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IMPROVING EARLY DIAGNOSIS AND TREATMENT OF ACUTE RHEUMATIC FEVER IN CHILDREN

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Abstract:

Introduction. Despite significant progress in disease reduction, acute rheumatic fever (ARF) has been observed in many countries of the world in recent decades. Determining the course of the disease requires a complete analysis of clinical, laboratory and instrumental data and is very important for timely diagnosis.

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

Materials and methods. During the research, children aged 5 to 15 who were being treated in the multidisciplinary clinic of Samarkand State Medical University in 2023 participated. Clinical and anamnestic characteristics of ARF were determined in children from all districts and cities of Samarkand region. ARF was diagnosed according to the Kissel-Jones criteria. Data studied: indicators of clinical blood analysis, biochemical analysis data, bacteriological studies, C-reactive protein (CRP), rheumatoid factor (RF), ASLO, amount of cytokines in blood; data analysis of instrumental research methods: EKG, Exo-KG, ultrasound analysis of internal organs.

Results. Most (75%) of the 108 patients with ARF were hospitalized between September and April, with the highest rate of hospitalization in December. Articular syndrome was observed in 45 (41.67%) children. 21 (19.44%) children had arthritis and 39 (36.1%) had arthralgia. Polyarthritis was characterized by migratory character. Chorea was recorded in 25 (23.15%) children. Among 22 patients with chorea, 3 ARF were diagnosed as isolated chorea, and 16 children developed chorea in combination with other manifestations of ARF. Annular erythema in 3 (2.77%) children. Rheumatic nodule was not detected in our study. ECG changes in children with cardia: tachycardia was observed in 26 (24.07%) children, sinus arrhythmia - 27 (25%), bradycardia - 14 (12.96%) children. Prolongation of the PQ interval, indicating minor criteria for ARF, was observed in 7 (6.48%) patients. Echocardiography revealed tachycardia, mitral insufficiency in 66 (61.1%) children, combined mitral and tricuspid insufficiency in 40 (37%) children, aortic insufficiency in 2 children.

Conclusion. Our study highlights the need for careful analysis of further research to improve the diagnosis and treatment of ARF. The significant rate of misdiagnosis in hospitalized children with ARF suggests that physicians in our region need to conduct more research and primary care physicians need to receive adequate training in this disease.

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), in the form of 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), developing in predisposed individuals, mainly young people (7–15 years), due to the body's autoimmune response to streptococcal antigens and their cross-reactivity with similar autoantigens of the listed affected individuals human tissues (the phenomenon of molecular mimicry). Despite the significant advances

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achieved during the second half of the last century in the treatment and prevention of ARF, in recent years it has become obvious that the problem is far from over and remains relevant today. This disease constantly reminds itself of itself with new outbreaks, unexpected turns in statistical indicators, and the originality of clinical manifestations, which pose new questions for researchers in solving differential diagnostic problems and require different motivations in the choice of therapy and prevention.

As for epidemiology, the recently observed favorable situation with ARF in developed countries is by no means a reason to rest on our laurels. Suffice it to recall how inattention to the diagnosis and treatment of pharyngeal infections caused by group A betagemolytic streptococcus (GABHS) and ARF in the United States led to the fact that in this country in the mid-1980s. A number of epidemic outbreaks of the disease have been recorded. At the same time, the incidence of ARF has increased 5–12 times in more than half of the states. With the collapse of the USSR, the incidence of ARF increased sharply in a number of former Soviet republics, reaching 234 cases per 100,000 children in Kyrgyzstan [1]. At the beginning of the 21st century. A trend towards an increase in the incidence of ARF was noted in Italy and the Eastern Mediterranean. In developing countries, the incidence of ARF remains high, predominantly among disadvantaged populations. Among the indigenous people of Australia, the primary incidence of ARF reaches its maximum values compared to other regions of the world – 504 per 100 thousand population [2]. The "global burden" of ARF among children 5–14 years old amounts to 337 thousand new cases annually. When extrapolated to all age categories, this figure rises to 471 thousand per year. The annual increase in the number of patients with chronic rheumatic heart disease (CRHD) worldwide ranges from 15.6 to 19.6 million patients. The global annual mortality rate from CRHD is 1.47%, reaching a maximum in the countries of the Asian region – 3.28% [3]. According to the State Statistical Report, in the Russian Federation in 2014, the primary incidence of ARF was 1.7 per 100,000 children aged 0–14 years and 2.6 per 100 thousand of the total population. At the same time, in the North Caucasus Federal District (FD), these parameters were significantly higher – 12.1 and 8.3, respectively. The prevalence of CRHD in 2014 was 11.7 and 118.3 per 100 thousand population in these age categories, respectively. At the same time, the maximum values of these indicators were also registered in the North Caucasus Federal District - 93.6 and 200.2 per 100 thousand population, respectively. These data cannot but be alarming [4]. Understanding the causes of wide variations in the incidence of ARF and CRHD within communities and between regions is critical not only to combating current epidemics, but also, more importantly, to preventing future outbreaks in populations where the incidence is currently low. In all likelihood, variability in the frequency of ARF and, as a consequence, CRHD may be due to the changing epidemiology of GABHS infections of the pharynx, both in general, and the predominance of highly virulent ("rheumatogenic") A-streptococcal strains in particular. At the same time, the potential for "rheumatogenicity" of A-streptococcus is by no means directly related to certain M-serotypes, as was demonstrated during recent outbreaks of ARF in Africa and Oceania. It seems necessary to dwell on the widely discussed clinical aspects of ARF, the understanding of which allows not only to correctly predict the course of the disease, but also to formulate rational therapeutic tactics that influence its outcome. It is generally accepted that carditis is the leading syndrome of ARF, which determines the severity and outcome of the disease. The fundamental component of carditis is considered to be valvulitis (mainly of the mitral valve, less commonly of the aortic valve), clinically manifested by an organic heart murmur. Heart damage such as isolated myocarditis in the absence of valvulitis is considered uncharacteristic of ARF. This is confirmed by the following data. No increase in the concentration of markers of myocardial damage - creatine phosphokinase (CPK)-MB fraction, cardiac troponins I and T, as well as myoglobin. Normal indicators of left ventricular systolic function and myocardial contractility on echocardiography Radionuclide scanning of the heart using technetium and indium did not reveal any evidence of myocardial damage. Endomyocardial biopsy did not confirm the presence of myocarditis. Normalization of heart size and reverse development of signs of congestive heart failure in patients unsuccessfully receiving aggressive anti-inflammatory therapy only after mitral or aortic valve replacement. Pathomorphological changes in rheumatic carditis are localized mainly in the subepicardial, subendocardial areas, as well as in the perivascular interstitium, practically without affecting cardiomyocytes. Aschoff-Talalaev nodes - an immunopathological marker of rheumatic lesions - contain lymphocytes, macrophages and giant cells; at the same time, the nodes lack cells and derivatives of myocardial origin (actin, myosin, desmin).

Based on the above, it is believed that the development of congestive heart failure in ARF is due to acute volume overload resulting from mitral and/or

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aortic regurgitation, but not myocarditis per se [5]. In this regard, the descriptions of cases of so-called non-rheumatic post-streptococcal myocarditis that have appeared in the literature in recent years deserve special attention, the main symptoms of which include: young age of patients previous GABHS/GABHS infection of the pharynx short latent period (3–5 days) intense cardialgia (due to which such patients are often hospitalized in the intensive care unit with a presumptive diagnosis of myocardial infarction) increased levels of troponin I, CPK -MB fractions, antistreptolysin-O (ASL-O) ST segment elevation on the electrocardiogram (ECG) no signs of valvular pathology with echocardiography (EchoCG) results of magnetic resonance imaging (MRI) of the heart with contrast, which allows detecting inflammatory changes in the myocardium (increased contrast concentration associated with myocardial edema) absence of pathology during coronary angiography good response to antibacterial therapy favorable prognosis. According to the vast majority of authors, the above symptoms are not any subtype of ARF, but, on the contrary, represent a separate nosological form, like non-rheumatic myocarditis of a different etiology (in particular, viral), which is based on direct damage to myocardial structures. The problem of neurological disorders in ARF remains no less important. Thus, certain difficulties in recognizing the disease arise with a frequent combination of functional tics and symptoms of minor chorea in children with consequences of perinatal pathology, which allows us to talk about the comorbidity of these conditions, as well as with the development of post-streptococcal neurological disorders. At the end of the 20th century. a specific syndrome is described, designated by the acronym PANDAS (Pediatric Autoimmune Neuropsychiatric Disorder associated with group A Streptococcal infection - pediatric autoimmune neuropsychiatric disorder associated with infection caused by group A streptococcus). The characteristic signs of this syndrome are: 1) obsessive-compulsive disorders - (OCD, obsessive thoughts + obsessive movements); 2) onset of the disease in the prepubertal period (up to 12 years); 3) acute onset and paroxysmal course; 4) a proven chronological connection with a previous GABHS infection of the pharynx, confirmed by microbiological (isolation of the pathogen in a throat smear) and serological (increased titers of ASL-O and anti-DNase B) methods; 5) neurological abnormalities (hypermotility, choreiform hyperkinesis). Prescription of adequate antistreptococcal antibiotic therapy (penicillins or oral cephalosporins) led to rapid regression of neuropsychiatric symptoms in such patients. Since its description, PANDAS has become a very popular conceptual model among practitioners and researchers. However, numerous attempts to establish its frequency among children with tics and OCD have been unsuccessful. The pathogenesis of the disease remains unclear and real diagnostic biomarkers have not yet been identified. Significant difficulties have arisen in confirming the relationship between repeated GABHS - pharyngeal infections and exacerbation of tics or OCD during the further course of the disease. In addition, in these patients, no correlations were found between the presence of antibodies to the basal ganglia, increased cytokines in the cerebrospinal fluid and exacerbation of neurological symptoms. The issue of long-term prophylactic use of antibiotics, as required for patients with rheumatic chorea, remains unresolved. In this regard, many authors emphasize the need for further research to determine the clinically defined post-streptococcal syndrome and distinguish it from the mass of acute pediatric neuropsychiatric disorders [6–8].

For many years, the diagnosis of ARF has been based on the Kisel-Jones criteria, which are a unique diagnostic tool that has stood the test of time. Priority in developing criteria belongs to the largest domestic pediatrician A.A. Kisel, who gave a brilliant description of the main manifestations of this disease, calling them the absolute symptom complex of the disease. These include polyarthritis, cardiac damage, chorea, erythema annulare, and rheumatic nodules. Somewhat later (1944), criteria for recognizing ARF were formulated and published by the American researcher T.D. Jones. Subsequently, they were modified several times (1956, 1965, 1984, 1992) by the American Heart Association (AHA). The results of research in recent years have prompted AKA experts to once again revise these criteria [9]. At least three circumstances were considered as the reasons for this: the epidemiological situation with ARF, the clinical polymorphism of the disease, as well as the active and widespread introduction of echocardiography into widespread clinical practice. In October 2015, at the Federal State Budgetary Institution NIIR named after. V.A. Nasonova held a round table during the annual scientific conference, during which leading rheumatologists of the Russian Federation discussed the significance of these criteria and the possibility of their application in our country. Detailed materials from the round table were published in the available literature [10]. Within the framework of this article, I would like to focus the reader's attention on the following. Recognizing the undoubted merit of the developers - AKA experts, it

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should be emphasized that this version of the revised Jones criteria is an undoubted step forward in improving the diagnosis of ARF. The authors proposed the principle of variability in the application of criteria in populations with low and high risk of ARF, substantiated the expediency of introducing the term "subclinical carditis", presented detailed EchoCG criteria for rheumatic valvulitis, characterized the definitions of repeated attacks of ARF and the "possible" diagnosis of the disease. At the same time, when analyzing AKA criteria, at least 2 questions arise, unambiguous answers to which do not lie on the surface. Firstly, regarding the different approach to diagnosing ARF depending on the degree of risk in the population. On the one hand, the authors' desire to eliminate overdiagnosis in populations with a low incidence of ARF and underdiagnosis in high-risk populations is understandable. On the other hand, in countries within which there are sufficient differences in the incidence of ARF and CRHD, for example in the Russian Federation, the application of the above principle seems practically impracticable. Secondly, a shift in diagnostic emphasis towards echocardiography is completely justified, primarily when recognizing subclinical carditis, and also due to poor knowledge of cardiac auscultation techniques, in particular among young doctors. However, with such an approach, especially in cases of subclinical carditis as the only major criterion, high-quality echocardiography and accurate interpretation of the data obtained by an experienced specialist are of course important. Otherwise, the frequency of diagnostic errors may increase significantly, especially since making a clear distinction between ARF and CRHD based on EchoCG criteria alone is not always possible. Here I would like to note that EchoCG signs of mitral and/or aortic regurgitation have already appeared in the domestic classification of ARF since 2003 as minor diagnostic criteria . It should be noted that a number of provisions contained in the new recommendations deserve approval. First of all, this concerns the need to take into account the risk of developing ARF in each patient, taking into account the epidemiological situation in the region of his residence. An equally important point is the need to verify valvulitis as a manifestation of subclinical carditis using Doppler EchoCG, as well as a more attentive attitude to the analysis of articular syndrome in ARF. As before, a mandatory condition for diagnosing ARF is a confirmed connection between the clinical picture of the disease and a previous infection of the pharynx caused by group A beta-hemolytic streptococcus (GABHS), verified by microbiological and/or immunological methods. At the same time, certain provisions remain controversial. It is not always possible to clearly divide regions into high- and low-risk populations for the incidence of ARF. Concerns have arisen regarding the adequacy of including monoarthritis and/or polyarthralgia in the core criteria for ARF, even in a high-risk population. Existing EchoCG criteria do not always allow a clear distinction between subclinical carditis and CRPS. Overall, the revised Jones criteria have implications for regions with a high incidence of ARF. However, their use in the Russian Federation is problematic due to large interregional differences in the incidence of ARF. Making changes to the existing Russian classification and nomenclature of ARF seems premature. Without dwelling on the issues of therapeutic tactics for ARF in the conditions of modern reality, we consider it appropriate to highlight some aspects of its prevention. Currently, issues of high-quality primary prevention of ARF, primarily timely diagnosis and adequate antimicrobial therapy for GABHS tonsillitis/pharyngitis, are constantly in the focus of attention of national and international scientific medical associations. Thus, over the previous five years, updated versions of the recommendations prepared by expert groups of the AHA and the American Academy of Pediatrics [12], as well as the Infectious Diseases Society of America [13], were released. In accordance with current recommendations, penicillin antibiotics retain their role as the drugs of choice for the treatment of acute A-streptococcal pharyngeal infections. In conditions of increasing resistance of GABHS to macrolides, the latter should be considered only as an alternative means for the treatment of A-streptococcal tonsillitis and should be prescribed only to patients with an allergy to beta-lactams. Failure to comply with this requirement, i.e., the widespread use of macrolides as initial empirical therapy for GABHS infection of the pharynx, can lead to very serious consequences, including the development of ARF [14].

Antibiotics - lincosamides (lincomycin, clindamycin) also have high antistreptococcal activity, but they are prescribed for GABHS tonsillitis only in case of intolerance to both b-lactams and macrolides [15]. It should be noted that the use of tetracyclines, sulfonamides and co-trimoxazole for GABHS infection of the pharynx is currently not justified due to the high frequency of resistance and, consequently, low rates of treatment effectiveness. The prescription of early fluoroquinolones (ciprofloxacin, pefloxacin, ofloxacin, lomefloxacin) is not justified due to the low natural antistreptococcal activity of these drugs. Second generation fluoroquinolones (the so-called

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"respiratory" - levofloxacin, moxifloxacin), despite their high antistreptococcal activity, are not indicated for the standard treatment of GABHS infections of the pharynx due to a wide spectrum of antimicrobial action (which may serve as an incentive for the formation of resistance to these drugs from other infectious agents), a less favorable (compared to penicillin) profile of adverse drug reactions, as well as a higher cost. It is emphasized that in temperate climates in the winter-spring period, about 20.3% of school-age children may be asymptomatic carriers of pharyngeal GABHS infection. Moreover, against the background of GABHS colonization (which can last ≥6 months), the development of intercurrent viral pharyngitis is possible. In most cases of GABHS carriage, antibacterial therapy is not indicated. However, there are special situations in which the prescription of antibiotics is justified: 1) during an outbreak of ARF, post-streptococcal glomerulonephritis or invasive GABHS infections in a given region; 2) during an outbreak of GABHS tonsillitis/pharyngitis in closed and semi-closed groups (military units, boarding schools, etc.); 3) if there is a history of ARF in the patient or close relatives; 4) in a family whose members are overly concerned about GABHS infection; 5) when determining indications for tonsillectomy due to GABHS carriage. In these cases, 10-day courses of treatment with amoxicillin/clavulanate or clindamycin are appropriate. The use of benzathine penicillin (in some cases lifelong) still forms the basis of secondary prevention of ARF. Currently, the superiority of prescribing benzathine-penicillin according to the regimen once every 3 weeks has been proven. over its monthly introduction. In the literature of recent years, the possibilities of creating new dosage forms of benzathine penicillin based on nanotechnology, in particular microemulsions and micellar systems, have been actively discussed. It is believed that the introduction of these technologies will provide clear advantages, primarily regarding the pharmacokinetics of the drug, but this is a matter of the near future [16]. The previously widely practiced daily use of erythromycin in patients with a history of ARF and intolerance to beta-lactam antibiotics is currently inappropriate due to the widespread increase in resistance of A-streptococcus to macrolides. As an alternative, in this category of patients, timely course treatment with macrolides for each case of verified A-streptococcal tonsillitis/pharyngitis may be considered.

Despite the fact that new antibacterial agents that have appeared in recent years have significantly expanded the possibilities of antimicrobial therapy for GABHS tonsillitis, they have not completely solved this problem. In this regard, many researchers have high hopes for the streptococcal vaccine. The results of studies involving 30 healthy volunteers showed that the created recombinant vaccine against A-streptococcus stimulates the immune response without any signs of toxicity. According to the creators, it is capable of providing protection against most A-streptococcal strains, including those that cause acute tonsillitis, streptococcal toxic shock syndrome and necrotizing fasciitis. However, today the readiness for the active introduction of the GABHS vaccine seems to be quite low. Thus, in a survey conducted by American researchers among pediatricians, it turned out that in the absence of consent from parents, GABHS vaccination was recommended by only 40% of respondents .[17]. However, some authors believe that "the M protein approach to vaccine development has not provided the necessary breakthrough over the past 40 years." Therefore, the most promising way to create a GABHS vaccine seems to be the identification of new A-streptococcal components that are common to all strains and have immunoreactive properties. These components could presumably be other streptococcal cell wall proteins, glycoproteins, polysaccharides, etc.[18]. Thus, the problem of ARF remains truly multifaceted, relevant and inexhaustible. Many years of experience in monitoring patients of different age groups shows that ARF, changing its "appearance" following the solution of new problems, constantly raises new questions that require solutions in the near future.

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