endogenous infection. Other diseases affect the incidence of tuberculosis. Mortality from tuberculosis and morbidity largely depends on the effectiveness of treatment measures, infection and morbidity – on preventive measures.

In recent years, quite diverse and complex combinations have been observed in the development and interrelationships between tuberculosis and other chronic pulmonary and non-pulmonary diseases, as a result of which new complex patterns of diseases are formed, which are not only more difficult to recognize, but also the schemes of anti-tuberculosis therapy, which are traditionally used, turn out not to be effective In all cases of the development of tuberculosis against the background of other diseases and, conversely, the development of diseases against the background of tuberculosis, its course and prognosis are modelled in the same way as it models the course and prognosis of another infectious process. In such cases, questions arise: is there a causal relationship between tuberculosis and other diseases; which of the diseases at this stage of the simultaneous course is the leading one, and how do the various relationships of both diseases affect the general prognosis, etc.? [4]

Recently, the combination of tuberculosis, AIDS and drug addiction is increasingly common. This combination is not a simple summation of pathological conditions, but the emergence of a qualitatively new pathological complex. It
requires a fundamentally different understanding of the significance of the problem not only by medical specialists but also by the entire world community. These problems have become especially important in Ukraine, which has taken a leading place among the countries of Eastern Europe in terms of the dynamics of the development of HIV/AIDS, drug addiction and tuberculosis epidemics [5].

At the same time, the atypical course, the frequency of non-pulmonary localization, and the combination with other opportunistic diseases make it difficult, and sometimes impossible, to diagnose the tuberculosis process promptly, which affects the implementation of adequate therapy, as well as the quality and life expectancy of patients. When immunodeficiency deepens, anergy increases and tuberculin tests completely lose their diagnostic significance. The results of an X-ray examination also depend on the degree of immunosuppression, on the course of tuberculosis in the form of a mixed infection.

The elimination of any infectious agent is the result of the interaction between defence forces of the macroorganism and infectious agents. Antimicrobials will be of little or no effect in immunocompromised individuals, especially in cases where microbes have the capacity to become antibiotic resistant. This is relevant not only to tuberculosis but to almost all infectious diseases, especially those with a sluggish course, relapsing, and those that tend to become chronic.

Tuberculosis is one of the diseases in which changes in the body's reactivity become important. The development of both pulmonary and extrapulmonary tuberculosis, its course and outcome depend not only on the massiveness and virulence of the pathogen but to a greater extent on the state of the organism's reactivity. A few data indicate that the tuberculosis process begins only in an organism with reduced initial reactivity. Thus, the importance of the primary reactivity of the body in the development and course of the tuberculosis process is clearly visible under the influence of factors on the body that suppress the body's ability to resist the disease, intercurrent diseases, poor living conditions, low social status, operations, a difficult environmental situation, etc. During this period, the tuberculous process, which runs imperceptibly, can intensify and turn into manifest forms.

In favour of the fact that a decrease in primary reactivity is a factor that contributes to the emergence of tuberculosis, the peculiarities of the course of tuberculosis in early childhood and old age speak. Under unfavourable conditions (violation of immune homeostasis) at any age of a person, latent tuberculosis infection leads to endogenous reactivation of old primary tuberculosis foci with the development of secondary tuberculosis.

According to the current understanding, alveolar macrophages and various subpopulations of T cells play a key role in the formation of immunity to tuberculosis infection. The outcome of the interaction between macrophages and tuberculosis mycobacteria depends on the balance of the antimicrobial activity of phagocytic cells and the resistance of mycobacteria to the bactericidal action of macrophages. At the same time, type 1 T-helper cells play an important role in the generation of antimicrobial activity [6]. The functional activity of macrophages can be different in different people, thus affecting the risk associated with MBT implantation and their ability to lead to the development of infection. If the macrophage is “weakened”, then
mycobacteria multiply inside it. A macrophage "overflowed" with mycobacteria bursts, and the mycobacteria leave it.

Studies of indicators of cellular immunity revealed that the course of tuberculosis infection is associated with the development of secondary immunodeficiency syndrome. The presence of immunodepression causes an increase in the frequency of rapidly progressing forms of tuberculosis and the formation of multidrug resistance. In addition, the state of immunodeficiency leads to a violation of repair processes in the postoperative period, which significantly reduces the effectiveness of surgical treatment [6].

In recent years, convincing evidence has appeared in favour of the fact that immunosuppression can be formed during chronic viral infections, which last throughout life. The list of viruses that cause long-term immunosuppression will increase due to pathogens that have the property of long-term persistence in the cells of the immune system. In full, the above applies to herpes viruses (HS). The development of persistent infection in humans is due to genetic factors, primarily the activity of immune resistance factors, which determine the sensitivity and immune reactions to exogenous HBV infection and the specifics of its development. Hormonal changes, B-cell activation, etc. are the factors that activate the persistent virus. One of the main mechanisms of persistent HBV infection is the integration of their DNA and the DNA of the host's cells. By methods of specific hybridization, the HV genome was found in blood cells, splenocytes, etc. Immunosuppression or immunostimulation activates the persistent virus with the transition of the infectious process to the acute stage, the manifestation of the clinical picture and the appearance of serological markers of the IgM type. Changes in the synthesis processes of cellular DNA, RNA, and proteins are of great importance in the activation of persistent GVs. Viruses can be activated and replicated under the influence of superinfection [7].

The possibility of GV reproduction in T- and B-lymphocytes, as well as in human macrophages, is shown. A virus that has penetrated the cells of the mononuclear phagocyte system (MSF) can cause an abortive infection in them, against the background of which a depression of phagocytic activity and a loss of Fc receptors have been detected. Viral RNA was detected in T-helpers and T-suppressors in the remote periods of convalescence. GVs enter into direct interaction with immunocompetent cells. At the same time, the functions of virus-damaged cells are selectively disrupted. Thus, it has been shown that GVs change such functions of the cells of the mononuclear phagocyte system as the completion of phagocytosis, the processing of antigens, their presentation to Th for further recognition, the formation of cytokines, direct and indirect cytotoxicity. Thus, herpes virus infections (HVI) and immunological insufficiency are interconnected and interrelated problems [8].

Recently, the concept of "virus-induced antigen-specific immunomodulation" (AI) has been formed in the literature, which is characterized by the fact that the immune system of an infected organism changes the nature of the response to antigens unrelated to the infectious agent. Virus-induced suppression of the immune response or its enhancement changes the host's response to a variety of pathogenic microorganisms, including mycobacterium tuberculosis. VAI was first...
described in 1908 by Pirke, who showed inhibition of the skin reaction to tuberculin in patients with measles. AI disrupts the mechanisms of immunological surveillance, which leads to the development of immunopathological processes, which is manifested in the features and nature of post-vaccination and post-infection immunity. It is because of this that AI should be taken into account when studying the manifestations of diseases of viral and bacterial aetiology.

However, the acquired immunodeficiency state is the result not only of HIV infection. Long-term herpesvirus persistence also leads to a virus-induced immunodeficiency state. Representatives of the Herpesviridae family (HHV 1-8) are representatives of lymphotropic DNA viruses. Today, several mechanisms of the immunosuppressive effect of herpesviruses are known, which in many respects coincide with the processes underlying the immunopathogenesis of tuberculosis. One of the most severe forms of herpes infection that develops in immunocompromised individuals is pneumonia. Herpesviruses, like Mycobacterium tuberculosis (TB), infect macrophages and dendritic cells, which under the influence of infection reduce the production of interleukin-12 (IL-12), which can disrupt the functional activity of the Th 1 response and lead to a more severe course of the tuberculosis process. This assumption is supported by the results of a pilot study, according to which patients with pulmonary tuberculosis had a concomitant subclinical infection caused by herpes simplex virus (HHV 1, HHV 2) in 40% and cytomegalovirus (HHV 5) in 53.3% of cases, as well as mixed herpesvirus infections in 40% of cases. It has been established that the activation of opportunistic, especially herpetic, infections increases the risk of infection with MBT. Tuberculosis, in turn, has a clinically more severe course against the background of secondary immunodeficiency. In childhood, the immaturity of the immune system is added, which in turn can also serve as a prerequisite for the progression of the tuberculosis process. A so-called vicious circle is formed: a persistent, latent herpes infection leads to the appearance of an immunodeficiency state, in turn, mycobacterium tuberculosis – contributes to the further deepening of immunological dysfunction, which leads to the development of the syndrome of violation of anti-infective protection and creates the basis for the progression of the tuberculosis process.

However, studies aimed at studying the immunosuppressive potential of herpesviruses in the context of association with MBT are isolated and mainly concern the pathogenetic effect of cytomegalovirus on tuberculosis. Research on the features of the tuberculosis process in modern conditions in children infected and not infected with herpes viruses in Ukraine is completely absent [9].

The functioning of the immune system is a chain of successive intercellular interactions. That is why the formation of an adequate anti-infective response is possible only with the full functioning of all its components and the normal activity of immunocompetent cells.

The reason for violations of the processes of immunological regulation is the ability of viruses to reproduce in the cells of the immune system – B-lymphocytes, T-cells, natural killers, and cells of the mononuclear phagocyte system. The fate of infected immunocompetent cells is not the same. On the one hand, it is their elimination because of the cytopathic action of viruses or the destructive action of the effector mechanisms of immunity, which perceive infected cells as foreign
because of the expression of viral antigens on their surface. On the other hand, viruses cause a chronic process without cytopathic changes, when immune cells turn into a reservoir of viruses that are not recognized by the body’s immunological surveillance system, with subsequent development of persistence and damage to SMF cells. This leads to the emergence of an immunodeficiency state as a result of functional defects of immunocompetent cells and damage to individual links of the immune system [10].

Research by scientists is mainly aimed at determining specific immune disorders that lead to the development of clinical manifestations of GVI or tuberculosis and the degree of their influence on the course of either a viral or bacterial process. There are quite a large number of such works both in the field of virology and in the field of phthisiology. Currently, the actual goal of scientific research is to establish the specific weight of herpesvirus infections among tuberculosis patients, their impact on the occurrence, spread and course of various forms of tuberculosis, the study of virological, immunological, and clinical-epidemiological aspects of the problem of co-infection of tuberculosis and herpesviruses. The resolution of the issue of combined infection as a new aspect of tuberculosis can play a decisive role in the effective diagnosis and prediction of the severity of the course of tuberculosis in childhood at the current stage and will improve the epidemiological situation with tuberculosis in general.

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