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MODERN PROSPECTS FOR THE DIAGNOSIS AND TREATMENT OF ACUTE RHEUMATIC FEVER

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Abstract:

Introduction. Despite significant progress in reducing the incidence, acute rheumatic fever (ARF) has been observed in all countries of the world over the past decades. Determining the features of the course of the disease is important for timely diagnosis, which requires a thorough analysis of clinical, laboratory and instrumental data.

Purpose of the work. Improving the diagnosis of children with acute rheumatic fever based on the analysis of anamnestic data and the clinical course of rheumatic fever in children in the Samarkand region.

Materials and methods. The prospective study involved children aged 5 to 16 years who were treated at the multidisciplinary clinic of the Samarkand State Medical University in 2023. Clinical and anamnestic features of ARF in children from the Samarkand region were revealed. ARF was diagnosed according to the Kissel-Jones criteria. It was studied: indicators of a clinical blood test, data of biochemical analyzes, bacteriological studies, C-reactive protein (CRP), rheumatoid factor (RF), ASLO, the level of cytokines in the blood; data analysis of instrumental research methods: ECG, Echo-KG, ultrasound of internal organs.

Results. Most of the 112 patients (82.5%) with ARF were hospitalized between September and April, with a peak hospitalization in December. Articular syndrome occurred in 48 (42.8%) children. Arthritis was noted in 24 (21.4%) children and arthralgia in 40 (35.7%). Polyarthritis was characterized by a migratory character . In 28 (25%) children, chorea was noted. Among 24 patients with chorea, 4 ARF were diagnosed as isolated chorea, and 17 children developed chorea in combination with other manifestations of ARF. Erythema annulare 4 (3.57%) children. Rheumatic nodules were not detected in our study . ECG changes in children with carditis: tachycardia was observed in 28 (25%) children, sinus arrhythmia - in 29 (25.9%), bradycardia - in 16 (14.2%) children. Prolongation of the PQ interval, which refers to the small criteria for ARF, was observed in 8 (7.1%) patients. Echocardiography revealed tachycardia, mitral regurgitation in 68 (60.7%) children, a combination of mitral and tricuspid regurgitation in 41 (36.6%) children, and aortic regurgitation in 2 child .

Conclusion. Our study shows the need for further research to improve the diagnosis and treatment of ARF. The significant rate of misdiagnosis in children with ARF upon admission to the hospital indicates that doctors need more research in our region and awareness of primary care physicians.

Keywords: acute rheumatic fever, criteria Kiselya -Jones, children, clinical and anamnestic features, cytokines.

Acute rheumatic fever (ARF) is a post-infectious complication of tonsillitis (tonsillitis) or pharyngitis caused by group A beta-hemolytic streptococcus (GABHS), manifested as a systemic inflammatory disease of connective tissue with a predominant localization in the cardiovascular system (carditis), joints (migratory polyarthritis), brain (chorea) and skin (ring-shaped erythema, rheumatic nodules). ARF as a disease was known already in the 5th century. BC. For a long time, doctors believed that inflammation in the joints was caused by some toxic liquid spreading throughout the body. This is where

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the original name of the disease came from – "rheumatism" (from the Greek "rheumatismos" - flow of fluid). Damage to the cardiovascular system was considered a complication of articular syndrome. Only after the publication of the outstanding works of the French doctor J.-B. Bouillaud and Russian doctor G.I. Sokolsky (1836) identified rheumatism as an independent disease involving heart damage. ARF is one of the few rheumatic diseases whose etiology has been precisely proven. According to the figurative expression of academician. A.I. Nesterov, who stood at the origins of the domestic rheumatological school, "without streptococcus there is neither rheumatism nor its relapses." The introduction of diagnostic, treatment and prevention systems contributed to a widespread decline in the incidence of ARF by the mid-twentieth century, but in developing countries it still remains a widespread disease. Moreover, at the end of the 80s of the twentieth century. outbreaks of ARF have been recorded in Japan and several US states among wealthy segments of the population, as well as "a truly dramatic increase in streptococcal infections" in developed countries [2–3]. This trend has not spared the Russian Federation either. Thus, in 2002, an outbreak of ARF incidence was registered in the Khabarovsk Territory. In Moscow, since 2003, there has been an increase in the prevalence of ARF. In addition, with long-term observation, the rates of primary detection of chronic rheumatic heart disease (CRHD) do not decrease. The dissociation between the prevalence of ARF and CRHD may indicate the predominance of latent forms of ARF, which often remain unrecognized.

Back in 1889, W. Cheadle drew attention to the fact that the chances of developing ARF in a person with a family history of this disease are approximately 5 times higher than in those without it. This fact was confirmed by later studies, which showed that hereditary predisposition to ARF is not of a simple monogenic nature. Studies of global gene expression, carried out in vitro on human cell cultures after their activation by various bacteria and in vivo on mice, demonstrated the unique ability of GABHS to induce massive expression of genes for cytokines, apoptosis and cytotoxicity, and activate macrophages as in the classical , and by alternative mechanisms. Despite many years of work in this area, the task of identifying genetic markers of predisposition to ARF is far from complete. There are suggestions that some molecules of the major histocompatibility complex class II (HLA-DR4, HLA-DR53), polymorphism of immune response genes (tumor necrosis factor-α gene - TNF-α; immunoglobulin Fc- gamma-RIIA; Toll-like receptors responsible for the innate antibacterial immune response) [4], however, specific alleles or nucleotide sequences associated with ARF have not yet been identified. The most reliable marker of predisposition to ARF is currently recognized as the surface antigen of B lymphocytes D8/17, which has been studied, among other things, by domestic authors [5]. It has been shown that the content of D8/17-positive B cells in patients with ARF is much higher than in healthy people, including in regions endemic for GABHS infection, however, the role of D8/17 in the pathogenesis of autoimmune reactions also remains unclear. The sensitivity and specificity of the classical Kisel-Jones criteria, traditionally used for diagnosing ARF, according to some authors, were insufficient, especially in regions with a high prevalence of the disease. Thus, in some cases of the disease, atypical manifestations of articular syndrome are possible - damage to small joints of the hands and feet, asymptomatic sacroiliitis, more often in young men. Against the background of pronounced arthritis or minor chorea, the clinical symptoms of carditis can be weakly expressed, which was described by V.N. Anokhin [6] and G.H. Stollerman [7]. In addition, with a small degree of valvular regurgitation ("0+, silent, but significant" [8]), rheumatic valvulitis may not be accompanied by a characteristic noise on auscultation of the valve (subclinical carditis). An important aid for the doctor in such cases is the method of echocardiography (EchoCG). EchoCG criteria for rheumatic endocarditis of the mitral valve are as follows [9]: club-shaped marginal thickening of the mitral valve; • hypokinesia of the posterior mitral leaflet; • mitral regurgitation; • transient dome-shaped diastolic bending of the anterior mitral leaflet. Rheumatic endocarditis of the aortic valve is characterized by: • marginal thickening of the valve leaflets; • transient prolapse of the valves; • aortic regurgitation. The World Health Organization (WHO) has proposed a number of signs of valvular regurgitation in rheumatic valvulitis, allowing it to be differentiated from physiological regurgitation [8]: • length of the regurgitation jet >1 cm; • regurgitation must be fixed in at least 2 positions; • in color Doppler mode, the speed of the mosaic volume of regurgitation is · 2.5 m/s; • regurgitation persists throughout systole (mitral valve) or diastole (aortic valve). However, the EchoCG method for ARF was classified by WHO as only an additional method and was not included in the modified Jones criteria [8]. This approach has been criticized by a number of authors. Thus, in 2006, in the National Guidelines of Australia and New Zealand for the diagnosis, treatment and secondary prevention of ARF [10–11], EchoCG signs of subclinical valvulitis were recognized as a "major" diagnostic criterion for ARF (even in the absence of a characteristic murmur).) in a group of patients at high risk of developing the disease (indigenous population). At the same time, in addition to the blood flow

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indicators characterizing valvular regurgitation, signs are also taken into account that make it possible to clarify the rheumatic genesis of changes in the valves: a combination of mitral and aortic lesions, the direction of the mitral regurgitation jet is posterior, multiple jets of mitral regurgitation, significant thickening of the valve leaflets, the occurrence of deformation of the anterior mitral leaflet in the form of an elbow or a dog's leg. In the Kisel-Jones criteria modified by the Association of Rheumatologists of Russia in 2003, mitral and/or aortic regurgitation is among the "minor" instrumental criteria for diagnosing ARF (see table). To date, such a GABHS-associated disease as poststreptococcal arthritis remains insufficiently studied. In some patients whose first episode of the disease proceeded as a persistent, recurrent monoarticular lesion with a weak effect from salicylate therapy, signs of rheumatic valvulitis were subsequently revealed during dynamic observation. In addition, in one of the recent studies, in 19 patients who had poststreptococcal arthritis, D8/17 expression was higher than in the control group [12]. As a result, patients with post-streptococcal arthritis, formally satisfying the Kisel-Jones criteria (with the exception of carditis), are currently considered as patients with ARF with all the ensuing consequences regarding treatment and prevention. An important role in the diagnosis of ARF is played by confirmation of respiratory GABHS infection - a positive bacterial culture from the throat or a rapid test to determine the group GABHS antigen. When carrying out a retrospective diagnosis of past infection, serological studies are indispensable to detect elevated or (more importantly) increasing titers of antistreptococcal antibodies - antistreptolysin-O (ASL-O) and antideoxyribonuclease B (anti-DNase B). Treatment of ARF is traditionally based on the early administration of complex therapy aimed at suppressing streptococcal infection and the activity of the inflammatory process, which helps prevent the development or progression of heart disease. Despite the long-term use of penicillin-group drugs in clinical practice, most GABHS strains remain sensitive to them, which makes semisynthetic penicillins, including those combined with β-lactamase inhibitors, the drugs of choice for sanitizing the focus of streptococcal infection. In cases of intolerance to penicillin drugs, one of the macrolide antibiotics or lincomycin is prescribed. Nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed for mild carditis, rheumatoid arthritis without valvulitis, minimal activity of the process after the subsidence of high activity and withdrawal of glucocorticosteroids (GCS), with the re-development of ARF against the background of an already formed heart defect. It is preferable to use modern drugs - type 2 cyclooxygenase inhibitors. GCS is prescribed for ARF complicated by severe carditis and/or polyserositis, more often in children. In case of isolated chorea, the use of corticosteroids and NSAIDs is practically ineffective; in this situation, the use of psychotropic drugs - antipsychotics or tranquilizers from the benzodiazepine group - is more indicated; in case of severe hyperkinesis, the use of anticonvulsants is recommended. With the development of cardiac decompensation as a consequence of acute valvulitis (usually in childhood), the use of cardiotonic drugs is inappropriate, since in these cases a clear therapeutic effect can be achieved only with the use of high doses of prednisolone. In patients with recurrent development of ARF due to RHD, when choosing drugs used in the treatment of chronic heart failure, their possible interaction with anti-inflammatory drugs should be taken into account. The most important and integral role in the management of patients with ARF is played by secondary prevention of relapses of the disease, first developed by the domestic rheumatology school under the leadership of Academician. A.I. Nesterova. For this purpose, long-acting penicillin preparations (benzathine benzylpenicillin) are used, administered intramuscularly once a month, with the course duration individually determined for each patient [13]. A significant component of complex therapy for patients who have suffered ARF is the sanitation of foci of streptococcal infection, primarily chronic tonsillitis. The use of conservative therapy does not always give the desired effect, therefore, for persistent decompensated variants of chronic tonsillitis, tonsillectomy is indicated, which is performed in the subacute period of the disease, i.e. no earlier than 3–4 months after the start of the attack. All patients who have suffered ARF are subject to clinical observation by a rheumatologist. At a minimum, annual monitoring of indicators of inflammatory activity, the severity of valvular pathology of the heart and hemodynamic status is carried out. In conclusion, I would like to note that in the 21st century. The problem of ORF still remains relevant. This is confirmed by the regular appearance in the periodical literature of more and more new articles devoted to both general issues of pathogenesis and descriptions of specific clinical examples of the disease [14]. It is expected that the main attention of researchers in the coming years will be focused on the mechanisms underlying the predisposition to the development of ARF. Their detailed study will give impetus to the development of highly sensitive diagnostic tests and new treatment methods, including gene therapy, and the creation of a specific streptococcal vaccine containing epitopes of M-proteins of "rheumatogenic" GABHS strains that do not cross-react with tissue antigens of the human body.

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