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THE PATHOGENESIS OF RHEUMATIC FEVER

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Annotation: Group A β-hemolytic streptococci cause postinfectious sequelae (including acute rheumatic fever/rheumatic heart disease) associated with the immune response. Acute rheumatic fever and rheumatic heart disease are global problems. The streptococcal response causes autoimmune reactions that target the heart, joints, brain, skin, and subcutaneous tissue. The recently modified Kissel-Jones criteria remain relevant for the diagnosis of the disease with population risk stratification and include subclinical carditis detected by echocardiography as the main criterion. The article examines the connection of molecular mimicry with streptococcus in the pathogenesis of rheumatic fever **.**

Key words: molecular mimicry, streptococcus, autoimmune reactions.

Acute rheumatic fever (ARI) and its corollary, rheumatic heart disease (RHD), cause significant morbidity and mortality in developing countries, but are not recognized as global health problems [1]. Recent advances in the scientific research of ORI and RYU have led to alternative hypotheses regarding the pathogenesis of ORI, newly revised diagnostic criteria for the disease. These scientific advances have been reflected in the World Heart Federation (WHF) [1], World Health Organization (WHO) [2] and other international agencies declaring their commitment to end CVD.

URI incidence peaks in children between 5 and 15 years of age and is rare beyond the age of 30, with approximately 60% of individuals infected with URI in endemic communities later developing URI [8, 9]. The incidence of ORI is the same in boys and girls, but the risk of RHYuK is 1.6-2.0 times higher in girls [10]. According to the most recent estimates of the global prevalence of RYuC, 9 million disabilities, 33 million common cases and 275,000 deaths occur each year, mostly in low- and middle-income countries [7–8].

The fact that acute rheumatic fever usually occurs in children between the ages of 5 and 15 years is explained by the high prevalence of streptococcal A infections of the throat and skin in this population. After untreated streptococcal infections, 3% of cases provide the risk of developing ORI; however, the risk of recurrence is greater than 50% in young children who have experienced a previous episode of URI [4].

Acute rheumatic fever affects the heart (carditis), joints (arthritis and arthralgia),

brain (Sydenham's chorea), skin (erythema annulare) and subcutaneous tissue (subcutaneous nodules) is an organ inflammatory disease [6]. Although episodes of ORI can cause significant short-term disability, the main effect is that it often causes long-term irreversible damage to rheumatic heart valves and causes rheumatic heart disease [7].

The epidemiological situation related to the spread of streptococcal infection and post-streptococcal diseases has been maintained throughout the world in recent decades. According to the World Health Organization, more than 616 million cases of streptococcal pharyngitis are reported annually in the world [2020.]. Group A beta-hemolytic streptococci (BGS) are the most common cause of infectious disease morbidity and mortality and are one of the major human pathogens. Worldwide prevalence of severe BGS infection has affected 18.1 million people. At the same time, in recent years, epidemics of scarlet fever have been recorded in many countries.

Despite the important achievements of the measures to combat RI, the statistics of rheumatic fever, changes in clinical manifestations and distribution continue to resemble the disease with epidemics. And, in turn, a new approach is required to treat and prevent RI. In the developing countries of Africa and Asia, the level of RI is still high, while in the countries of North America and Europe, the level of RI is low. In the United States, which has the most favorable medical and statistical indicators, an epidemic of ORI occurred in 1985-1997 among soldiers recruited at a military base in San Diego (California) and later among children in incontinent states (Utah, Ohio, Pennsylvania). It is noted that the majority of cases were diagnosed with ORI. After careful analysis of the situation, the following reasons for the spread of ORI in the United States were determined [14–16]:

• weakening of doctors' vigilance;

• due to the fact that it is a rare disease (in the USA), there is insufficient information about the clinical symptoms of the acute stage of the disease;

• delay in providing qualified medical assistance in full examination and treatment of patients with streptococcal pharyngitis;

• change in virulence of streptococci ("rheumatogenicity").

In Russia in 1998, RYuK caused the death of 8687 people out of 140 million people. In 2002, ORI was diagnosed for the first time in Russia at 1.9 per 100 thousand population, RYUK - 7.0 per 100 thousand population [2,9].

The pathogenesis of acute rheumatic fever is associated with the production of antibodies, which are characteristic of autoimmune diseases and are the result of the body's immune response to group A streptococcal infection. Cross-reactive antigens are group A streptococcal molecules that are "host ” molecules and induce an autoimmune response against host tissues during infection or immunization [3,4]. Molecular mimicry is a term used to describe the immunological cross-reactivity

between a "host" antigen and bacteria [6, 7, 15].

The pathogenesis of acute rheumatic fever is associated with autoantibodies characteristic of autoimmune diseases, which are the result of an immune response specific to group A streptococcal infection. The sharing of host and streptococcal epitopes results in molecular mimicry between streptococcal and host antigens. The use of modern antibacterial, immunocorrective, anti-inflammatory drugs, on the one hand, led to a decrease in the severity of carditis, and on the other hand, it led to the appearance of vague forms of this disease (Nasonova VA, 2001; Filipchenko EM, 2004). The result of these changes in the clinical course of rheumatism was a critical evaluation of diagnostic criteria and the emergence of a new classification of rheumatic fever (Nasonova VA et al., 2004).

Molecular mimicry between “host” antigens and bacteria was initially identified as identical amino acid sequences shared by various molecules present in tissues and bacteria [10–17], such as the alpha helix like the streptococcal M protein. molecules and the host proteins myosin, keratin, tropomyosin, vimentin, and laminin, which share regions containing 40 percent identity.

Currently, much attention is being paid to the study of the clinical significance of soluble adhesion molecules, neopterin, cytokines and their soluble receptors, which are involved in the development of inflammation and heart failure in many diseases of the immune, hemostasis, and connective tissues. It is known that at the onset of acute rheumatic fever, there are significant disturbances in cellular immunity: there is an increase in the concentration of IL-1, neopterin and soluble cytokine receptors.

The effect of cytokines in the coagulation relationship of hemostasis is carried out by cells involved in the production of procoagulants. IL-1 and TNF-α have been found to have a stimulating effect on endothelial cells, which leads to the expression of tissue factor. Activation of a cascade of pro-enzymes in the presence of tissue factor leads to thrombin generation, platelet activation and fibrin deposition (Wharram BL et al., 1991; Seghatchian MJ, Samama MM, 1996). Increased thrombus formation can be one of the important factors in the development of rheumatic endocarditis, which leads to the formation and development of rheumatic heart diseases (Harris E N., 1990; Bobkov VA, Lebedeva AV, 1997).

In the last decade, intercellular interactions have been extensively studied, which are based on signaling mechanisms mediated by cytokines. Adhesive interactions between platelets and leukocytes are the leading links of the mechanisms that ensure the migration of leukocytes to the injured area and the development of immune and reparative reactions there. The interaction of leukocytes, platelets and endothelial cells is a key link in the formation of an adequate balance between hemostatic and inflammatory reactions in tissue damage.

With the development of inflammation, immunocompetent cells release reactive

oxygen species, which leads to a decrease in antioxidant protection, which can lead to uncontrolled lipid peroxidation and membrane damage (Byshevsky AM, 1999; Pankin VZ et al., 2000). An excess of free radicals can stimulate the extramyocardial production of cytokines, which contributes to increased tissue hypoxia and disruption of oxidative processes (Pankin VZ, 2000; Belenkov Yu.A., 2001).

In recent years, the prevalence of acute rheumatic fever has decreased dramatically in developed countries due to the widespread use of antibiotics and improved socioeconomic conditions. However, high rates of disease persist in developing countries, particularly among populations with low socioeconomic status. In our country, acute rheumatic fever occurs regularly, and their diagnosis and treatment often face serious difficulties.

The emergence of an autoimmune reaction against basal ganglia antigens is based on the molecular mimicry hypothesis, which suggests that antigenic determinants of streptococcus and certain groups of neurons in the basal ganglia are similar, which leads to the appearance of interacting antibodies [11, 14]. Immunological studies show that the occurrence of an autoimmune reaction in rheumatic fever may depend on the M-protein located on the surface of streptococci. Antibodies to specific M-protein epitopes have been shown to interact with cardiac muscle and basal ganglia tissue [7, 9]. M-protein is highly variable and serves as a marker of individual serotypes of group A beta-hemolytic streptococci. According to another hypothesis, streptococcal infection leads to hyperproduction of some intracellular neuronal antigens that are inaccessible to the immune system and metabolic diseases, which leads to a violation of the tolerance of immune cells to the nervous system.

Rheumatic heart damage occurs in 23-84% of patients (in recent years, the use of echocardiography has significantly improved the detection of heart pathology). Studies of human mAbs from rheumatic carditis and Sydenham's chorea Antibodies against the group A streptococcal carbohydrate epitope GlcNAc can trigger the onset of carditis and rheumatic heart disease in cardiac valves and neuronal cells in the brain. T cells present in the rheumatic valve recognize cardiac myosin and streptococcal M protein epitopes and enter the valve through the activated endothelium, leading to a Th1 response in the valve.

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