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CARDIOVASCULAR DAMAGE IN PATIENTS WITH JUVENILE ARTHRITIS

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Abstract: The article is devoted to a review of the literature, which presents current data on the features of the cardiovascular system in patients with juvenile arthritis, as well as aspects requiring detailed study on this issue.

Keywords: juvenile arthritis, cardiovascular system, features of the lesion.

Juvenile arthritis (JA) is the most common childhood chronic rheumatic disease. Epidemiological studies show that RA leads not only to early disability, but also to a significant reduction in the life expectancy of patients. The mortality rate in RA is almost 70% higher than the average in the population, and in patients with severe RA, it is comparable to that in patients with three-vessel coronary artery disease, type 2 diabetes mellitus, lymphoproliferative tumors, and stroke. The risk of premature death in these patients is associated with severe disability, the presence of systemic manifestations, rheumatoid factor seropositivity [28, 29, 55, 67, 80].

Today, the possibilities of its diagnosis, treatment and rehabilitation in the world are at a fairly high level. However, the issue of dealing with long-term extra-articular consequences remains open, and the first place in the structure of mortality among patients with rheumatic diseases is occupied by damage to the cardiovascular system (CVS) [9,10].

The main cause of premature mortality in rheumatoid arthritis, according to most authors, is damage to the cardiovascular system (myocardial infarction, congestive heart failure, sudden cardiac death). The risk of mortality from cardiovascular diseases is high not only in patients with long-term rheumatoid arthritis, but also in the first years of the disease, especially in women seropositive for rheumatoid factor [29,30].

High cardiovascular risk in patients with RA is beyond doubt. Thus, in one of the latest meta-analyzes, a 50% excess of the risk of cardiovascular mortality in patients with RA was demonstrated [12]. In this regard, of particular interest is the study by H. Maradit Kremers et al., which convincingly proves that a severe systemic inflammatory process (persistent increase in ESR above 60 mm/h, rheumatoid vasculitis, rheumatoid lung disease or pneumonitis) is associated with a significant increase in the risk of death from diseases of the cardiovascular system [55].

In contrast to the adult population with rheumatoid arthritis (RA), there is little evidence of an increased cardiovascular risk in children with JA, especially those with a systemic variant of the disease. Patients with RA have a shorter life expectancy compared to the general population. Cardiovascular disease is the leading cause of death in this population [35,36].

In 2009, the European League Against Rheumatism (EULAR) presented its guidelines for screening tests for circulatory diseases in patients with RA and other forms of arthritis, according to which RA is a disease associated with an increased risk of developing cardiovascular diseases [51].

Currently, the issue of accelerated atherogenesis in patients with autoimmune diseases, in particular, with rheumatoid arthritis, is widely discussed [72,77].

According to recent studies, chronic inflammation is recognized as a risk factor for

atherosclerosis in patients with RA [18, 56]. The authors found that there is a correlation between inflammatory processes during RA and the development of atherosclerotic lesions. The synovial membrane in RA and atherosclerotic plaques has a pathological similarity. Similar mechanisms in the synovial membrane in RA and the development of atherosclerotic plaques include T and B cells, macrophages, adhesion molecules, pro-inflammatory cytokines: tumor necrosis factor (TNF) alpha, interleukin 1 (IL-1), interleukin 6 (IL-6) and chemokines [82].

This point of view is based on data from prospective studies that have demonstrated a clear association of a more severe course of atherosclerosis in young patients with an increase in the concentration of serum C reactive protein, as well as a significantly higher incidence of cardiovascular complications (myocardial infarction, stroke) in patients with rheumatoid arthritis compared with population. data [83, 84].

According to many studies, it is the cardiovascular complications associated with atherosclerotic vascular disease that are the leading cause of life expectancy reduction in rheumatoid arthritis [42,77].

In recent years, immunological markers of atherosclerosis have been intensively studied. These are, first of all, proteins of the acute phase of inflammation (CRP, serum amyloid A), indicators of immunity activation (pro-inflammatory cytokines, their soluble receptors, neopterin), organ-nonspecific autoantibodies (for example, antibodies to phospholipids and oxidized low-density lipoproteins) [3-73].

In most children, the degree of vascular damage is insignificant, and the rate of progression is slow. On the contrary, in chronic inflammatory diseases, including JA, it is suggested that the chronic inflammatory process plays an important role in accelerating atherosclerosis, which contributes to the development of cardiovascular diseases (CVD), including heart failure [40,47].

In addition, in recent years, coronary artery disease in rheumatological diseases often manifests itself at a younger age as a result of premature atherosclerosis. Together with the already known classical risk factors for CVD, systemic inflammatory molecules make an additional contribution to the progression of atherosclerosis. Over the past 15 years, the survival of patients with JA has continued to increase due to the emergence of new therapeutic agents, such as biologics. However, this result caused an increase in the prevalence of coronary heart disease. [8,10,15]

A meta-analysis of prospective studies indicates an increased risk of cardiovascular mortality in RA by 48% compared with the general population. This indicator is comparable to that in patients with type 2 diabetes mellitus (DM) [58]. The main causes of high mortality from CVC in RA are the accelerated progression of atherosclerosis and the development of chronic heart failure (CHF). The risk of coronary heart disease (CHD) and myocardial infarction (MI) in RA is increased by 2 times, cerebral stroke - by 1.9 times, CHF - by 1.8 times compared with the general population, and its significant increase was noted at the earliest stage of the disease. The results obtained at the FGBNU NIIR them. V.A. Nasonova confirm these data: in 40.3% of patients with RA, cardiac pathology was the main cause of mortality. Most often, CVCs develop in RA patients with low or moderate cardiovascular risk, according to the existing standard methods for its determination, but with high clinical and immunological activity of the disease [1]. CVCs caused by atherosclerosis in RA have features characterized by multivessel coronary artery disease, early relapses of acute coronary syndrome, increased mortality after the first MI, high frequency of "asymptomatic" MI, including even before the development of clinical manifestations of RA [6,54].

There was also a paradoxical relationship between body mass index (BMI) and cardiovascular mortality in patients with RA. A high BMI has a "protective" effect under

the condition of a low ESR, and a BMI deficiency, reflecting the severity of RA, is a risk factor for cardiovascular mortality [24].

In the light of the modern concept of the inflammatory nature of atherosclerosis, the study of the cardiovascular effects of HA is of undoubted interest [71]. Most randomized clinical trials have shown that in patients with RA, low doses of GCs for 1-3 years do not significantly increase cardiovascular risk, but long-term use of GCs leads to an increase in the risk of CVD. [68].

At the same time, morbidity and mortality in RA can be caused not only by complications associated with atherosclerosis, but also by other forms of pathology of the cardiovascular system - non-ischemic heart failure, microvascular dysfunction, cardiac autonomic neuropathy (an increase in the QT interval, a decrease in rrhythmia variability heart), cardiac arrhythmias [5,7,79].

It should be noted that the role of lipid and fat metabolism disorders in the development of cardiovascular catastrophes in RA patients has not been studied enough, and the clinical significance of TGF in the development of CVE in RA patients is "paradoxical" [24,60].

According to some authors, dyslipidemiais not asignificant predictor of cardiovascular mortality in RA.At the same time, the nature of changes in the lipid profile varies in different populations of RA patients and depends on the inflammatory activity and RA therapy [60, 62].

Indeed, inflammation is one of the important factors influencing and modifying the lipid profile in RA. It should be noted that the high inflammatory activity of RA is associated with low levels of lipids, in particular total cholesterol (TC) and low-density lipoprotein cholesterol (LDL), while adecrease in inflammatory activity during therapy with antirheumatic drugs may be accompanied by an increase in the level of total cholesterol and LDL [59]

In patients with RA, dyslipidemia is defined as higher total cholesterol and/or triglycerides and/or lower HDL.Dyslipidemiais dependent on disease activity, and the higher the disease activity score (DAS), the lower the total cholesterol level; however, the levels of the HDL fraction are reduced to a greater extent; therefore, the atherogenic index increases [62].

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It has been shown that in patients with high RA activity, the levels of cholesterol (CH) and low-density lipoprotein (LDL) cholesterol are lower than in the general population and inversely correlate with the concentration of inflammatory markers [83].

This pattern of changes in the lipid spectrum is called the "lipid paradox" and is associated with a high risk of cardiovascular accidents. The association between low LDL-C and high cardiovascular risk in RA is similar to the "paradoxical epidemiology" of cardiovascular risk factors in patients with end-stage CHF and chronic renal failure, in whom higher LDL-C was associated with better patient survival. This may be due to the fact that chronic inflammation plays an important role in the development of disorders in the blood cholesterol transport system and leads to changes in the quantitative and qualitative parameters of the blood lipid spectrum [25].

But high LDL-C is also associated with an increased risk of MI, suggesting the relevance of lipid-lowering statin therapy even against the background of effective anti-inflammatory treatment. [68]

Since it has become possible to determine CRP levels with a highly sensitive method, it has become possible to accurately detect low CRP levels indicative of mild inflammation, which is thought to contribute to the pathogenesis of atherosclerosis. Elevated levels of CRP are a risk factor for cardiovascular disease [74].

Studies in children with JA show different results [50], but cardiovascular complications in patients with JA are the second most common cause of death.

Pericardial, myocardial, or endocardial lesions are well-known conditions seen in patients with JA. The most common, as well as benign, lesion of the heart is pericarditis, which occurs in 30-36% of patients, although rarely endocardial and myocardial involvement contributes to morbidity and mortality from the disease [63,76].

Most patients with endocarditis have aortic regurgitation, others have mitral regurgitation, which may sometimes require valve surgery [45].

Myocarditis can be life-threatening with congestive heart failure and arrhythmias [63]. In addition to inflammation of the three layers of the heart, subsequent pericardial effusion and valvular problems are common in JA and are extra-articular manifestations [34]. Among them, pericarditis is most often affected, the frequency of which in JA is 30% [11]. Some authors consistently report pericarditis rates of 30-36%, even in the absence of overt clinical signs [13,64]. In the studies of some authors, neither clinical nor echocardiographic signs of effusion were found [14,34]. Myocarditis occurs in JA with a frequency of 1.2-10% [16, 31,46].

In patients with chronic active JA, myocardial fibrosis leads to a further deterioration in diastolic function. Thus, impaired myocardial relaxation may be due to various etiologies, including thickened and rigid pericardium, LV hypertrophy, fibrosis, coronary heart disease, and amyloid accumulation [31].

The defeat of the intermediate and small vessels of the myocardium leads to microinfarctions and ischemia, which causes a decrease in the function of the left ventricle; therefore, an increase in left ventricular filling pressure causes diastolic dysfunction. In addition, myocardial dysfunctions can cause a decrease in systolic function. [43].

Conduction system disorders are a significant cause of cardiovascular morbidity and mortality in patients with JA. According to the literature, conduction disturbances and sudden cardiac death are more pronounced in patients with rheumatic diseases than in

the healthy population [63]. In patients with rheumatological diseases, sudden cardiac death and arrhythmias are caused by myocarditis, coronary heart disease, vasculitis, myocardial ischemia, pulmonary hypertension, and arrhythmias. [43]

Prolongation of the QT interval (QT) is an early sign of ventricular arrhythmias and therefore a marker of cardiovascular morbidity and mortality. In patients with rheumatoid arthritis (RA), a longer QT interval was found compared to the general population [43].

Patients with RA have a high risk of death compared to the general population, with a standardized mortality ratio of approximately 2%. CVD is responsible for about half of the premature deaths in this group of patients. The high incidence of malignant arrhythmias may explain, at least in part, the high mortality observed in RA [38,80].

Rheumatoid factor is an independent risk factor for CHD both in RA patients and in the general population [23]. Recent studies have shown that the level of anticitrullinated antibodies (ACCP) in RA is independently associated with the development of CAD [48].The mechanisms of this relationship need to be clarified [39].Patients with RA are more likely to suffer from hypertension, obesity, but do not differ from the general population in the prevalence of diabetes mellitus or an increase in the level of CHLDL [17,57]. Age and hypertension correlate with increased cardiovascular risk in RA. There is an interrelation of these factors with the number of neutrophils and the radiographic index.

There is no doubt that the presence of systemic inflammation, an increase in the level of pro-inflammatory mediators (C-reactive protein, TNF-?, IL-6, IL-1), the level of which exceeds normal values in most patients with RA, affect the function of the endothelium, myocardium, insulin resistance. The blood concentration of C-reactive protein measured by highly sensitive assays (hsCRP) is an important predictor of mortality in patients with inflammatory arthritis. There are works proving that CRP carries independent prognostic information and supplements the data of traditional risk factors [69]. Presumably, CRP may be a link between inflammation, endothelial dysfunction, coagulation, and thrombosis. Thus, it has been established that CRP has a direct proatherogenic effect on the vascular wall, stimulating the production of cytokines and adhesion molecules, and also facilitating the uptake of oxidized LDL by cells of the monocyte-macrophage system. CRP increases in them the expression of cytokines, matrix metalloproteinase 1, and tissue factor, which initiates a cascade of serine proteases of the coagulation system [20,37].

An increase in cardiovascular risk in RA patients compared with the general population is a generally accepted fact. At the same time, the safety issues of the use of synthetic and genetically engineered biological drugs for the treatment of patients with RA remain debatable [53].

Indeed, high cardiovascular morbidity and mortality in RA cannot be explained only by the influence of CVR factors [32, 33], although they make a significant contribution to its formation in this category of patients [4,19.,22].

Such markers of damage to the cardiovascular system, such as endothelial dysfunction, decreased elasticity of small and large vessels, diastolic dysfunction of the myocardium of the left and right ventricles, are recorded in 35-50% of cases already in the early stages of the disease, and the severity of these changes increases with the duration of the disease. [2.41]. At the same time, morbidity and mortality in RA can be caused not only by complications associated with atherosclerosis, but also by other forms of pathology of the cardiovascular system - non-ischemic heart failure, microvascular dysfunction, cardiac autonomic neuropathy (an increase in the QT interval, a decrease in rhythm variability heart), cardiac arrhythmias [5,7,70,79]

The main reasons for the development of CHF in RA, in addition to ischemic

cardiopathy, include myocarditis, pathology of the microvasculature, and vasculitis of the coronary arteries [79].

The polymorphism appears to be associated with CV risk regardless of the presence of traditional cardiovascular risk factors [49,65]. Associations have been found between alleles of the common HLA-DRB1* 04 epitope and endothelial dysfunction [27] or CVD [26].In RA patients, genetic polymorphism has also been associated with dyslipidemia [66,75] and biomarkers of endothelial dysfunction such as asymmetric dimethylarginine [21], which has the ability to inhibit nitric oxide (NO) synthase.

It is critically important to timely identify the threat of their severe complications in patients with different types of JA even before the formation of the clinical picture [9].

Thus, the analysis of the available data indicates that the conducted studies mainly affect the adult contingent of patients with RA. Studies on the defeat of the cardiovascular system in various types of JA in children against the background of modern possibilities are practically absent or are controversial. There is very little evidence to suggest an increased cardiovascular risk in children with systemic-onset JA. Therefore, the study of the features of CVS lesions in children with JA with a systemic onset remains relevant.

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