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The Prognostic Importance of Clinical-Pathogenetic and Genetic Aspects of Kidney Damage in Systemic Lupus Erythematosus

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***Abstract*:** *Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease characterized by the presence of pathogenic autoantibodies, immune dysregulation and chronic inflammation, which can lead to an increase in morbidity and early mortality from end organ damage. More than half of all SLE patients develop lupus nephritis. Genetic association studies have identified more than fifty polymorphisms that contribute to the pathogenesis of lupus nephritis, including genetic variants associated with altered programmed cell death and defective immune clearance of residues. These variants can support the formation of autoantibody-containing immune complexes that contribute to the development of lupus nephritis. Genetic variants associated with lupus nephritis also affect the initial phase of innate immunity and the reinforcing, adaptive phase of the immune response. Finally, genetic variants associated with a renal-specific effector response may affect damage to end organs and progression to end-stage renal failure and death. This review discusses the genetic understanding of key pathogenetic processes and pathways that can lead to lupus nephritis, as well as the clinical implications of these findings in relation to recent advances in biological therapy.*

Key words: *SLE, lupus nephritis, genetics, immune response.*

Kidney damage in systemic lupus erythematosus (SLE) remains one of the most common, severe and prognostically important visceritis. The possibilities of modern immunosuppressive therapy, on the one hand, made it possible to reduce the proportion of patients with terminal renal insufficiency, and on the other hand, demonstrated the prognostic importance of kidney damage for the course of the disease as a whole [1-5]. With a random sample, 25-50% of patients with SLE have signs of kidney

damage at the beginning of the disease, and later they are diagnosed in almost 60% of adults and 80% of children [1, 5]. Kidney damage in SLE today appears to be multifaceted (Table 1).

Table 1. Variants of kidney damage in SLE

1. LUPUS NEPHRITIS
2. INTERSTITIAL NEPHRITIS
3. VASCULAR LESIONS

Undoubtedly, the above classification is conditional. It is rare to detect morphological and clinical signs of only one of the listed options. SLE is characterized not only by a multifaceted kidney injury, during the course of the disease; transformation of one variant into another is possible. This applies both to the morphological classes of lupus nephritis itself and to the combination or independent development of nephropathy due to vascular lesions [6-8]. Lupus nephritis is a paradigm (model) of immunocomplex inflammation, the mechanism of development of which reflects the pathogenesis of SLE as a whole. The basis of the disease is polyclonal hyperactivity of the B-cell system, manifested by uncontrolled production of antibodies, and / or defects in cellular self-regulation, leading to disruption of cell apoptosis and recognition process with loss of immune tolerance to its own antigens, primarily nuclear. Among the effector mechanisms of renal damage are complement, polymorphic cells, monocytes, their adhesion factors and attractant molecules, synthesis of cytokines, chemokines, eicosanoids, endothelins, etc., great importance is attached to damage by CD8- and CD4+ T cells and interstitial macrophages with the subsequent development of fibrosis and loss of peritubular capillaries. To date, a large number of antibodies to various fragments of nuclear structures have been identified. Their role in the pathogenesis of SLE is unequal, but it can determine the clinical features of the disease. Antibodies are directed against nucleic acids and proteins related to intracellular transcription and translation mechanism: their main targets are nucleosomes (DNA histones) or four antigens from their own chromatin, small nuclear ribonucleoproteins (sn RNP) and small cytoplasmic ribonucleoproteins (sc RNP). Antibodies directed against native DNA, Smith (Sm) antigen and C1q are considered to be diagnostically significant. Antibodies to double-chiral (native) DNA have the greatest specificity and pathogenicity. Potentially nephritogenic antibodies to the DNA of the IgG2b isotype are considered to trigger the classical complement activation pathway. In addition to antibodies to native DNA, importance is attached to other autoantibodies to various cellular structures. Thus, anti-Ro- and anti-C1q +-antibodies are associated with severe kidney damage. Antibodies associated with the development of antiphospholipid syndrome (AFS) – antiphospholipid antibodies (AFA) have a special effect on the clinical picture of the disease and the prognosis of lupus nephritis. AFA is a heterogeneous population of antibodies to antigenic determinants of negatively charged (anionic) phospholipids and/or phospholipid–binding (cofactor) plasma proteins. The AFA family includes: antibodies that cause a false positive Wasserman reaction, antibodies that react with cardiolipin (aCL) and other phospholipids, as well as the so–called lupus anticoagulant (VA) - antibodies that lengthen in vitro blood clotting time in phospholipid-dependent coagulation tests. Recently, it has become known that in the implementation of the interaction of AFA with phospholipids, the central role belongs to mutations of cofactor proteins: β2-glycoprotein 1 (β2-GP 1), prothrombin, X, XIII coagulation factor, proteins C and S, methyltetrahydrofolate reductase, etc. Polymorphism of genes of procoagulant proteins and natural anticoagulants can cause the development of macro- and microangiopathies and transform the clinical and morphological picture of nephropathy in SLE [1, 4].

The morphology of lupus nephritis is characterized by significant polymorphism both in different glomeruli and within one glomerulus and is characterized by proliferation of glomerular cells,

expansion and interposition of the mesangium, membranous changes, damage to the tubules and interstitium. Specific (although not pathognomonic) morphological signs for lupus nephritis are fibrinoid necrosis of capillary loops, nuclear pathology – karyorexis and karyopycnosis, sharp focal thickening of the basement membranes of glomerular capillaries in the form of "wire loops". An important element of the damage is intravascular thrombosis (fibrin and hyaline thrombi in the lumen of capillaries), possibly combined with the presence of AFA or immune complexes containing cryoglobulins. Immunohistochemistry reveals class G immunoglobulins, mainly IgG1 and IgG3; sometimes, however, IgA or IgM predominates clinically, lupus nephritis differs from bright nephritis in a peculiar manifestation and severity of the main nephrological syndromes. With "renal" masks of the disease, i.e. in cases of the debut of SLE with kidney damage, such features make it possible to suspect the underlying disease, and in the absence of morphological data, to assume the severity of kidney damage and choose an adequate treatment regimen. Features of the main nephrological syndromes in lupus nephritis Proteinuria is an absolute sign of lupus nephritis, is highly non–selective, and rarely reaches large values, as with bright nephritis. Nephrotic syndrome (NS) – with lupus nephritis does not have such a prognostic value as with bright nephritis. The 10-year survival rate in patients with NS and severe urinary syndrome is similar, with the exception of cases of the onset of the disease with NS. The peculiarity of the latter in lupus nephritis is the rarity of the development of hypovolemia, and the frequent combination of hypertension and hematuria in these patients suggests a frequent combination with acute nephritic syndrome. This explains the lower severity of NS in lupus nephritis and rare hypovolemic crises. Another distinctive feature of NS is a lower tendency to relapse than with bright nephritis. Hematuria is an important criterion for the activity of lupus nephritis, in 2-5% of cases there is macrohematuria. Leukocyturia is aseptic, with predominant lymphocyturia. Renal insufficiency – the growth rate of serum creatinine is of great importance.

A double increase in less than 3 months is a criterion for rapid progression. Acute renal failure is 5-10%. It should be particularly noted that, unlike bright nephritis, patients with lupus nephritis in the stage of chronic renal failure often have high activity of the disease, i.e. lupus nephritis does not always "burn out" even in the presence of clinical signs of uremia and other signs of renal tissue sclerosis, and many patients on programmed hemodialysis should receive immunosuppressive therapy. Arterial hypertension (AH) occurs in 60-70% of patients. The frequency of hypertension and the state of hemodynamics are closely related to the degree of activity of lupus nephritis. The damaging effect of hypertension on the kidneys, heart, brain and blood vessels in SLE is aggravated by autoimmune damage to these same target organs. Hypertension worsens overall and "renal" survival, increases the risk of death of patients from cardiovascular complications. The reversibility of an increase in blood pressure when remission of lupus nephritis is achieved also confirms the connection of hypertension in this disease with the activity of the process. Nephrosclerosis affects the blood pressure level only in cases when it reaches significant severity. The risk of developing steroid hypertension in patients with SLE is 8-10%, and with kidney damage – up to 20%. For the development of steroid hypertension, not only the dose is important, but also the duration of treatment with glucocorticoids (HA). With moderate activity of the process, APS acquires a special role as the cause of hypertension.

Genes of susceptibility to SLE associated with LN.

HLA-DR. The main region of the histocompatibility complex containing the human leukocyte antigen (HLA) gene is located on human chromosome 6. This locus contains more than 200 genes, many of which function in the immune system. The HLA class II region contains the HLA-DR, -DQ and –DP genes. They are highly expressed on antigen-presenting cells and are important for the activation of CD4+ T cells and other immune responses. Polymorphisms in the HLA region were among the first to

be detected as risk factors for SLE, and this locus remains the strongest common genetic risk factor for SLE [16].

The ITGAM gene is located on human chromosome 16. It encodes CD11b-integrin (Alpha-M), which is the subunit that makes up Alpha-M beta-2 integrin (also called complement receptor 3 or Mac-1). Mac-1 is highly expressed in granulocytes, macrophages and dendritic cells. Complement is one of the ligands, and iC3b-coated particles, such as apoptotic cells, induce phagocytosis by phagocytes through interaction with Mac-1. Mac-1 also controls the migration of leukocytes to the inflammatory focus and facilitates adhesion to the vascular endothelium [17].

FCGR

The locus of the FCGR gene is located on human chromosome 1 and encodes Fc-gamma receptors (FCGR). One of the key roles of FCGR is to remove immune complexes (ICs) [33], and FCGR2A and FCGR3A are expressed on antigen-presenting cells (for example, macrophages and dendritic cells). Defective clearance of apoptotic cells is detected in patients with SLE and is believed to contribute to the pathogenesis of the disease [19]. Violation of the corresponding phagocytosis will allow apoptotic cells to move to secondary necrosis, leading to the release of nuclear self-antigens, which should lead to greater formation of IR in combination with SLE-associated anti-nuclear antibodies. There is one high-affinity receptor (e.g. FCGR) and two low-affinity receptors (e.g. FcgR2A and FcgR3) that are activating FCGR, and there is one inhibitory FCGR known as FCGR2b. Each of these receptors has a different binding affinity to IgG subclasses and is present in most myeloid cells [36].

Genetic factors play an important role in the predisposition of patients with SLE to LN. The prevalence and severity of LN vary between individuals and ethnic groups, and there are some examples of differences in genetic factors predisposing to LN in different populations. Despite the identification of numerous genes of general predisposition to SLE, only a small number of these genes of general predisposition to SLE are associated with LN. It should be noted that the RR value for the genes of general susceptibility to SLE as risk factors for the development of LN was lower than their effect on SLE as a whole. This supports the idea that these common SLE susceptibility genes affect SLE more broadly than their effect on LN alone. The more recent discovery of kidney function genes that are specifically associated with LN is exciting and provides additional insight into the pathogenesis of LN. Apparently, the predisposition to LN includes a combination of genes of a general predisposition to SLE and genes with kidney function that are specifically associated with LN. Figure 3 shows some potential functional connections between the loci considered in this review. Moreover, the new generation sequencing method revealed not only a genome mutation, but also a posttranslational modification that can contribute to the pathogenesis of SLE and LN. Further epidemiological and functional studies will make it possible to better determine the relationship of these genes with the pathogenesis of LN and, probably, to identify additional loci of genes involved in this serious manifestation of the disease.

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