IMMUNE-HEMATOLOGICAL RISKS OF PROGRESSION OF CHRONIC KIDNEY DISEASE IN CHILDREN WITH LYMPHATIC DIATHESIS

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Abstract. In order to study the immuno-hematological risk of chronic kidney disease (CKD) progression in children with lymphatic diathesis (LD), 120 children aged from 7 to 11 years old suffering from CKD (nephrotic form of chronic glomerulonephritis (CGN) were examined. Of them: 35-CKD without LD-1-group; 35-CKD with LD-2 group; 25- LD- 3-group. It was determined that LD is a risk factor that affects the progression of CKD (nephrotic form of CGN) in children, which is confirmed by more pronounced (1.5-2 times more often) manifestations of clinical, laboratory and immunological changes in children with CKD with LD compared with children with CKD without LD. In CKD with LD, the progression of immunopathological changes and aggravation of hematological changes occur closely interconnected, manifesting a high informative combination of various immunological and hematological parameters, such as: ABL of kidneys, ABL of lungs, IgA, CIC, IL-2, CD8, NAF, hemoglobin, lymphocytosis, hypoalbuminemia, hypercholesterolemia. Highly informative combinations of various immunological and hematological parameters affecting the progression of the pathological process in CKD with LD are the criteria for an early immuno-hematological diagnosis and make it possible that LD is a predictor of the progression of renal anemia and chronic kidney deficiency in such patients.

Key words: lymphatic diathesis, chronic kidney disease, immunity, combination, progression

I. Introduction

Currently, there is a significant increase in the pathology of the organs of the urinary system in comparison with the 80s of the last century [1, 2, 3, 4]. However, not all risk factors have been studied, the modification of which would reduce the rate of progression of chronic kidney disease (CKD) in pathology of the urinary system [5, 6, 7]. Among children, CKD attracts attention by the seriousness of the prognosis. In this case, the development of chronic renal failure (CRF) is considered as the main criterion for the progression of CKD, which determines the quality and duration of patients' life, the fight against which has not only medical, but also socio-economic importance [8, 9, 10].

The term CKD was first used by R.J. Hogg in 2003 as borrowed from therapeutic practice. The definition of CKD and its classification by stages in pediatrics currently do not differ from those in adults [11]. The 2003 K / DOQI

(Kidney Disease Outcomes Quality Initiative) guidelines define CKD as the presence of kidney damage for 3 months or more, characterized by structural or functional renal impairment with or without a decrease in the glomerular filtration rate (GFR) [12, 13, 14]. The main goal of CKD therapy in the early stages is to slow down the progression of the pathological process in the kidneys, achieve its regression, if possible, and ensure the best possible quality of life for the patient, including the correction of anemia is also a key factor in which the mortality rate of children with CKD decreases [15, 16.17]. The main factor in the development of anemia in CKD is a decrease in the formation of erythropoietin (EP), that is, a violation of the endocrine function of the kidneys. However, factors such as increased blood levels of EP inhibitors, hemolysis, iron deficiency, blood loss, hyperparathyroidism, infections, and impaired hormonal homeostasis are also important [18, 19]. In this regard, he pays attention to CKD in children suffering from background pathology, including lymphatic diathesis (LD).

Diathesis (from the Greek diathesis - inclination to something, predisposition) is an anomaly of the constitution, characterized by a predisposition to certain diseases or inadequate responses to common stimuli. The individual characteristics of the child's reactivity largely determine the tendency to certain diseases, the peculiarities of their course. Every thinking pediatrician (whether he agrees or disagrees with the existence of "diathesis") takes into account constitutional features in the treatment and implementation of preventive measures. Since the beginning of the XX century the concepts of "constitutional anomalies" and "diathesis" were actively introduced into the pediatric literature. The term "lymphatic diathesis" was introduced by the Austrian pathologist A. Paltauf and pediatrician Theodor Escherich in 1889-1890. [20, 21, 22].

LD is characterized by various phenotypic signs, which are manifested by the following syndromes: *lymphoproliferative syndrome:* diffuse hyperplasia of lymphoid tissue, generalized, persistent enlargement of peripheral lymph nodes and thymus gland (even in the absence of signs of infection), with a peculiar habitus of a child (pallor, lethargy, "adenoid appearance" , signs of paratrophy); *endocrinopathic syndrome:* hypoplasia of internal and external genital organs (vagina, uterus, phimosis, cryptorchidism); *dysontogenetic syndrome:* hypoplasia of the heart and large vessels, kidneys; syndrome of *sympatho-adrenal* and *glucocorticoid insufficiency:* hypo- and dysfunction of the thymus gland, adrenal glands, "status thymico-lymphaticus", thyroid dysplasia, marbling of the skin, arterial hypotension, hyperhidrosis, collaptoid state with reduced adaptation to environmental influences [20, 23, 24, 25].

Children with LD are often characterized by a high infectious index, insufficient local immunity of the respiratory and gastrointestinal tract, anemia, lymphocytosis, dysproteinemia, hormonal imbalance, and further formation and development of the syndrome of secondary immune deficiency of the body [26, 27, 28].

II. Purpose of the research

To study the immuno-hematological risks of progression of chronic kidney disease in children with lymphatic diathesis.

III. Materials and Methods

The studies were carried out on the basis of the Urgench branch of the Tashkent Medical Academy, in the department of pediatric nephrology of the Khorezm regional children's multidisciplinary medical center (ODMPMC) and in the 1-family polyclinic in Urgench. We observed 95 children aged 7 to 11 years suffering from CKD (nephrotic form of chronic glomerulonephritis (CGN)) during 2017-2019. Of these: 35 - CKD without LD - 1-group; 35 - CKD with LD - 2-group; 25- LD- 3-group. The control group consisted of 25 apparently healthy children of the same age. The clinical diagnosis was made on the basis of anamnesis, clinical laboratory and functional research methods according to the ICD-10 classification, as well as clinical and laboratory markers of LD. We studied the state of peripheral blood, cellular and humoral immunity, antigen-binding lymphocytes (ASL) of the kidneys and lungs by the method of F.Yu. Garib. and coauthors [29, 30]. Phagocytic activity of neutrophils (PAN) was studied using the nitro blue tetrazolium test using latex particles [31]. The concentration of circulating immune complexes (CICs) was determined by the precipitation method [32], the production of interleukin-2 (IL-2) was studied by ELISA [33]. GFR was determined using the Schwartz formula [34] and used to determine the stages of CKD. The material for the study was venous blood taken in the morning on an empty stomach. Statistical processing of the results was carried out using the method of variation statistics with the calculation of the reliability of numerical differences according to the Student on a personal computer, and also used the mathematical method of "artificial neural networks" - ANN [35]. The classification for ANN was set in the form of a "mathematical experiment" on different types: a qualitative and quantitative indicator, the gradation of the interval was (0-1). The essence of the mathematical experiment consisted in setting various classifications on a sample and medical interpretation of the ANN learning results in relation to CKD with LD.

IV. Results and Discussion

The selection of patients was carried out taking into account the comparability in terms of age, severity, state of premorbid background and the nature of the course of the disease in general. We studied the distribution of the surveyed children by sex and age (Table-1).

Table -1

Distribution of examined children by sex and age

Sex	Total, n=95					
	CKD, n=35 1-group		CKD c LD, n=35 2- group		LD, n=25 3- group	
	Quantity	%	Quantity	%	Quantity	%
Boys	21	60,0	26	74,3	17	68,0
Girls	14	40,0	9	25,7	8	32,0
Age: 7-11	35	100	35	100	25	100

Based on the results obtained, it can be said that LD is more common in male children (2-2.5 times more often), which coincide with the literature data, since it also indicates that LD is 1.5-2 times more common in boys [21]. All examined children were of primary school age, that is, up to puberty. The choice of this age group is due to the peculiarities of physiological changes in the immune system in children, that is, during the growth of a child, there are certain "critical" periods in the development of the body's immunobiological reactivity [26]. 7-11 years old belongs to the IY-critical period, which is important in the manifestation of LD and in the increased risk of chronicity of various pathological processes.

Analyzed the nature of the course of the disease in the observation groups. The relapsing course of CKD was statistically significant more often in children in group 2 (CKD with LD) - 12 (42.0%), than in group 1 (CKD) - 8 (22.9%).

It is known that a feature of the course of CKD in children is a nonlinear decrease in renal function, while the critical point of progression of the pathological process is puberty. As a result of their scientific research, scientists have confirmed [26] that three periods can be divided along the course of CKD in children: 1-initial - duration of 3 years, accompanied by a slow improvement in renal function; 2-period of stable renal function (in 50% of children), duration 8 years; 3-period of progressive decline in renal function with an outcome in the terminal stage of chronic renal failure.

We also analyzed the progression of CKD in the observed children by the duration of the disease, taking into account LD. The duration of the disease in the examined children varied within wide limits: in the 1st group (CKD) - 7 years, averaging 3.7 ± 1.6 years; in the 2nd group (CKD with LD) - 9 years, averaging 5.8

± 1.7 years; in the 3rd group (LD) - 11 years, averaging 6.5 ± 2.6 years. This indicates that children with background pathology, including LD, are early exposed to kidney damage, including CKD, and they also have clinical manifestations of LD from early childhood.

As a result of studying the functional state of the kidneys in children, it was noted: impaired renal function in patients of group 1 (CKD) -6 (17.1%), in group 2 (CKD with LD) - 10 (28.6%) patients. The progression of CKD to stage 2 CRF in the 1st group was noted in 2 (5.7%), in the 2nd group - in 4 (11.4%); up to stage 3 CRF: in the 1st group it was noted in 1 (2.9%), in the 2nd group in 2 (5.7%) patients. This indicates that the course of CKD in children against the background of LD is characterized by deeper immunopathological changes in the kidney tissue compared to CKD without LD.

When studying GFR, it was determined that the difference in the frequency of different stages of CKD in the groups was statistically insignificant, however, the following tendency to the progression of CKD was revealed: children of the 2nd group were characterized by a lower frequency of I and II stages of CKD with a relative increase in the number of children with III and IY stage (1.5-2 times more often). The average GFR in CKD with LD (group 2) was 52.3 ± 4.34 ml / min, which is significantly lower than in CKD without LD (group 1) 57.8 ± 3.45 ml / min.

Analysis of the distribution of patients in terms of sensitivity to glucocorticoid therapy showed that hormone sensitivity in 33 (94.3%) and hormone resistance in 2 (5.7%) patients was statistically reliably detected in group 1. In children of the 2nd group, hormone sensitivity - 24 (68.6%), hormone resistance - 4 (11.4%), at the same time, hormone-dependent form of CKD was revealed in 8 patients (22.8%).

It is known that the main factors in the development of LD are both the pathological course of pregnancy in the mother and the effect of various infectious and non-infectious (allergic) agents on the child's body in the ante- and postnatal period. Taking these circumstances into account, we also studied the formation and development of LD in the examined children in conjunction with clinical and laboratory signs, based on anamnestic materials.

When evaluating indicators for identifying clinical and laboratory markers of LD in the examined children (Fig. 1), a statistically significant high frequency was found: high infectious index, imbalance in physique, pasty face, hypotension and hypodynamia, nervous lability, thymomegaly, bradycardia, "fountain vomiting", lymphocytosis, increased ESR, decreased serum IgA and monocytosis, which are more pronounced in children with CKD with LD (group 2) compared with children with LD (group 3).

In addition, some LD markers in both groups accounted for a significantly large percentage, respectively, which differ little in severity from each other: pathological course of pregnancy and childbirth in the mother (100%; 96%), large birth weight (48.6%; 48 %), hereditary predisposition to LD (71.4%; 68%), enlargement of peripheral lymph nodes (86%; 80%), chronic focus of infection (100%; 96%), pathology of the neonatal period (40%; 36%), predisposition to allergies (45.7%; 40%), "cockcrowing" when crying (37.1%; 32%), endocrine system dysfunction (42.9%; 40%), paratrophy (40%; 32%) , and eosinophilia (34.8%; 28.4%).

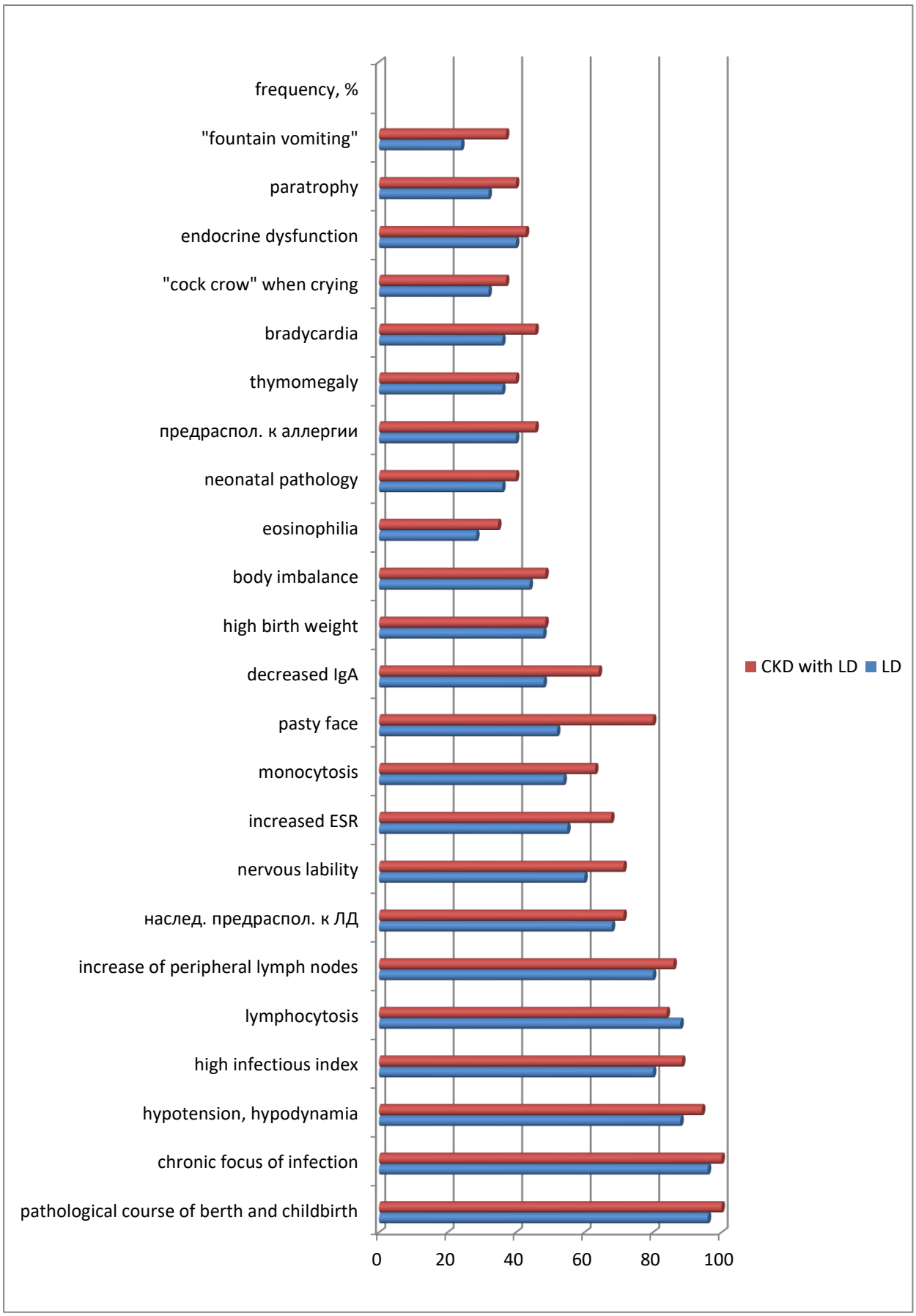

Fig.1. Identification of clinical and laboratory markers of LD in the examined children

When assessing the clinical manifestations of nephrotic syndrome (NS) in a group of examined children, with CKD (group 1) and CKD with LD (group 2), a tendency was found for a statistically significant higher frequency of the following symptoms in group 2 compared with group 1 the first group, respectively: "chalky" pallor of the skin (62.0% -70.8%), decreased appetite (37.2% -44.0%), oliguria (87.0% -93.7%), fatigue (63.9% -74.9%), a positive puffing symptom (29.8% - 34.5%), widespread edema (68.0% -85.7%), ascites (43.7% -64, 8%), hepatomegaly (17.5% -29.4%).

When studying the functional state of the kidneys and the biochemical parameters of blood in the examined groups, respectively, there was a significant decrease in daily urine output (0.6 ± 0.12; 0.4 ± 0.17), an increase in daily proteinuria (2.45 ± 0.19; 2, 73 ± 0.14), total cholesterol (6.8 ± 0.54; 9.5 ± 0.39), fibrinogen (476 ± 22.3; 589 ± 24.1), hypoalbuminemia (25.6 ± 0, 54; 19.5 ± 0.87), hypergammaglobulinemia (24.2 ± 0.24; 28.5 ± 0.46), increased urea content (7.9 ± 0.34; 9.9 ± 0.76) , creatinine (0.09 ± 0.032; 0.12 ± 0.015), which were also significantly higher in the second group than in the first group.

The main disease in the observed children (Fig. 2) was statistically significantly accompanied by the following pathologies, which also accounted for a large percentage in children in group 2 compared with group 1: anemia (78.2%; 83.4%), chronic tonsillitis (80.6%; 87.1%), adenoids (28.0%; 36.0%), helminthiasis (25.9%; 34.4%), recurrent bronchitis (32.9%; 48.0 %), gastroduodenitis (12.7%; 28.3%), respectively.

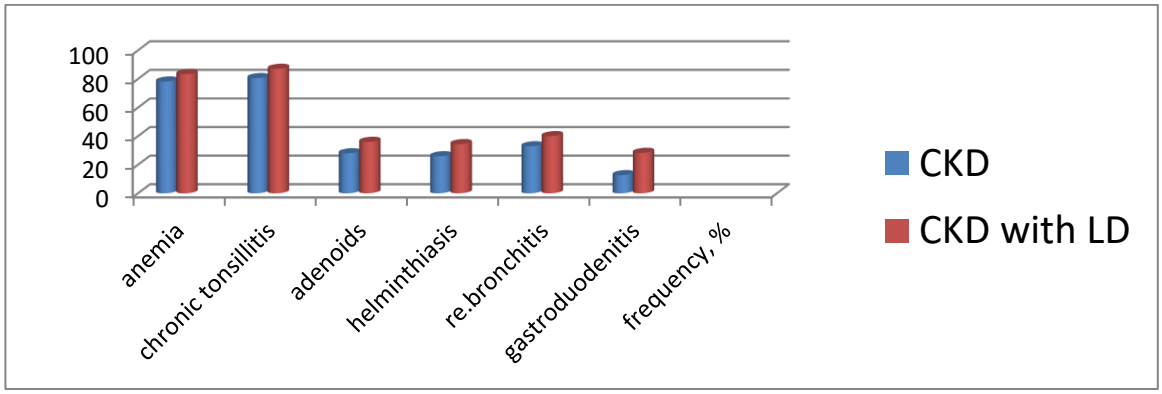

Fig. 2. The frequency of concomitant pathologies in the examined children

Comparative evaluation of the results of immunological studies (table-2) with the control group showed a significant decrease in T-lymphocytes (CD3), T-suppressors (CD8), T-helpers (CD4), PAN, IgA and IL-2 production; an increase in the number of B-lymphocytes (DM19), ABL of the kidneys, lungs and CIC

concentration, which were also higher in the 2nd group (1.5-2 times) than in the 1st and 3rd groups of children.

The obtained results of immunological studies show that the body's immune system has a morphological synonym - it is the lymphoid system, as a set of all lymphoid organs and accumulations of lymphoid cells, which play an important role in the mechanism of immune defense, manifested in the form of antigenic structural homeostasis (ASH), carrying out specific processes of immunological reactivity.

Significant changes in peripheral blood parameters (Fig. 3) in the examined children, when compared with the control group, were as follows: in the acute period of the pathological process, anemia, lymphocytosis, leukocytosis, monocytosis, neutropenia, eosinophilia, increased ESR were detected, which were also more pronounced in children of the 2nd group compared with the 1st and 3rd groups.

Table -2

Immunity indices in examined children (M±m)

Indicators	Healthy children, (n=25)	CKD, (n=35), 1-group,	CKD with LD, (n=35), 2- group	LD, (n=25), 3- group,
CD3, %	54,67±0,94	47,55±1,4***	38,35±1,5***	49,52±1,1***
CD4 %	33,13±0,83	26,45±1,3***	21,54±1,2***	24,36±1,2***
CD8, %	19,90±0,72	15,16±1,5**	11,42±1,4***	14,19±1,5***
CD19, %	11,60±0,89	15,51±0,43*	19,35±0,68**	13,76±0,49**
ABL kidneys, %	-	2,2±0,47	7,0±0,75***	3,9 ±0,56**
ABL lungs	-	0,44±0,42	9,0±0,89***	5,1±0,47***
IgA, g/l	1,45±0,16	0,86±0,12*	0,47±0,14**	0,54±0,11**
CIC, un.wh.pl	0,002±0,003	0,039±0,003**	0,098±0,004***	0,031±0,005**
PAN,%	50,50±1,11	45,31±0,35***	38,26±0,41***	47,37±0,54***
IL-2, pg/ml	2,8±0,09	2,6±0,05*	2,0±0,06***	2,5±0,04*

Note: the significance of differences compared to the group of healthy children. ABLs are compared between groups 1, 2 and 3. *** - p <0.001; ** - p <0.01; * -p <0.05

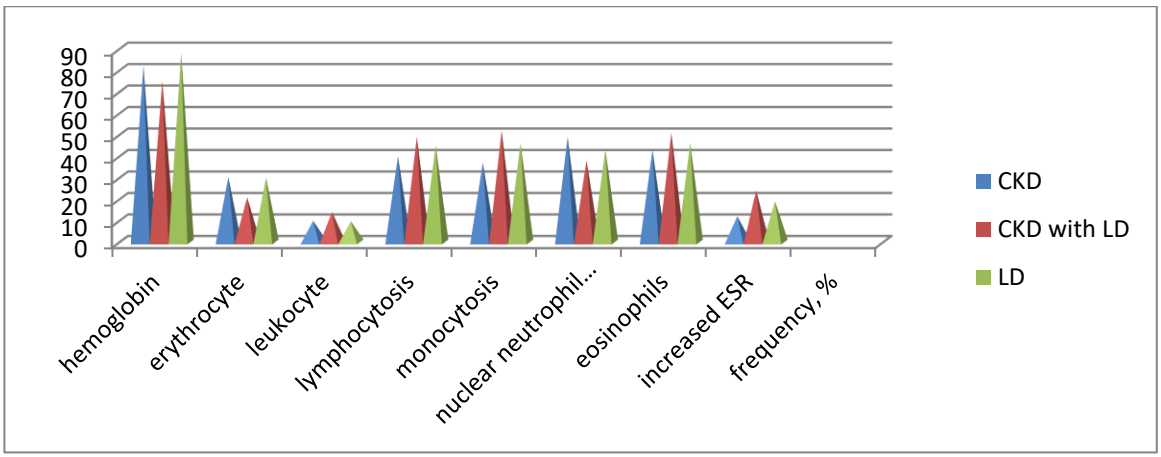

Fig. 3. Peripheral blood parameters in the examined children

When studying the clinical, laboratory and immunological results by the ANN method, it was revealed that in children with CKD, CKD with LD and LD, immunopathological shifts and hematological changes are interrelated, which were manifested by a high informative combination of various quantitative (hematological and immunological) indicators (table-3), (fig. 4.).

Table 3

Informative and comparative quantitative indicators in the examined children

Quantitative indicators	Weight of nominal signs (before treatment)		
	CKD, n=35, 1-group	CKD with LD, n=35, 2-group	LD, n=25, 3-group
Hemoglobin, g / l	0,5676	1.000	0,5489
Erythrocytes, 10^{12} / l	0,7845	0,9965	0,5962
Leukocytes, 10^{9} / l	0,4871	0,8693	0,5829
Lymphocytes, %	0,4983	1.000	0,6232
Monocytes, %	0,1326	0,8612	0,5876
eosinophilia	0,2869	0,5455	0,3187
ESR, mm/h	0,3467	0,7952	0,4987
Urea, mmol / l	0,8591	0,8887	0,2321
Creatinine, mmol / l	0,3519	0,4969	0,0120
Total protein, g / l	1,000	1,000	0,3354
Albumin, %	0,5767	0,8763	0,2110
gamma globulin, %	0,5365	0,7654	0,1276
Calcium, mmol / l	0,7865	0,8667	0,6142
Total cholesterol, mmol/l	0,4789	0,9698	0,5473
Fibrinogen, g / l	0,5065	0,6885	0,2496

Proteinuria	1,000	1,000	0,0119
Erythrocyturia	0,5875	0,7782	0,0124
Leukocyturia	0,4695	0,6793	0,0113

Note: The numbers obtained are indications of the degree of difference between the readings before treatment.

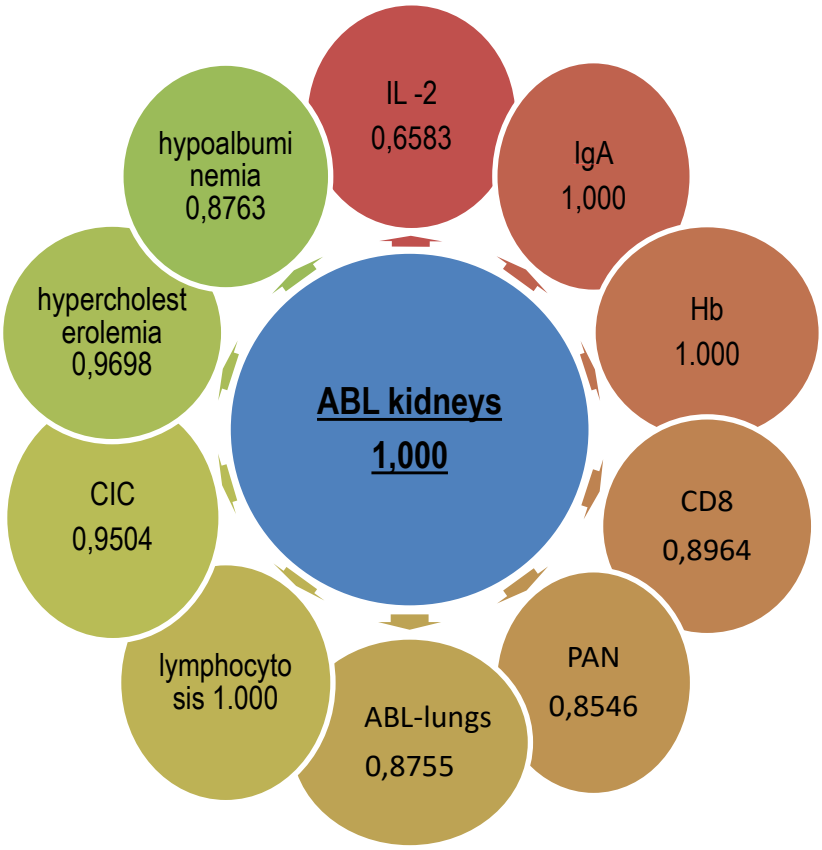

Fig. 4. Combinations of immune-hematological parameters in patients with CKD with LD

V. Conclusion

1. Lymphatic diathesis is a risk factor influencing the progression of clinical, laboratory and immunological symptoms of CKD (nephrotic form of CGN) in children, which is confirmed by more pronounced (1.5-2 times more often) manifestations of clinical, laboratory and immunological changes in children with CKD with LD compared with children with CKD without LD.

2. In CKD with LD, the progression of immunopathological changes and aggravation of hematological changes are closely interrelated, manifested by a high informative combination of various immunological and hematological parameters,

such as: ABL-kidneys, ABL-lungs, IgA, CIC, IL-2, CD8, PAN, hemoglobin, lymphocytosis, hypoalbuminemia, hypercholesterolemia.

3**.** Highly informative combinations of various immunological and hematological parameters affecting the progression of the pathological process in CKD with LD are criteria for early immuno-hematological diagnosis and suggest that LD is a predictor and risk factor for the development of nephrogenic anemia and CRF in such patients.

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