Original Article

# ASSESSMENT OF IMMUNOPATHOLOGICAL DEVELOPMENTS IN CHILDREN WITH NEPHROTIC SYNDROME WITH BACKGROUND PATHOLOGY

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## Abstract

In order to assess immunopathological changes in children with nephrotic syndrome with underlying pathology, 120 children aged 7 to 11 years were examined. Of these: group 1 - 35 children with NS (nephrotic form of CGN); group 2 - 35 children with NS against the background of LD; group 3 - 25 children with LD. Healthy group: 25 practically healthy children of the same age. It was determined that in children with nephrotic syndrome (nephrotic form of chronic glomerulonephritis) occurring with underlying pathology (lymphatic diathesis), specific clinical symptoms are characteristic, such as increased edema (100.0%), oliguria (100.0%), "chalky" pallor (74.2%), anasarca (9.0%) and hepatosplenomegaly (57.1%), in parallel with this, the development of severe anemia, a decrease in cortisol, an increase in lymphocytosis, proteinuria, fibrinogen, gamma globulin and cholesterol, contributing to the development of steroid-dependent and steroid-resistant forms of the disease. In nephrotic syndrome with lymphatic diathesis, a deficiency of the cellular link of immunity, a violation of the production of the cytokine IL-2, an increase in the content of ABL-kidneys, ABL-lungs, which remain preserved even in the period of remission of the disease, are characteristic, which confirm that in the treatment of such contingents of patients it is necessary to include in therapy adequate methods of immunocorrection.

**Keywords:** lymphatic diathesis, nephrotic syndrome, interleukin-2, immunity

## Introduction

It is known that nephrotic syndrome (NS) in children in most cases is idiopathic and often develops with primary glomerulopathies, autoimmune, oncohematological and cardiovascular diseases. The annual incidence of NS is 2-7 primary cases per 100,000 children [8].The relevance of this problem in pediatric practice is due to the complexity of treatment and management of patients, frequent cases of resistance to steroid therapy. In NS, including the nephrotic form of chronic glomerulonephritis in children, 85% of the morphological substrate is a disease of minimal changes, up to 5-7% is focal segmental glomerulosclerosis [3, 6, 9, 10, 11,13]. Currently, the features of interleukin-2 (IL-2) production in NS in children with underlying pathology, including lymphatic diathesis (LD) [7, 16], are not well understood, since LD is often recorded in children with a high infectious index

(81 %) and is about 12-35% among the child population, which is characterized by chronicity of various acute inflammatory processes (nephritis, hepatitis, vasculitis, carditis) and is manifested by dysontogenetic, endocrinopathic, lymphoproliferative, sympathetic-adrenal and glucocorticoid syndromes [12, 14, 15].Daily analysis of the causes of frequent relapse, the development of steroid-resistant and steroid-dependent forms of NS require an assessment of IL-2 production in children with NS against the background of LD.

**The purpose of the study** was to evaluate the production of interleukin-2 in children with nephrotic syndrome against the background of lymphatic diathesis.

## Materials and methods

Under our supervision were 120 children aged 7 to 11 years. Of these: *group 1* - 35 children with NS (nephrotic form of CGN); *group 2* - 35 children with NS against the background of LD; *group 3* - 25 children with LD. Healthy *group*: 25 practically healthy children of the same age. The clinical diagnosis was made based on anamnesis, clinical laboratory and functional research methods according to the ICD-10 classification, as well as clinical and laboratory markers of LD [12, 14]. We studied the state of the cellular link of immunity, antigen-binding lymphocytes (ABL) of the kidneys and lungs according to the method of Garib F.Yu. and co-authors [4, 5]. The phagocytic activity of neutrophils (FAN) studied using the method of T.K.Bumagina [2]. The production of interleukin-2 (IL-2) was studied by ELISA [1]. The glomerular filtration rate (GFR) was determined using the Schwartz formula [17]. The material for the study was venous blood taken in the morning on an empty stomach. Statistical processing of the obtained results carried out using the method of variation statistics with the calculation of the reliability of numerical differences according to Student.

## Results and its discussion

Based on the results of our studies, we found that LD was diagnosed 1.5-2.0 times more often in male children, which coincides with the literature data [12,14].

The main disease in the observed patients was statistically significantly ($p<0.05$), accompanied by various pathologies that were characterized by variety in all groups, such as: chronic tonsillitis - 20 (57.0%), 29 (83.0%), 19 (76 .0%); recurrent bronchitis - 3 (8.6%), 7 (20.0%), 8 (32.0%); anemia - 23 (66.0%), 26 (74.2%), 13 (52.0%); thyroid gland - 3 (8.6%), 9 (26.0%), 8 (32.0%); pneumonia - 1 (2.9%), 4 (11.4%), 2 (8.0%); adenoid vegetations - 1 (2.9%), 14 (40.0%), 7 (28.0%); allergic reactions - 1 (2.9%), 3 (8.6%), 5 (20.0%), respectively. The results of the anemia degree study, showed that in children of the 2nd group (NS with LD), a large percentage were moderate 18 (51.4%) and severe 4 (11.4%) forms, as well as Itsenko-Cushing's syndrome 4 (11.4 %) statistically significantly ($p<0.05$) more was recorded in this group, which confirms that the underlying pathology provokes an aggravation of steroid toxicity in NS.

When evaluating indicators for the detection of clinical and laboratory markers of LD in patients of the 2nd (NS with LD) and 3rd (LD) groups, a statistically significant ($p<0.001$; $p<0.05$) high frequency hypotension and physical inactivity -33 (94.3%), 22 (88.0%); high infectious index - 31 (88.5%), 20 (80.0%); pastosity of the face -28 (80.0%), 13 (52.0%); increase in ESR - 28 (80.0%), 10 (40.0%); lymphocytosis - 27 (77.0%), 15 (60.0%); nervous lability -25 (71.4%), 15 (60.0%); decrease in serum IgA - 23 (64.2%) 12 (48.1%); body disproportion - 17 (48.5%), 11 (44.0%); bradycardia -16 (45.7%), 9 (36.0%); monocytosis - 14 (40.0%), 10 (40.0%); thymomegaly at an early age - 14 (40.0%), 9 (36.0%); "Projective vomiting" - 13 (37.1%), 6 (24.0%); which are more pronounced in patients of the 2nd group compared with the 3rd group ($p<0.001$-$0.01$), respectively.

When assessing the clinical manifestations of NS, a statistically significant ($p<0.01$-$0.05$) high frequency of the following symptoms in the 2nd group compared with the 1st and 3rd groups was found: "chalky" pallor of the skin – 22 (62.8%), 26 (74.2%), 6 (24%); positive effleurage symptom - 22 (65.0%), 29 (72.5%), 0 (0%);

hepatomegaly - 20 (57.1%), 23 (65.7%), 1 (4.0%); loss of appetite - 13 (37.1%), 16 (45.7%), 3 (12.0%); ascites 7 (20.0%), 11 (31.4%), 0 (0%); anasarca - 1 (2.9%), 3 (9.0%), 0 (0%); respectively. Analysis of the results of laboratory studies showed that in NS, NS against the background of LD and LD, there was a statistically significant decrease in hemoglobin, erythrocytes, an increase in ESR, leukocytosis, lymphocytosis and monocytosis compared with the control group ($p<0.001$). In addition, in patients of the 2nd group, the level of total protein was lower by 1.7 times ($p<0.05$) when compared with the 1st and 3rd groups. This was manifested in significant shifts in the spectrum of proteins with a relative decrease in albumin levels in the 2nd group by 1.3 times ($p<0.05$) and cortisol levels by 1.2 times ($p<0.05$). On the contrary, the amount of the gamma globulin fraction increased by 1.02 ($p<0.05$) and 1.03 ($p<0.05$) times in the NS and NS with LD groups, respectively, compared with the control group and with the LD group. The levels of urea and creatinine increased compared to the control 1.7 ($p<0.05$) and 1.8 ($p<0.05$) times in the 1st and 2nd groups. An analysis of the results of laboratory studies of urine showed (Table 1) that in NS and NS with LD, the relative density of urine and GFR were significantly lower than normal ($p<0.001$; $p<0.01$; $p<0.05$). When comparing groups I, II and III, proteinuria, erythrocyturia and leukocyturia were significantly higher than the norm ($p<0.001$; $p<0.01$). When studying the glomerular filtration rate (GFR), it was found that against the background of LD, NS is characterized by a twofold increase in the number of patients with stage II CKD.

Table 1. Urine parameters in the examined children. M±m.

| Indicators | Total n=120, age 7-11 years | | | |
|---|---|---|---|---|
| | Healthy children, control, n=25 | NSHC, n=35 | NS with LD, n=35, | LD, n=25, |
| | | I-group | II-group | III-group |
| | M±m (%) | M±m (%) | M±m (%) | M±m (%) |
| Relative density of urine | 1014,0±0,23 | 1015,0±0,48* | 1010,0±0,57*# | 1018,00±0,45*#• |
| Proteinuria, $^{0}/_{00}$ | 0,03±0,002 | 2,78± 0,35* | 2,98±0,48*# | 0,03±0,00*#• |
| Erythrocyturia, /1 | 1,00±0,01 | 5,2±1,62* | 6,3±1,97*# | 2,8±0,06*#• |
| Leukocyturia, /1 | 5,52±0,14 | 9,60±0,25* | 11,30±0,29*# | 5,20±0,07*#• |
| GFR, ml/min/1.73m$^2$ | 118,94±1,97 | 99,81±7,36* | 75,40±5,39*# | 117,4±0,96*#• |

Note: *P-reflects the difference in significance compared to the control group, #P-reflects the difference in significance with group I, •P-reflects the difference in significance with group II. ($P<0.001$; $P<0.01$; $P<0.05$).

The obtained results of the studies confirm that in NS, including the nephrotic form of chronic glomerulonephritis in children, occurring with underlying pathology (LD), the manifestation of clinical and laboratory symptoms

have their own specific features that affect the progression of the pathological process. In such patients, comorbidities also have their own characteristics, that is, in terms of the frequency of detection, a large percentage of the group of children is NS against the background of LD. The results of the study of the immune status showed that in all groups of patients, compared with the control group, a significant decrease in T-lymphocytes (DM3), T-helpers (DM4), T-suppressors (DM8) and phagocytic activity of neutrophils (FAN) was recorded ($p<0.001$ ), a significant increase in antigen-binding lymphocytes (ASL) of the kidneys and ASL of the lungs ($p<0.001$). Identified immune disorders in patients with NS and NS against the background of LD indicate an imbalance in the mechanisms of control of the inflammatory response, which is the pathogenetic basis for the progression of immunopathological damage to the renal tissue, that is, an increase in the ASL of the kidneys indicates the development of autoimmune processes. In the observed patients, the production of IL-2 in all groups was significantly reduced compared to the control group ($p<0.001$-$0.01$). In patients of group II, the level of IL-2 compared with groups I and III was significantly low ($p<0.001$), which is explained by the fact that IL-2, acting autocrine on Th1 cells and paracrine on the subpopulation of Th2 cells, affects Thl/Th2 balance, stimulates the cytotoxic activity of CD8-lymphocytes and promotes the formation of a population of T-cells. Based on the results obtained, it can be confirmed that the cytokine imbalance between Th1 and Th2 determines the direction of immune response disorders, and the imbalance in the production of pro- and anti-inflammatory cytokines can be of pathogenetic significance in deregulated inflammation and autoimmune pathology, including NS and NS with LD.

Clinical example from observed patients:

Patient: Javokhir. Age: 11 years old.

**Clinical diagnosis:**

Main: Nephrotic syndrome (nephrotic form of chronic glomerulonephritis), stage of exacerbation. Hormone sensitive. Impaired kidney function.

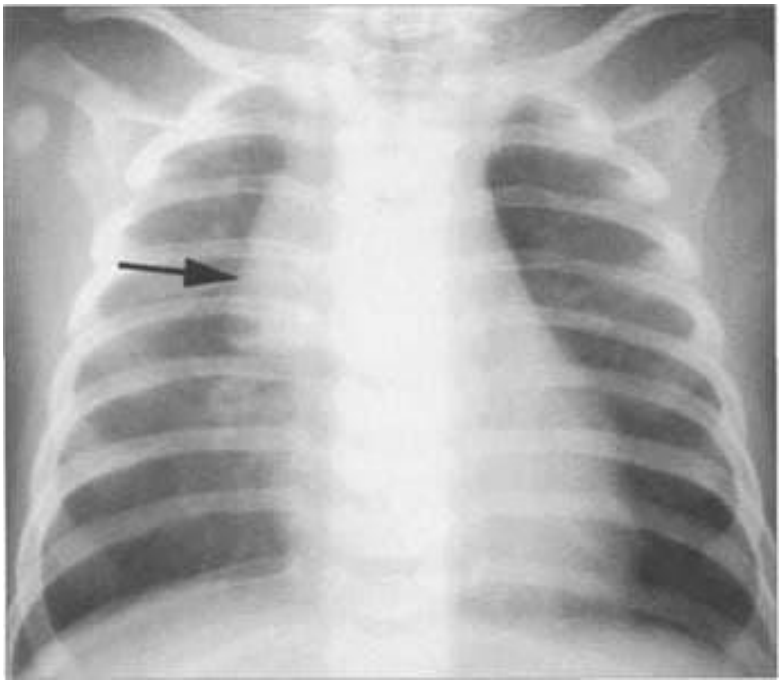
Complications: Chronic renal failure stage 2. Companion: LD. Chronic tonsillitis. Hypoplasia of the thyroid gland I st. Moderate anemia.

**Complaints**: swelling on the face, abdomen and limbs, a decrease in daily diuresis to 400-300 ml, cloudy urine, lethargy, fatigue and loss of appetite.

**Anamnesis morbi:** Pathology of newborns: fetal asphyxia, catarrhal omphalitis. Preventive vaccinations: complicated, with a medical exemption.

Past diseases: Thymomegaly I-degree at an early age (Fig. 2), SARS, tonsillitis, bronchitis. High infectious index: the incidence rate is 5-6 times a year.

Fig.2. Thymomegaly I-degree at an early age.



**Anamnesis vitae:** Maternal age at pregnancy: 20 years. According to the score: pregnancy - I, childbirth - I. Weight at birth: 4300 gr. Feeding: artificial.

**Pathology of pregnancy and childbirth:** toxicosis of the I and II half, psycho-emotional stress, Somatic pathology in the mother: severe anemia.

**Status preaseans:** Height - 130 cm, weight - 38 kg. The structure of the body is hypersthenic. Body disproportion - long limbs, short torso and neck (Fig. 3).

Subcutaneous fat is normally developed, hydrophilic. The osseous-articular system is rachitically deformed ("chicken breast", "X" shaped legs). The muscular system is hypotension.

Peripheral lymph nodes - enlarged (submandibular, parotid, cervical), hypertrophy of the tonsils. Skin - pale, "marbling of blood vessels".

The mucous membrane is pale. Face and eyelids - pasty, edematous. Nervous system - labile, lethargic, quickly tires.

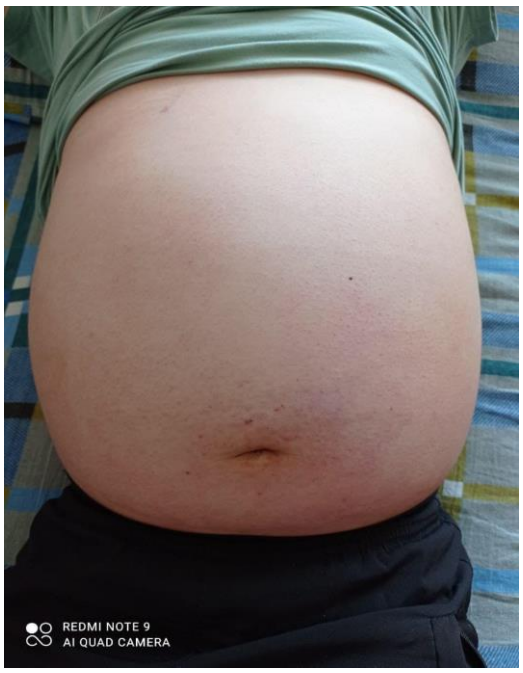
Cardiovascular system: pulse rate - 98 per minute, A/P - 90/60 mm Hg, heart sounds are muffled, rhythmic, tachycardia.

Respiratory system: chest - deformed, respiratory rate - 24 times per minute, decreased voice timbre, vesicular breathing in the lungs.

Digestive system: appetite is normal, the tongue is slightly covered with white coating, the abdomen is enlarged due to ascites, the symptom of "anasarca" is noted (Fig. 4), stool 1-2 times a day; liver +2.5 cm, spleen +0.8 cm enlarged, but painless - hepatosplenomegaly.

Fig.3. Body disproportion

Fig.4. Symptom "Anasarca". (short body and neck).


Urinary system: daily diuresis is reduced - 350 ml, urination is painless, Pasternatsky's symptom is positive on both sides.

Endocrine system: thyroid hypoplasia. Foci of chronic infection: chronic tonsillitis.

Complete blood count: erythrocytes - 2.8 * 1012 / l, hemoglobin - 77.0 g / l, leukocytes - 13.2 * 109 / l, lymphocytes - 35.0%, monocytes - 2.0%, ESR - 9 mm/hour.

Urinalysis: urine relative density - 1015, protein - 5%, erythrocytes - 0-5, leukocytes - 6-7.

Biochemical blood test: urea - 9.0 mmol / l, creatinine - 162.4 mmol / l, calcium - 2.0 mmol / l, total cholesterol - 8.6 mmol / l, fibrinogen - 6.0 g / dl, total protein - 44.0 g/l, albumin - 24.8%, gamma globulin - 29.5%, C-reactive protein - 16.0 mmol/l, ASL-O - 373.0 U/ml, GFR - 43.6 ml / min.

Hormonal status: cortisol - 154.0 nmol/l.

Immune status: CD3 (T-lymphocytes) - 38.0%, CD4 (T-helpers) - 20.0%, CD8 (T-suppressors) - 12.0%, ASL of the kidneys - 5.0%, ASL of the lungs - 4.0%, FAN - 30.0%, IL-2 - 1.7 pg/ml.

ECG - violation of myocardial metabolism. Ultrasound: a picture of the nephrotic form of CGN and hepatosplenomegaly.

Endocrinologist's consultation: Hypoplasia of the thyroid gland I-degree. Thymomegaly I degree at an early age.

This example confirms that the course of NS with LD in this group of patients has peculiar clinical, laboratory and immunological features that depend on the frequency of NS relapses and the severity of LD.

Thus, on the basis of the conducted immunological studies, it can be said that the body's immune system is closely related to the function of the lymphoid system, which plays an important role in the mechanism of immune defense and manifests itself in the form of antigen-structural homeostasis (ASH), carrying out specific processes of immunological reactivity, since immunopathological shifts in NS, NS with LD and LD were characterized by a decrease in the functional activity of the cellular link of immunity and a violation of the production of the cytokine IL-2.

## CONCLUSIONS

1. In children with nephrotic syndrome (nephrotic form of chronic glomerulonephritis) occurring with underlying pathology (lymphatic diathesis), specific clinical symptoms are characteristic, such as increased edema (100.0%), oliguria (100.0%), "chalky" pallor (74, 2.%), anasarca (9.0%) and hepatosplenomegaly (57.1%), in parallel with this, the development of severe anemia, a decrease in cortisol, an increase in lymphocytosis, proteinuria, fibrinogen, gamma globulin and cholesterol, contributing to the development of steroid-dependent and steroid-resistant forms of the disease .

2. In nephrotic syndrome with lymphatic diathesis, a deficiency of the cellular link of immunity, a violation of the production of the cytokine IL-2, an increase in the content of ASL-kidneys, ASL-lungs, which remain preserved even in the period of remission of the disease, are characteristic, which confirm that in the treatment of such contingents of patients it is necessary to include in therapy adequate methods of immunocorrection.

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