FEATURES OF THE COMPLEMENT SYSTEM AND THE EFFECTIVENESS OF IMMUNOCORRECTION IN CHILDREN WITH NEPHROTIC SYNDROME IN THE CONDITIONS OF THE ARAL SEA REGION

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Annotation

In order to study the features of the complement system and the effectiveness of immunocorrection for nephrotic syndrome in children in the Aral Sea region, we observed 55 children aged 7 to 11 years suffering from NS (nephrotic form of chronic glomerulonephritis) against the background of LD. Of these: 30 - NS with LD - group 1; 25-LD-2-group. The control group consisted of 25 practically healthy children of the same age. It was found that children in the Aral Sea region with NS on the background of LD are characterized by a deep multi-link immunological deficiency, manifested in the form of a decrease in T-lymphocytes (CD3), T-suppressors (CD8), T-helpers (CD4), FAN, IgA, production IL-2 and indicators of C3, C4 complement components; an increase in kidney ABL, pulmonary ABL and CIC concentration, which persist during the period of remission of the disease. In case of NS against the background of LD, disruption of the alternative pathway of complement regulation plays an important role and membranoproliferative glomerulonephritis is formed as part of C3 glomerulopathy, in combination with low levels of serum C3, C4 complement components. The high efficiency of immunocorrection with the drug Wobenzyma allows us to recommend it for widespread use in complex therapy of NS against the background of LD.

Key words: *C3, C4, immunocorrection, kidneys, children, Aral region*

Introduction

Currently, nephrologists and pediatricians around the world are paying serious attention to children with nephrotic syndrome (NS), due to its relentless progression towards chronic kidney failure (CKD) and other complications that lead to increased morbidity and mortality among patients [11,8]. Another pressing issue is the increase in the incidence of steroid-dependent and steroid-resistant forms of NS, which are characterized by a high frequency of unfavorable disease prognosis, observed in 40-50% of patients over 5-10 years [7,16].

The complement system is a cascade of proteolytic enzymes that is part of the innate humoral immune response. It consists of more than 40 different

proteins, both dissolved in blood plasma and expressed on the membranes of body cells [12,14].

The complement system is an evolutionarily ancient defense mechanism, and deficiency in many complement components or, conversely, excessive activity of the complement system underlies many human diseases. Anomaly in the alternative complement pathway can lead to C3 glomerulonephritis (C3GN), which is characterized by the deposition of C3 (not immunoglobulin) in the glomeruli of the kidneys [18,6]. This study focuses on the course of NS in children in the Aral Sea region, who suffer from secondary immunodeficiency, including lymphatic diathesis (LD).

Children with LD are characterized by deficiencies in local immunity of the respiratory and gastrointestinal tracts, lymphocytosis, dysproteinemia, hormonal imbalance, anemia, high infection index, and development of secondary unclassified immunodeficiency syndrome [10,15].

Given the above, improving immunotherapy methods for NS in the Aral Sea region is clinically important, allowing for early prevention of various complications.

Objective of the study – to investigate the characteristics of the complement system and the effectiveness of immunocorrection in children with nephrotic syndrome in the conditions of the Aral Sea region.

Materials and Methods

Our observation included 55 children aged 7 to 11 years, suffering from NS (nephrotic form of chronic glomerulonephritis) against the background of LD. Among them: 30 - NS with LD - Group 1; 25 - LD - Group 2. The control group consisted of 25 practically healthy children of the same age. The clinical diagnosis was made based on the medical history, clinical-laboratory, and functional methods of investigation according to the ICD-10 classification, as well as clinical-laboratory markers of LD [10]. The state of cellular and humoral

immunity, antigen-binding lymphocytes (ABL) of the kidneys and lungs was studied by the method of Garib F.Yu. and co-authors [4,5]. Phagocytic activity of neutrophils (PHA) was studied using a nitroblue tetrazolium test with latex particles [3]. The production of interleukin-2 (IL-2) was studied by ELISA [1], and the concentration of circulating immune complexes (CIC) was determined by the precipitation method [2]. The concentration of C3 and C4 complement components was determined by immunoturbidimetry [13]. Glomerular filtration rate (GFR) was studied using the Schwartz formula [17].

The study material was venous blood, taken in the morning on an empty stomach. Statistical processing of the obtained results was carried out using the method of variation statistics, with the calculation of the significance of numerical differences using the student's t-test.

During the exacerbation of the disease, the complex therapy included the drug Wobenzym (Mukos Pharma, Germany, in tablets, state registration number B-250-95 №1999) at a dose of 1 tablet per 6 kg body weight per day for 1 month [9].

Before the start of therapy, patients were divided into two groups: Group I - NS + LD (15 children) - with traditional therapy, and Group 2 - NS + LD (15 children) - with traditional therapy + Wobenzym.

Results and Discussion

The children examined were in the primary school age range, i.e., 7-11 years old, corresponding to the critical immune period, which plays an important role in increasing the risk of chronic pathological processes and the manifestation of LD symptoms. According to the results of the conducted research, it was found that LD is more common in male children (2-2.5 times more frequent), which corresponds to the data in the literature.

The primary condition in patients with NS on the background of LD was associated with anemia (89.4%), chronic tonsillitis (81.8%), recurring bronchitis (69.2%), adenoids (44.2%), hypothyroidism (48.7%), and gastroduodenitis (24.6%).

When studying the glomerular filtration rate (GFR), it was found that for NS on the background of LD in the conditions of the Aral Sea region, there was a lower frequency of stages I and II of chronic kidney disease (CKD) with a relative increase in the number of children with stages III-IV (twice as frequent). The average GFR value was 55.5±2.56 ml/min.

When assessing clinical-laboratory markers of LD in the children of the 1st and 2nd groups, a statistically significant higher frequency was found for: chronic focal infection (98.8%; 91.2%), pathological course of pregnancy in the mother (97.9%; 93.2%), hypotension, hypodynamia (90.1%; 87.3%), high infection index (85.9%; 76.2%), lymphocytosis (81.7%; 84.2%), facial puffiness (80.0%; 55.1%), nervous lability (68.3%; 60.1%), increased ESR (65.8%; 58.7%), decreased serum IgA (62.7%; 52.7%), monocytosis (61.3%; 57.8%), disproportional body composition (45.5%; 42.4%), thymomegaly (40.5%; 38.5%), bradycardia (42.4%; 39.3%), and "fountain vomiting" (38.6%; 22.5%) respectively ($p<0.001$-0.01). These were more pronounced in the 1st group of children compared to the 2nd group.

When assessing the clinical manifestations of NS against the background of LD, a statistically significant higher frequency of the following symptoms was observed: edema (100.0%), oliguria (100.0%), fatigue (77.6%), "chalky" pallor of the skin (75.6%), ascites (60.9%), decreased appetite (56.2%), hepatomegaly (45.5%), positive percussion sign (34.7%) ($p<0.001$-0.01).

According to laboratory test results, NS showed a significant decrease in daily urine output, an increase in daily proteinuria ($p<0.001$), total cholesterol, fibrinogen ($p<0.01$), hypoalbuminemia, hypergammaglobulinemia ($p<0.001$), and an increase in urea and creatinine levels ($p<0.001$-0.01).

Comparative assessment of immunological test results with the control group showed a significant decrease in T-lymphocytes (CD3), T-suppressors (CD8), T-helper cells (CD4), FAN, IgA, IL-2 production, and C3, C4 complement components ($p<0.001$-0.01); a significant increase in ASL of kidneys, ASL of lungs, and CIC concentration, which were higher (twice as much) in group 1 compared to group 2 ($p<0.001$).

The results of immunological studies confirm that the immune system of the body is closely related to the function of the lymphoid system, which consists of all lymphoid organs and lymphoid cell clusters. These play an important role in the immune defense mechanism, manifesting as antigenic-structural homeostasis and carrying out specific processes of immunological reactivity.

It is known that the C3 component of the complement system is an acute-phase inflammation protein and an important part of the body's defense system against infections. It participates in both the classical pathway (its formation is activated by IgG and IgM) and the alternative pathway (its formation is activated by toxins, endotoxins, IgA) of complement system activation. As a result of C3 activation, histamine is released from mast cells and platelets, leukocyte chemotaxis occurs, antibody-antigen binding is supported,

phagocytosis is maintained, vascular permeability is enhanced, and smooth muscle contraction is stimulated.

The C4 component of the complement system is a glycoprotein synthesized in the lungs and bones. It participates only in the classical pathway of complement system activation. C4 supports phagocytosis, increases vascular permeability, and is involved in virus neutralization.

In the body, the regulation of complement system activation is finely balanced. In such cases, glomerular lesions are characterized by dense intramembranous deposits, which are only detectable by electron microscopy.

The results of our studies also confirm that in the pathogenesis of C3 glomerulopathy, as well as in immune complex-mediated glomerular diseases, the disturbance of the alternative pathway of complement regulation plays a significant role [19]. In our opinion, in NS in children with LD, a membranoproliferative glomerulonephritis (GN) may form within the framework of C3 glomerulopathy, combined with low serum levels of C3 and C4 complement components.

After immunocorrection as part of combined therapy, it was found that patients who received Wobenzym (group 2) showed a decrease in clinical manifestations of NS and LD (normalization of peripheral blood and urine parameters (hemoglobin, erythrocytes, leukocytes, ESR, proteinuria, daily diuresis), prolonged clinical remission period, and a decrease in the frequency of intercurrent pathologies compared to children who received traditional therapy (group 1). In addition, 85.0% of patients showed significant normalization of coagulation, a decrease in γ-globulins ($p<0.001$-0.01), reduction of dysproteinemia, and an increase in serum albumin levels, indicating improved oxidative-reductive processes in the body.

According to the results of the conducted studies (Table 1), it can be said that immunocorrection with Wobenzym positively affects the normalization of

clinical-immunological shifts in children with NS against the background of LD. In 80.0% of the observed patients who received Wobenzym as part of combined therapy, compared to healthy children and between groups 1 and 2, there was a significant increase in the content of T-lymphocytes (CD3), T-helper cells (CD4), T-suppressors (CD8), IgA, FAN, IL-2, C3, C4 components ($p<0.001$-0.01-0.05); a decrease in ASL of kidneys, ASL of lungs, and CIC in the blood ($p<0.001$), with more frequent and significant improvement observed already after 1 month, in contrast to traditional basic therapy. The content of B-lymphocytes (CD19) showed no significant difference from the values in healthy children.

Table 1

Indicators of immune status in children following immunocorrection (M±m)

Total - 30, Nephrotic Syndrome in Chronic Glomerulonephritis with Lymphatic Diathesis					
Indicators	Healthy children (n=25)	Traditional therapy, (n=15) (group 1), P^1	Traditional therapy+wobenzyme, (n=15), (group 2), P^2	P^1	P^2
CD3, %	54,67±0,94	35,31±1,2	50,61±1,2	p<0,001	p<0,001
CD4 %	33,13±0,83	22,31±1,4	26,85±1,3	p<0,001	p<0,001
CD8, %	19,90±0,72	13,51±1,2	16,14±1,3	p<0,001	p<0,01
CD19, %	11,60±0,89	15,34±0,74	13,57±0,34	-	-
ABL of blood, % ASL of kidneys	-	7,0±0,62	3,1±0,47	-	p<0,001
ABL of the lungs, %	-	8,5±0,44	4,9±0,47	-	p<0,001
IgA, g/l	1,45±0,16	0,57±0,15	0,76±0,16	p<0,01	p<0,05
CIC, opt. units/pl	0,002±0,003	0,089±0,001	0,027±0,003	p<0,001	p<0,001
FAN	50,50±1,11	31,09±0,38	45,82±0,26	p<0,001	p<0,001

IL-2	2,8±0,09	2,1±0,07	2,0 ±0,05	p<0,01	p<0,01
C3 component, g/L	1,8±0,12	0,88±0,15	1,1±0,12	p<0,001	p<0,01
C4 component, g/L	0,4±0,13	0,2±0,16	0,35±0,19	p<0,01	p<0,05

: P^1- The validity of the differences compared to the group of healthy children. P^{2-} The validity of the differences between group 1 and group 2.

Based on the results of the research, it can be confirmed that during immunocorrection with Wobenzym, the drug plays an important role in normalizing immune homeostasis, optimizing inflammation, providing a pronounced anti-edematous effect, enhancing the cytotoxic activity of macrophages, inducing or inhibiting cytokines, including IL-2, removing circulating and tissue-fixed immune complexes, inhibiting their formation, and positively affecting the function of complement components C3 and C4 [9].

In group 1 of children receiving traditional treatment, despite improvement in general well-being, biochemical, functional parameters, and symptoms of renal inflammation slightly decreased by the end of the treatment, but during the follow-up, they again increased, and in 6 (40.0%) patients, periodic swelling, proteinuria, hypercholesterolemia, and hypergammaglobulinemia persisted, which was due to the relapsing course of renal processes.

Normalization of clinical manifestations of nephrotic syndrome (NS) against the background of Lipoid Nephrosis (LN), such as oliguria, edema, fatigue, “chalky” pallor of the skin, ascites, loss of appetite, positive percussion sign, hepatomegaly, and prolonged remission period, was observed only in 5 (33.3%) patients.

CONCLUSIONS:

1. In children in the Aral Sea region with nephrotic syndrome (NS) against the background of lipoid nephrosis (LN), there is a deep multi-level immunological deficiency, manifested by a decrease in T-lymphocytes (CD3), T-suppressors (CD8), T-helper cells (CD4), FAN, IgA, IL-2

production, and C3, C4 complement components, as well as an increase in ASL of the kidneys, ASL of the lungs, and the concentration of CIC, which persist even in the remission period of the disease.

2. In NS on the background of LN, a disturbance in the alternative pathway of complement regulation plays an important role, leading to the formation of membranoproliferative glomerulonephritis within the framework of C3-glomerulopathy, in combination with low levels of serum C3 and C4 complement components.
3. High efficiency of immunoreaction with the Wobenzym drug recommends its wide use in the complex therapy of NS on the background of LN.

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