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Prognostic Significance of Clinical, Pathogenetic and Genetic Features Progression of Lupus Nephritis

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ABSTRACT:

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease characterized by the presence of pathogenic autoantibodies, impaired immune regulation and chronic inflammation, which can lead to an increase in morbidity and early mortality from damage to end organs. More than half of all patients with SLE 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 may contribute to the formation of immune complexes containing autoantibodies 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 kidney-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 discoveries in connection with recent advances in biological therapy.

Relevance and relevance of the topic.

Currently, lupus nephritis (LN), which is caused by systemic lupus erythematosus, is considered one of the urgent problems of the medical and social health system due to high disability and mortality, and the number of such patients is increasing day by day (1). Despite advances in nephrology, lupus nephritis is one of the most common manifestations of systemic lupus erythematosus, where the incidence of the disease is 40-60%. The importance of hemodynamic, metabolic and genetic factors in the development of lupus nephritis is currently being discussed. The role of genetic factors that cause the development of lupus nephritis is being studied with great interest. But the clinical, pathogenetic and prognostic significance of genes in patients with HF have not been fully studied and there is no unambiguous answer to the question of the genetic predisposition that causes the development of HF. According to the conducted studies devoted to this problem, currently the assessment of the role of genes in the pathogenesis of LP development requires in-depth study (2,3).

A number of studies are being conducted worldwide to assess the prognostic value of clinical, pathogenetic and genetic aspects of the development of lupus nephritis in patients with systemic lupus erythematosus. It is necessary to substantiate the prevalence and course of lupus nephritis in the Uzbek population, the influence of metabolic and hemodynamic factors on the development of the disease; the role of the Arg25Pro polymorphism mutation of the TGFß1 gene in the mutation of the transforming growth factor -β1 gene and the prevalence of C-159T polymorphism mutation of CD14 monocyte differentiation antigen and their alleles in the Uzbek population. Special attention should be paid to the study of the Arg25Pro polymorphism of the TGFß1 gene, which leads to mutation of the transforming growth factor- β1, and the differentiation of monocytes in the Uzbek population of patients with SLE, the predominance of alleles and genotypes of the polymorphism C159T of the CD14 mutant antigen, as well as the development of a diagnostic algorithm of informative genetic markers aimed at the formation of risk groups that cause the development of lupus- jade(4,5).

Given by foreign geneticists Melissa E. Munro and Judith A. James, the role of genes in the development of LN was emphasized. The TNFRSF1B, KLK1, KLK3, ACE, AGE, AGT, APOL1 genes have been found to be predisposing factors for the occurrence of intrarenal inflammatory

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process(7,8). Also in Europe, the IRF5, BLK, STAT4, and ITGAM genes have been identified as an important genetic factor in the development of VN. These results indicate that genetics plays an important role in the diagnosis of lupus nephritis (Ilana B. Richman, Kimberly E. Taylor, Sharon A. Chang, Laura Trupin, Michelle Petri, Edward Elin, Robert R. Graham, Annette Lee, Timothy W., Behrens, Peter K. Gregersen, Michael F. Seldin, Lindsay A. Criswell 2012) (6). The Q222R polymorphism of the DNase I gene has been identified as a risk factor in patients with LN in South India (D.Panner, P.T.Antony, V.S.Negi 2013).

Despite the fact that there is currently a lot of information about the significance of various genes involved in the development of VN, there is no clear understanding of the role of these factors. Therefore, it is urgently necessary to continue scientific research in this area. The development and implementation of new innovative methods for predicting the development of VN in our country is one of the important tasks of the healthcare system. They make it possible to assess the risk of developing the disease at an early stage, lengthen the period before dialysis, prevent early disability resulting from it and reduce mortality(10,12).

A purposeful approach to the development of the foundations of evidence-based medicine, including such important aspects as the development of formation mechanisms, effective diagnostic methods and their implementation in our republic, allows us to predict the risk of severity of the course of community-acquired.**The aim of the research** is to optimize the assessment of the influence of clinical pathogenetic and genetic factors on the development of lupus nephritis based on the results of a comprehensive analysis in the Uzbek nation(9,14).

The object of the research work in 2019-2021, the object of the study was 117 patients with SLE who were treated in inpatient and outpatient departments of cardiorheumatology, rheumatology and nephrology of the multidisciplinary clinic of the Tashkent Medical Academy. Also, 138 healthy individuals (108 genetic and 30 clinical studies) were selected for the control group.

The subject of the study. As the subject of the study, the results of EchoCG, dopplerography of renal vessels, genotype and alleles of the CD14 and TGFß1 genes in the blood plasma of patients with SLE were obtained.

Research methods. The study used clinical (general blood analysis, general urine analysis), biochemical (urea, creatinine, microalbuminuria, cholesterol, triglycerides, high-density lipoproteins, low-density lipoproteins, glomerular filtration rate), instrumental (dopplerography of renal vessels, ECHOCG), genetic (CD14 gene to determine polymorphisms of C159T and Arg25Pro gene TGFß1 used electrophoretic detection and statistical methods.

255 people took part in the study, of which 117 people made up the main group and 138 people (108 for genetic examination, 30 for laboratory and instrumental examination) were external to the control group. In turn, the main group was divided into 2 groups according to the type of case-control.Group 1 is a group of patients with SLE who did not develop HF (n=47), of which men n=4 (8.5%), women n=43 (91.5%), the average age was 36.4±1.9 years**.** Group 2 is a group of patients with SLE, with developed LV (n=70). There were 6 men (8.6%), n=64 women (91.4%), the average age was 36.7±2 years.

For the control group, DNA samples of healthy donors were taken from the DNA bank for laboratory and instrumental studies, blood of healthy individuals for genetic studies.

Before the start of the study, patients who applied to the hospital were selected, and all patients included in the study were examined on the 2nd day of inpatient treatment and on the 1st day of outpatient treatment. The studies were conducted from January 2019 to May 2021. Before the start of the study, the functional state of the kidneys in each patient was assessed by glomerular filtration rate (GFR) and creatinine concentration using the 2011 modification of the 2009 formula, and all the results were documented.

In order to study the influence of various factors on the pathogenetic mechanisms of the development of HF and changes in kidney function, biochemical (urea, creatinine, total cholesterol, triglycerides, high and low density lipoproteins, albumin), hemodynamic (echocardiography, dopplerography of renal vessels, mean blood pressure) included the determination of the results of genetic testing and evaluation of the obtained indicators.

Biochemical studies were carried out specifically by the following methods: microalbuminuria was checked by an indicator rapid test of a stick. All biochemical analyses were carried out in the central laboratory of the 3rd TTA clinic, and hemodynamic studies were carried out in the departments of functional diagnostics and nephrology. The EXOCG study was carried out using the traditional Simson technique on a 3.5 MHz sensor on a SONOSCAPE S20 ultrasound machine.

The glomerular filtration rate was determined by the formula SKP-EPI (ml/min/1.73 m2).

DNA isolation and analysis of polymorphic gene markers were carried out at the Center for Scientific and Practical Medicine of Hematology of the Ministry of Health of the Republic of Uzbekistan. In the process of molecular genetic

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research, electrophoretic detection methods were used to isolate DNA from peripheral blood lymphocytes. To control the population, DNA samples (n=108) of conditionally healthy donors (without SLE markers) were provided from the DNA bank of the Department of Molecular Medicine and Cellular Technologies of this center.

"Evaluation of the results of clinical examination in groups with developed and not developed VN" presents the results of biochemical and hemodynamic studies. Creatinine clearance index was used to evaluate GFR and select patients. In patients of groups 1 and 2 included in the study, biochemical parameters were studied, namely urinary microalbuminuria (MAU), biochemical blood analysis for urea, creatinine, cholesterol (HC), triglycerides (THL), high and low density lipoproteins (HDL, LDL) and GFR, as well as dopplerography of renal vessels, echocardiography (EchoCG) and indicators of average blood pressure.

According to the results of the study, a comparative analysis of the 1st and 2nd groups of patients was carried out, and in the 2nd group there was significantly greater excretion of MAU in the urine and amounted to 22.6±0.825 and 248.5±5.39 ($p < 0.05$), respectively. An increase in the amount of MAU in urine has a significant ($p<0.01$) positive correlation with the level of blood urea ($r=0.48$), creatinine ($r=0.49$) and the resistance index (IR) of renal vessels, and with GFR ($r=-0.75$) showed a significant negative correlation ($R<0.01$) (see Table 1).

Table 1

The ratio of biochemical parameters in groups of patients with systemic lupus erythematosus with and without developed lupus nephritis

Показатели	**1- группа**	**2- группа**
Age	36,4±1,9	36,7±2
Duration of the disease	8,5 ±0,927	8,6±0,84
MAU	22,6±0,825	248,5±5,39*
Urea	6,5±0,320	8,9±0,81*
Creatinine	65,3±2,445	99,4±9,23*
eGFR	103,8±3,134	86,6±3,93*
XC	6,2±0,081	8,6±0,27*
TG	2,1±0,047	6,8±3,64*
IDL	1,8±0,130	3,3±0,13*
LDL	3,17±0,096	2,1±0,08

Note: *- confidence level ($p<0.01$)

Urea, creatinine, and GFR values were determined in the study groups. Accordingly, when comparing the results of patients of the 1st and 2nd groups, a decrease in the above indicators of the functional state of the kidneys was observed and reliably recorded in the group of patients with developed lupus nephritis by 8.9±0.81, 99.4±9.23 and 86.6± 3.93, respectively. ($p<0.05$).

There was an increase in urea and creatinine in the blood with a decrease in GFR.

It was found that there is a significant ($p<0.05$) positive correlation between urea and creatinine ($r=0.63$) and a significant ($p<0.05$) negative correlation between GFR and urea and GFR and creatinine ($r=0.59$ and $g=0.74$, respectively).

The values of HC, TG, HDL and LDL in the blood were compared and analyzed between the groups. In the study of HC, TG, LDL between groups 1 and 2, it was noted that the above-mentioned indicators were higher in group 2 compared to group 1, and a significant difference was noted ($p<0.05$). There was an increase in the amount of LDL in the blood with a positive correlation with the vascular resistance index and pulse index ($r=0.22$, $r=0.18$) and a negative correlation between LDL and GFR ($r=-0.22$).

The functional state of the kidneys was assessed by studying the hemodynamics of the studied groups. The initial systolic velocity (Vmax), end-diastolic velocity (Vmin), resistance index (RI), pulse index (PI) and systolic diastological index (S/D) of interlobular blood flow were studied. Accordingly, when comparing groups 1 and 2, there was a significant decrease in renal blood flow in patients of group 2 ($p<0.05$). The decrease in blood flow positively correlated with RI 0.65±0.01-0.78±0.01*, PI 1.17±0.02-1.29±0.01* ($r=0.29$). A significant negative correlation ($p<0.05$) was noted with

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the end-diastolic rate, pulse index and systolic-diastolic index (see Table 2).

An increase in renal vascular resistance led to a decrease in GFR, that is, GFR had a significant negative correlation (p<0.05) with RI and a significant positive correlation (R<0.05) with Vmax (r=0.37).

Table 2

Indicators of dopplerography of renal vessels in groups of patients with systemic lupus erythematosus with and without developed lupus nephritis

Dopplerography of renal vessels Duration of the disease	**1- группа**	**2- группа**
Age	35,2±0,81	38,2±2,81
Duration of the disease	4,49±0,34	16,41±1,4
Vmax	0.48±0,02	0,42±0,02*
Vmin	0,17±0,01	0,11±0,01*
RI	0,65±0,01	0,78±0,01
PI	1,17±0,02	1,29±0,02*
S/D	2,03±0,02	2,21±0,02*

Note: *- confidence level (P<0.05)

Along with this, an increase in RI, PI and S/D indicators led to an increase in blood urea and creatinine, that is, there was a positive correlation at a reliable level (p <0.05). An increase in renal vascular resistance led to a significant (p <0.05) increase in urine MAU, that is, RI had a positive correlation with MAU (r=0.62). The resistance index (RI) and pulse index (PI) in the renal vessels positively correlated with the end-diastolic volume of the left ventricle (BDO) and the end-diastolic size of the left ventricle (CDR) at a significant level (p<0.05) (r=0.25, r=0.33, r=0.25, r=0.32 respectively).

In addition, an increase in renal vascular resistance was reflected in an increase in blood pressure, namely, there was a significant positive correlation between the resistance index (RI) and systolic blood pressure (SAD) (p<0.05), diastolic arterial pressure (DAD) and mean blood pressure (SrAD).

The structural and functional state of the left ventricle was studied in the study groups. When comparing groups 1 and 2, systolic dysfunction of the left ventricle was observed in group 2, that is, there was a significant difference (p<0,05) 141,3±0,01-160±0,01*;50,9±0,02-74,2±0,02* accordingly. At the same time, in the 2nd group there was a significant difference (p<0.05) in the indicators of end-diastolic LV volume (BWF), end-diastolic LV size (CDR) and LV compared with the 1st group- 5,4±0,02-5,7±0,02*,; 3,5±0,01-4,1±0,01*; 64±0,01-53,6±0,01* accordingly (see Table 3).

Table 3

Показатели функционального ремоделирования структуры левого желудочка первой и второй групп больных

Показатели	**1- группа**	**2- группа**
Age	35,2±0,81	38,2±2,81
Duration of the disease	4,49±0,34	16,41±1,4
LVEDV (ml)	141,3±0,01	160±0,01*
LVESV (ml)	50,9±0,02	74,2±0,02*
LVEDS (ml)	5,4±0,02	5,7±0,02*
LVESS(ml)	3,5±0,01	4,1±0,01*

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LVIDs (sm)	1,0±0,01	1,1±0,01*
IVSd (g)	244±0,02	287±0,02*
IIVSd (g/m^2)	192±0,01	226±0,01*
PWd	1,0±0,02	1,0±0,02
LV EF(%)	64±0,01	53,6±0,01*
ShV	90,4±0,01	85,8±0,01*

An increase in the size and volume of the heart, namely CDR, BWW positively correlated ($p<0.05$) with LVEDV, LVEDS, ShV ($r=0.37$, $p=0.37$, $p=0.70$, $r=0.67$ $g=0.62$, $g=0.58$, respectively). However, there was a significant ($p<0.05$) negative correlation between the magnitude and size of LV and PV.

There was a significant ($p<0.05$) negative correlation between CSR, BWR, CSR, CDR and GFR ($r=0.38$, $r=-0.36$), ($r=0.38$, $r=-0.36$, respectively). These indicators positively correlated directly with blood urea by ($p<0.05$) ($r=0.30$, $r=0.34$, respectively) and ($r=0.27$, $r=0.27$, respectively). An increase in cardiac parameters led to a decrease in renal GFR and an increase in stagnation and urea indices. It follows that the size and volume of the heart are significantly correlated ($p<0.05$) with blood pressure, i.e. there is a positive correlation between BWW, CDR and SAD and DAD ($r=0.28$, $p=0.28$), and a negative correlation with PV ($r=-0.32$, $r=-0.34$).

The indicators of BWW and CDR had a positive correlation with the indicators of renal hemodynamics, i.e. with RI ($r=0.27$, $r=0.36$) ($p<0.05$). The increase in systolic and diastolic heart volume has a positive correlation with UO ($r=0.86$, $r=0.65$) and a negative correlation with PV ($r=-0.30$, $r=-0.34$). There was a positive correlation of cardiac parameters with blood pressure ($p<0.05$) ($r=0.29$, $r=0.35$, respectively).

The results of the study show that an increase in the parameters of central hemodynamics in developed lupus nephritis was accompanied by a decrease in the geometric parameters of the heart: BWW, CDR, MMLJ, TSSLJ, which led to an increase in the resistance index (RI) of the renal vessels and pulse index, which indicated the development of chronic heart and kidney failure.

Based on the above information and the results of all examinations, we recommend introducing genetic examination into the standard methods of examination of patients of Uzbek nationality. After all, this method allows you to determine the development of lupus nephritis before its clinical manifestation. This will help doctors diagnose patients, select appropriate treatment and lengthen the period before hemodialysis by early detection of the development of lupus nephritis. In addition, the risk of early disability caused by the disease will decrease.

Conclusions

As a result of the research carried out on the dissertation work on the topic "Prognostic significance of clinical, pathogenetic and genetic aspects of lupus nephritis development" for the degree (PHD) of Doctor of Philosophy, the following conclusions were made:

1. According to the results of the study in patients with advanced lupus nephritis, a decrease in GFR, which evaluates the functional activity of the kidneys, was inextricably linked with an increase in MAU in urine and was expressed by a corresponding increase in creatinine, while an increase in the amount of TG and LDL was associated with a decrease in maximum (Vmax) and minimum (Vmin) blood circulation in the kidneys, which caused further the development of chronic kidney disease.
2. According to the results of the indicators of central hemodynamics in the study groups, with the development of LV, there was an increase in the geometric parameters of the heart: BWW, CSR and MMLJ and a decrease in LV, which was a consequence of the development of chronic heart and kidney failure.

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