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Immunological Aspects of Chronic Rectifiing Herpestic Stomatitis

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Annotation. Modern views on the pathogenesis of chronic recurrent herpetic stomatitis are considered. It has been demonstrated that pathology can be characterized as a chronic multifactorial recurrent process with signs of combined secondary immunodeficiency with damage to the T and B components of immunity, suppression of the functional activity of NK cells and monocyte and macrophage cells, as well as damage to immunoregulatory changes in the immune system. In any of these cases, the herpes simplex virus has a chance to survive, mutate and, finally, be hidden.

Key words: chronic recurrent herpetic stomatitis, herpes simplex virus, herpes virus.

In recent decades, against the backdrop of growing immunodeficiency, allergic and autoimmune diseases, increasing the number of socially significant infections and infectious diseases. A major medical problem is the sluggish chronic inflammatory processes associated with the persistence of infectious elements of a viral nature [1-4]. Herpes infection is the most common and poorly controlled. Diseases due to herpes simplex virus (HSV), as the cause of death from infectious diseases of the second place (15.8%) after the flu (35.8%) [5].

The significance of these diseases is just that, beginning with the passage of time, they can become a disseminated form, even lead to disability. It has long been known that HSV is involved in carcinogenesis, secondary infertility, damage to the nervous system and internal organs [6]. Herpetic stomatitis is an acute infectious disease, the causative agent of which is HSV, widespread in nature, transmitted by contact or airborne droplets. The source of the infection is a sick person or a virus carrier [3, 7-9]. One of the mechanisms opposing the actual protective factors of immunity against viruses is the persistence of the latter in tissues that are not subject to immune surveillance. Cells that make up the stroma of data, I class HLA (the main complex of human histocompatibility) and are normally anatomically protected from virus multiplication [3]. The main reservoir of latent herpetic infection is the neurons of regional ganglia of sensory nerves [10].

Existing differences in infection of epithelial cells and lymphocytes of HSV. In epitheliocytes, the virus undergoes complete replication with the formation of a large number of virions, lysis of epithelial cells and subsequent infection of neighboring cells. With the infection of B-lymphocytes in only a small number of cells, the virus replicates, and in the remaining - is in a latent state [11, 12]. In the early stages, infection of T and NK cells with the development of a chronic infection with the persistence of the virus in lymphocytes throughout the whole life is possible [13]. The ability to persistence, despite the high immunogenicity, is that the virus produces a mechanism for escaping from the immune response [14].

Herpetic stomatitis clinic is directly related to the state of the body's immune system, which directly affects the development of the herpes infectious process by increasing or decreasing the activity of one or another of its components. Conversely, in patients with herpes simplex type 1 and 2, there are always some manifestations of immunodeficiency. This allows us to treat herpetic infection as a disease of the immune system [15]. Secondary (recurrent) herpesvirus infection occurs at any age after primary herpes has been transferred [16]. The manifestations of chronic recurrent herpetic stomatitis may be different - from asymptomatic viral or mild symptoms to very painful drainage ulcers [17]. Since relapses occur in the presence of antiviral antibodies in the blood serum, they occur with a slightly pronounced common infectious syndrome [16].

Macrophages play a central role in immune defense and are involved in both nonspecific and specific immune responses against HSV infection. They respond to viral infections by the rapid secretion of pro-inflammatory cytokines, which are important for primary protection [18-20]. On the other hand, with unfinished phagocytosis, HSV has the potential for intracellular persistence, which contributes to the emergence of mature extracellular forms of the virus in the focus of infection and causes a high contagious disease.

Polymorphonuclear leukocytes are also involved in the immune response in HSV and play a limiting role in the spread of HSV to sensory ganglia [21]. The defeat of polymorphonuclear leukocytes with herpesviruses disrupts their function and leads in combination with other factors to disruption of adaptation reactions [22]. Depression of enzyme activity of these leukocytes aggravates immunodeficiency, and also contributes to the preservation of activity of the pathological process [22, 23]. Reducing the reserve metabolic capacity of peripheral blood polymorphonuclear leukocytes during the period of clinical remission may be one of the reasons for the relapse of the disease [24, 25].

Numerous studies indicate the occurrence of secondary immune deficiency in patients with herpetic stomatitis, which is most often caused by a decrease in

the number of cells of the immune system or their functional insufficiency or imbalance in components of the immunoreactivity system [1].

Currently, chronic recurrent herpetic stomatitis is considered in some cases as an infectious (acquired) disease of the immune system, in which a prolonged persistence of the virus is accompanied by a productive infection of HSV in virtually all types of cells of the immune system, which is manifested by their functional insufficiency and contributes to the formation of immunodeficiency.

The production and secretion of proinflammatory cytokines (interferons-IFN-a / p, interleukins-IL-1, 6, 8, tumor necrosis factor-TNF-a) are among the earliest events in HSV infection [26] and influence subsequent specific immune response. Recurrent lesions on the skin and mucous membranes caused by HSV are infiltrated by macrophages and CD4 + and CD8 + T lymphocytes that secrete cytokines [27].

Cytokines, especially TNF-alpha, and possibly IL-6 may play a role in the elimination of the virus, as well as in maintaining the homeostasis of the nervous system through the repair and protection of neurons from damage. Elimination of signs of the disease against the background of the use of anti-cytokine antibodies (IL-1 and TNF-a) indicates the importance of these cytokines in the pathogenesis of recurrent disease [28].

TNF-a plays a leading role in antiviral immunity. Sufficient evidence has been obtained of the interferon-enhanced effect of TNF-a [29]. One of the possible mechanisms for the cooperative action of TNF-a and IFN-y is the ability of the latter to regulate the expression of TNF-a receptors. TNF-a is involved in the activation of T-lymphocytes, species-specific enhancement of the proliferation of lectin and antigen-reactive T-lymphocytes, increasing the expression of IL-2 receptor. In addition, TNF-a is one of the most effective factors, the effect of which extends to the activation of apoptosis, which is especially significant in viral infections [30].

The interferon and cytokine status register decrease in the production of stimulated IFN-y for recurrent herpes infection, indicating that depletion of antiviral defense mechanisms, and the tendency to overproduction of IL-4, indicating the presence of inflammation [31]. Hyperproduction of stimulated IFN-y in atypical herpetic infection may be due to a slight but constant antigenic stimulation [32].

The frequency of recurrence of the disease is related to the degree of reduction of IFN-y lymphocyte synthesis and NK-cell cytotoxicity [33]. The duration of the acute phase of inflammation is directly dependent on the

production of IFN-a. A direct correlation was found between the depth of disturbances in the IFN system and the cytotoxicity of NK cells and the severity of the course of the disease, primarily the rate of recurrence. It is shown that in patients with rare relapses (1-2 times per year) and in a part of patients with a moderate frequency of exacerbations (up to 3-4 times per year), immunity disorders are transient. Deep changes in the immune system that correspond to the secondary immunodeficiency state are observed with frequent manifestations of HSV (6 or more times per year) [34].

In patients with HSV infection, along with an adequate response to the activation of HSV cell type found paradoxical type when humoral activated in response to the aggravation of the infection [33, 34]. The mechanism of action of antibodies on infected cells is associated with the suppression of the release of the virus into the environment, which in turn limits the spread of the virus, but does not release the human body from it [34, 35]. Despite the significant content of specific antibodies in the blood and saliva, reactivation of HSV again leads to a relapse of the disease. Humoral immune mechanisms bind extracellular viral particles, connecting with the virus, block its receptors, change the physicochemical properties of the surface structures of the virion. As a result, the virus loses its ability to adsorb on a sensitive cell and penetrate it. In addition, there is agglomeration of virions and their opsonization, which promote and accelerate phagocytosis, stimulate the production of interferon by lymphocytes [35]. Many researchers associate the protective effect of antibodies with the activation of complement-mediated lysis and antibody-dependent cellular cytotoxicity against infected cells. A high content of virus-specific antibodies can not lead to the inactivation of a viral infection [36]. Perhaps the level and speed of a specific humoral response are factors that determine the prevalence of the virus [37].

Exacerbations always occur against the background of activation of humoral immunity. The level of its indicators directly depends on the frequency of relapses of the disease. Some researchers believe that humoral immunity plays an important role in relieving the relapse of the infection, but does not prevent it [38]. Along with this, there is an original point of view explaining the role of immunoglobulins in pathogenesis [39]. It is based on the fact that the result of each manifestation of the disease is a sharp increase in antibody titers. Despite the fact that immunoglobulins in the serum have high rates and outside the activation of the viral process, with relapses, the antibodies not only do not protect from exacerbation, but play a paradoxical role, participating in the formation of pathological immune complexes or the development of allergic reactions.

Sometimes antibodies do not provide a protective effect, but, on the

contrary, stimulate the infection, reversing its action against the cell. The immunoglobulin G molecule in NK cells can non-specifically bind to cells through receptors for the Fc fragment and provide a close contact between the cell surface and the viral envelope, thereby facilitating the entry of the virus into the cell [40].

Consequently, in patients with chronic recurrent herpetic stomatitis, there is a combined secondary immunodeficiency with violation of the T- and B-links of immunity, suppression of the functional activity of NK cells and monocyte-macrophage-number cells, as well as impaired immunoregulatory changes in the immune system. Therefore, with chronic herpetic stomatitis, the immune response is either quantitatively and qualitatively incomplete, or not specific enough. In any case, HSV gets the opportunity for survival, mutation and, ultimately, latency [41].

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