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# INNATE AND ADAPTIVE IMMUNITY STATE DETERMINATION IN CHILDREN WITH PYELONEPHRITIS ON CONGENITAL HYDRONEPHROSIS BACKGROUND IN ACTIVE STAGE OF THE DISEASE

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**Innate and adaptive immunity state determination in children with pyelonephritis on congenital hydronephrosis background in active stage of the disease**

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**Purpose:** to determine the state of adaptive and innate immunity depending on the age of children and the etiological factor of pyelonephritis on congenital hydronephrosis background in active stage of the disease.
**Methods:** The research was performed by using of conventional methods.
It was found that the leading causative agents of secondary pyelonephritis on congenital hydronephrosis background in young children were Escherichia coli, Enterococcus faecalis and Staphylococcus epidermidis; in middle-aged group were Pseudomonas aeruginosa, Proteus vulgaris, Proteus mirabilis, Klebsiella pneumoniae, Escherichia coli, Enterococcus faecalis, Staphylococcus epidermidis, Candida albicans, and in elder children were Proteus mirabilis, Klebsiella pneumoniae, Escherichia coli, Enterococcus faecalis, Staphylococcus epidermidis, Candida albicans. There was detected that a decrease in CD95+ lymphocytes in young children and a significant increase of this index in middle-aged and elder children took place. A potent elevation of pro-inflammatory cytokines production was shown, and in middle-aged and elder children with Enterococcus faecalis pyelonephritis the level of IL-1β was in 3.8 and 5.2 times, respectively, higher than in young children, and in Escherichia coli pyelonephritis in 3.4 and 5.9 times, respectively. A decreased neutrophils phagocytic activity was detected that may contribute to insufficient elimination of circulating immune complexes as evidenced by their significant increase in serum. The highest rates were determined in elder children, where the leading pathogens were mainly Enterococcus faecalis, Escherichia coli and Klebsiella pneumoniae.
**Conclusions:** Thus, there is no doubt about the presence of immune mechanisms in children with pyelonephritis on congenital hydronephrosis background, autoimmune syndrome is developed by damage of own cells membranes and sensitization to cell components mimicking the infectious agent antigens. Post-infectious autoimmune syndrome in combination with secondary immunodeficiency is a more severe condition because involves not only autoaggression, but also a lack of factors and components of immune response, manifested by severe course of pyelonephritis in children with congenital hydronephrosis. The existing immunodeficiency creates conditions for disease progression, stimulates other pathogenetic factors, and as the infectious inflammatory process is developing, an immunological insufficiency is worsening and associated not only with the persistence of microorganisms, their toxins, but also with depletion of immune system reserves.
***Keywords:*** *children, pyelonephritis, etiological factor, immunity, pro-inflammatory cytokines, immunoglobulins.*

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**Аурудың белсенді сатысында туа біткен гидронефроз фонында пиелонефриті бар балалардағы иммунитеттің ішкі және бейімделу жағдайын анықтау**

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**Мақсаты:** балалардың жасына және аурудың белсенді сатысында туа біткен гидронефроз фонында пиелонефриттің этиологиялық факторына байланысты адаптивті және туа біткен иммунитеттің жағдайын анықтау.
**Әдітер.** Зерттеу жалпы қабылданған әдістермен жүргізілді. Ерте жастағы балаларда туа біткен гидронефроз аясында қайталама пиелонефриттің жетекші қоздырғыштары Escherichia coli, Enterococcus faecalis және Staphylococcus epidermidis болып табылатыны анықталды; орта жастағы топта Pseudomonas aeruginosa, Proteus vulgaris, Proteus mirabilis, Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris, Proteus mirabilis, Klebsiella pneumoniae, Escherichia coli, Enterococcus faecalis, Staphylococcus epidermidis, Candida albicans, ал ересек балаларда - Proteus mirabilis, Klebsiella pneumoniae, Enteracocociae pneumoniae, E. coli. Albicans саңырауқұлақ микроорганизмдері.
**Нәтижелер.** Жас балаларда CD95 + лимфоциттердің төмендеуі және орта және ересек жастағы балаларда бұл көрсеткіштің едәуір артуы анықталды. Қабынуға қарсы цитокиндер өндірісінің күшті жоғарылауы байқалды, ал пиелонефриті бар орта және ересек балаларда Enterococcus faecalis il-1β деңгейі жас балаларға қарағанда тиісінше 3,8 және 5,2 есе жоғары және Escherichia coli тудырған пиелонефрит кезінде тиісінше 3,4 және 5,9 есе жоғары болды. Нейтрофилдердің фагоцитарлық белсенділігінің төмендеуі анықталды, бұл айналымдағы иммундық кешендердің жеткіліксіз жойылуына ықпал етуі мүмкін, бұл олардың сарысудағы айтарлықтай ұлғаюымен дәлелденеді. Ең жоғары көрсеткіштер ересек жастағы балаларда анықталды, онда жетекші қоздырғыштар негізінен Enterococcus faecalis, Escherichia coli және Klebsiella pneumoniae болды.
**Қорытынды.** Осылайша, туа біткен гидронефроз фонында пиелонефриті бар балаларда иммундық механизмдердің болуы күмән тудырмайды, аутоиммундық синдром өз жасушаларының мембраналарының зақымдануы және инфекциялық агенттің антигендерін имитациялық жасуша компоненттеріне сенсибилизация нәтижесінде дамиды. Инфекциядан кейінгі аутоиммунды синдром қайталама иммун тапшылығымен бірге ауыр жағдай болып табылады, өйткені ол аутоагрессияны ғана емес, сонымен бірге туа біткен гидронефрозы бар балалардағы пиелонефриттің ауыр ағымымен көрінетін иммундық жауаптың факторлары мен компоненттерінің болмауын да қамтиды.Бұл иммун тапшылығы аурудың өршуіне жағдай жасайды, басқа патогенетикалық факторларды ынталандырады, ал инфекциялық-қабыну процесі дамыған сайын иммунологиялық жеткіліксіздік күшейеді, бұл микроорганизмдердің, олардың токсиндерінің сақталуына ғана емес, сонымен бірге иммундық жүйенің резервтерінің сарқылуына да байланысты.
***Негізгі сөздер:*** *балалар, пиелонефрит, этиологиялық фактор, иммунитет, қабынуға қарсы цитокиндер, иммуноглобулиндер.*

**Определение внутреннего и адаптивного состояния иммунитета у детей с пиелонефритом на фоне врожденного гидронефроза в активной стадии заболевания**

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**Цель исследования** - определить состояние адаптивного и врожденного иммунитета в зависимости от возраста детей и этиологического фактора пиелонефрита на фоне врожденного гидронефроза в активной стадии заболевания.
**Методы.** Исследование проводилось общепринятыми методами.Установлено, что ведущими возбудителями вторичного пиелонефрита на фоне врожденного гидронефроза у детей раннего возраста являются Escherichia coli, Enterococcus faecalis и Staphylococcus epidermidis; в группе среднего возраста возбудителями были Pseudomonas aeruginosa, Proteus vulgaris, Proteus mirabilis, Klebsiella pneumoniae, Escherichia coli, Enterococcus faecalis, Staphylococcus epidermidis,

Candida albicans, а у детей более старшего возраста - Proteus mirabilis, Klebsiella pneumoniae, Enteracocociae pneumoniae, кишечные палочки, грибковые микроорганизмы альбиканс. Выявлено снижение CD95 + лимфоцитов у детей раннего возраста и значительное увеличение этого показателя у детей среднего и старшего возраста. Показано сильное повышение продукции провоспалительных цитокинов, у детей среднего и старшего возраста с пиелонефритом Enterococcus faecalis уровень IL-1β был в 3,8 и 5,2 раза соответственно выше, чем у детей раннего возраста, и при пиелонефрите, вызванном Escherichia coli в 3,4 и 5,9 раза соответственно. Обнаружена пониженная фагоцитарная активность нейтрофилов, что может способствовать недостаточной элиминации циркулирующих иммунных комплексов, о чем свидетельствует их значительное увеличение в сыворотке. Самые высокие показатели были определены у детей старшего возраста, где ведущими возбудителями были, в основном, Enterococcus faecalis, Escherichia coli и Klebsiella pneumoniae.

**Выводы.** Таким образом, не вызывает сомнений наличие иммунных механизмов у детей с пиелонефритом на фоне врожденного гидронефроза, аутоиммунный синдром развивается в результате повреждения мембран собственных клеток и сенсибилизации к компонентам клеток, имитирующих антигены инфекционного агента. Постинфекционный аутоиммунный синдром в сочетании со вторичным иммунодефицитом является более тяжелым состоянием, поскольку включает в себя не только аутоагрессию, но и отсутствие факторов и компонентов иммунного ответа, что проявляется тяжелым течением пиелонефрита у детей с врожденным гидронефрозом. Имеющийся иммунодефицит создает условия для прогрессирования заболевания, стимулирует другие патогенетические факторы, а по мере развития инфекционно-воспалительного процесса усиливается иммунологическая недостаточность, связанная не только с сохранением микроорганизмов, их токсинов, но и с истощением резервов иммунной системы.

***Ключевые слова:*** *дети, пиелонефрит, этиологический фактор, иммунитет, провоспалительные цитокины, иммуноглобулины.*

**Introduction**

Pyelonephritis is the most common childhood disease [1, 2] with a tendency to chronic inflammation and recurrence. At the same time, there is an increase in the frequency of secondary pyelonephritis in children associated with congenital anomalies of urinary tract, such as congenital hydronephrosis, which can lead to the development of chronic renal failure [3, 4, 5]. Despite the constantly increasing number of antibacterial drugs and administration according sensitivity of the pathogen, it is not always possible to provide effective antimicrobial therapy [6, 7].

The recurrent nature of pyelonephritis in children, resulting from congenital hydronephrosis, the absence of etiotropic therapy effect are explained not only by the presence of highly virulent microflora [8], but also by complex pathogenetic mechanisms [9, 10, 11], in the development of which immune system plays an important role [12, 13].

The role of immune mechanisms in the pathogenesis of secondary pyelonephritis in children becomes especially important due to immune system immaturity and imperfection of its many functions in the child's body [14], and also in children with congenital hydronephrosis, secondary pyelonephritis occurs on the background of already existing immunological body restructuring according to impaired differentiation of the urinary tract tissues [15].

The available literature data show a low level of local immune defense in urinary tract that creates favorable conditions for bacterial colonization [16, 17]. Inflammation in the urinary system appears due to the interaction of two main factors such as child's immunity characteristics and the pathogenic characteristics of pyelonephritis causative agent [18].

However, the literature analysis revealed that such issues as the intensity of phagocytosis, the role of apoptosis, the nature of the cytokine response are insufficiently studied and debatable, there are also no data on the phenotyping of T- and B-lymphocyte subpopulations, their activation during pyelonephritis in children with congenital hydronephrosis.

Therefore, the aim of this research was to determine the state of adaptive and innate immunity depending on the age of children and the etiological factor of pyelonephritis on congenital hydronephrosis background in active stage of the disease.

**Methods**

24 children aged 1 month to 18 years ill with pyelonephritis, who were in the Municipal Non-Profit Enterprise «Regional Clinical Children's Hospital № 1» were examined. 10 somatically healthy children formed a control group.

Collecting the material from children and bacteriological investigation were performed by conventional methods [19, 20].

Immunological methods included determination of levels of immunoglobulins main classes (A, M, G), cytokines, general complement, circulating immune complexes by using of enzyme-linked immunosorbent assay. Determination of lymphocyte subpopulations

were done by immunofluorescence using Fits-labeled monoclonal antibody kits. Phagocytic activity of neutrophils was determined by the number of phagocytic cells [21].

The work was carried out in accordance with the requirements of the Law of Ukraine «About Medical Products», 1996, articles 7, 8, 12, to the management of ICHGSP (2008), GLP (2002), in accordance with the requirements and norms, standard provisions on ethics of the Ministry of Health of Ukraine № 690 dated 23/09/2009. The research was performed with minimal psychological losses from sick children. Parents were fully informed about the methods and volume of the study.

Statistical analysis was performed using StatSoft STATISTICA Version7 [22, 23].

**Results**

Analysis of the research data revealed that the leading pathogens of secondary pyelonephritis on the background of congenital hydronephrosis in young children (1 group - children under 3 years) were Escherichia coli, Enterococcus faecalis and Staphylococcus epidermidis; in middle-aged (2 group - children from 4 to 7 years) were Pseudomonas aeruginosa, Proteus vulgaris, Proteus mirabilis, Klebsiella pneumoniae, Escherichia coli, Enterococcus faecalis, Staphylococcus epidermidis, Candida albicans, and in elder children (3 group - children from 8 to 18 years) were Proteus mirabilis, Klebsiella pneumoniae, Escherichia coli, Enterococcus faecalis, Staphylococcus epidermidis, Candida albicans (Fig. 1).

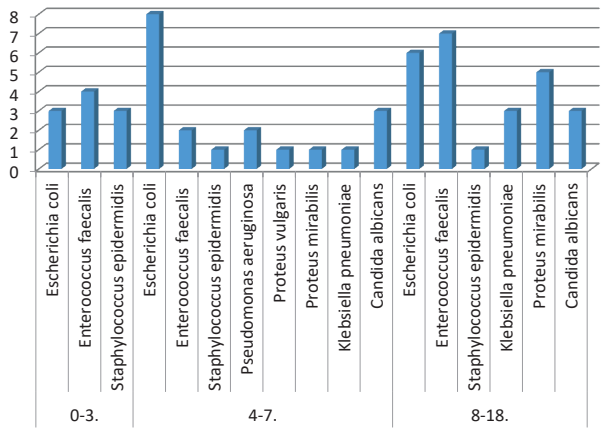


Figure 1. Leading pathogens of pyelonephritis in children with congenital hydronephrosis in the active stage of the disease.

Immunological studies in children with pyelonephritis on the congenital hydronephrosis background detected that the parameters of cellular immunity versus reference values appeared variable in children of different ages. Statistically significant changes regardless to child's age and the pathogen were observed in quantity of CD3+, CD4+, CD8+ and CD25+, indexes of which were decreased. There was found a reduced level of lymphocytes subpopulation with a marker of CD95+ differentiation in young children and a significant increase of this index in middle-aged and elder children (Fig. 2).

Analysis of immunoglobulin levels in children with pyelonephritis on congenital hydronephrosis background revealed that the serum IgA did not differ significantly from the reference values in young children, and in middle-aged and elder children there was a suppression of IgA production. There was a significant increase in IgM in children of group 1, in children of group 2 this index did not differ from the reference values, and in children of group 3 there was a tendency to elevation (Fig. 3).

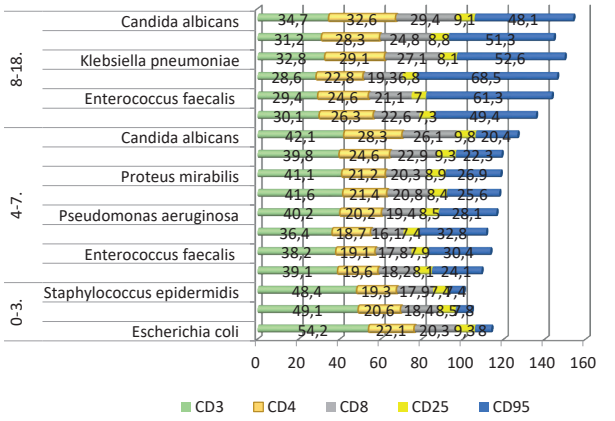


Figure 2. Parameters of the cellular immune system in children with pyelonephritis on congenital hydronephrosis background in the active stage of the disease.

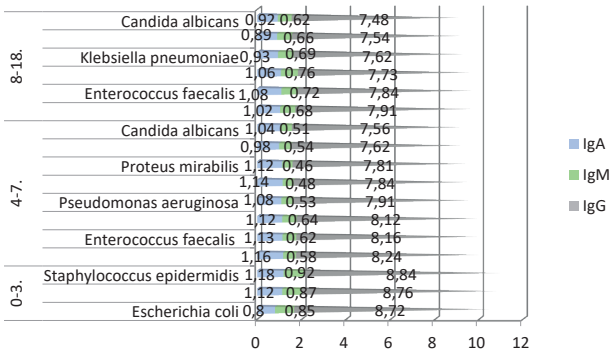


Figure 3. Immunoglobulins indexes in children with pyelonephritis on congenital hydronephrosis background in the active stage of the disease.

The main role in the immunopathogenesis of pyelonephritis on congenital hydronephrosis background belongs to the mediators of inflammation, which are formed in the body in response to the influence of aggression factors produced by causative agents. Cytokines are able to modulate the regulatory and effector functions of cells. In a healthy body, there is a balance between cytokines with pro-inflammatory and anti-inflammatory activity. A normally functioning immune system prevents the uncontrolled release of inflammatory mediators and provides an adequate response in macroorganism against microbial invasion.

Study of pro-inflammatory cytokine status in children with pyelonephritis on congenital hydronephrosis

background showed a significant increase in the production of IL-1β, IL-6 and TNFα, versus reference values, in all groups of children independently on leading pathogen (Fig. 4).

Thus, cytokine status parameters according to levels of pro-inflammatory cytokines indicate the active stage of inflammation, and a prolonged rising in TNFα leads to the development of autoallergic reactions, which in turn lead to depletion of the immune system, inhibition of non-specific defense. These processes are crucial in the formation of immunopathological mechanisms of cellular immunity suppression at the stages of T-cell differentiation and proliferation.

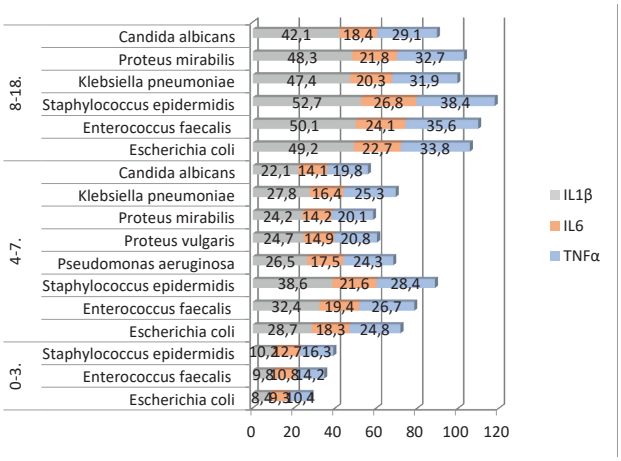


Figure 4. Proinflammatory cytokine status parameters in children with pyelonephritis on congenital hydronephrosis background in the active stage of the disease.

Phagocytosis is one of the important nonspecific immunity parameters that provides the protective properties of the body. The course of phagocytosis is manifested by time, however, at the present stage the process itself is not studied, but its results such as the fate of phagocytic cells, the number of absorbed by cells particles, its intensity is analyzed. Therefore, the study of phagocytosis allows to establish the quality of the immune nonspecific response.

It was found that the phagocytic number of neutrophils and their absorption capacity were below control values. Thus, significant changes were observed in the phagocytic activity of neutrophils. The percentage of phagocytic cells in children of different groups was significantly lower than the reference values, indicating a lack of effector functions of phagocytosis in children with pyelonephritis on congenital hydronephrosis background in the active stage, and is one of the mechanisms of low quality inflammatory response. The identified changes indicate the suppression of the body's defense systems (phagocytic chain), which can cause persistence of infection (including intracellular), weak immunogenicity and lack of intense immunity, which is clinically reflected in the torpid course of the disease and recurrent illnesses (Fig. 5).

Low efficiency of phagocytosis may contribute to insufficient elimination of circulating immune complexes, as evidenced by their significant increase in serum of children with pyelonephritis on congenital hydronephrosis background in all age groups, regardless of the pathogen and versus control group. The highest rates were found in children of elder group, where the leading pathogens were mainly Enterococcus faecalis, Escherichia coli and Klebsiella pneumoniae (Fig. 6).

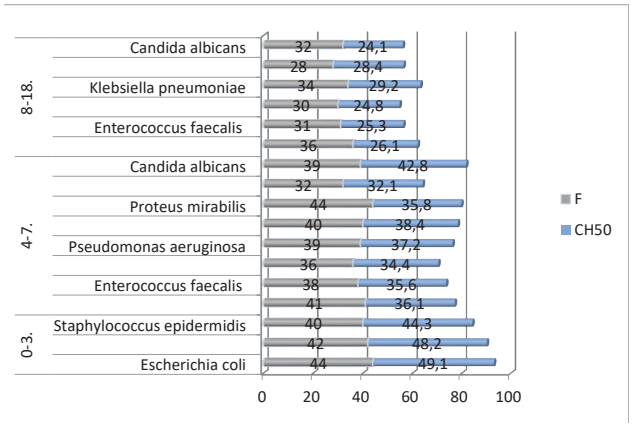


Figure 5. Indexes of phagocytosis in children with pyelonephritis on congenital hydronephrosis background in the active stage of the disease.

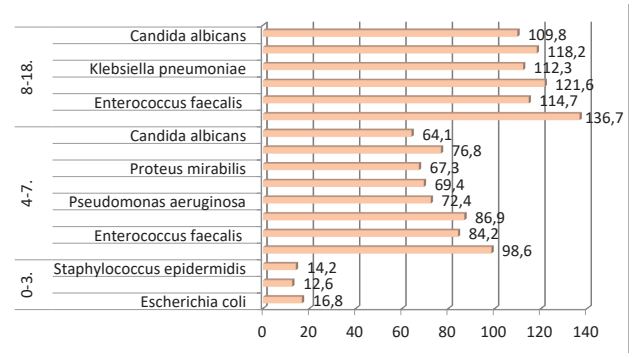


Figure 6. Circulating immune complexes index in children with pyelonephritis on congenital hydronephrosis background in the active stage of the disease.

In the comparative analysis of immunological parIn the comparative analysis of immunological parameters of cellular, humoral immune factors, phagocytic immune system and pro-inflammatory cytokine profile in children with pyelonephritis on congenital hydronephrosis background in the active stage of the disease, studying their participation and the importance of each contribution to the development of the pathological process certain peculiarities of immunopathogenesis were detected. A deficiency of complement system activity index (CH50) in middle-aged and elder children groups was established. In the 1st group (young children) the participation of CH50 in the mechanisms of elimination of circulating immune complexes which prevents their excessive accumulation and, consequently, damage of organs and tissues, was reliably shown. Therefore, this defect of the immune response in children of groups 2 and 3 can be regarded as a result of impaired secretory function of macrophages that produce CH50.

Cytotoxic effect of causative agents on lymphocytes

that lead to lymphopenia, may be indicative for suppression and functional disagreement of cellular immune response in general.

In addition, the state of immune cells apoptosis was studied indirectly by the value of the specific surface receptor CD95+. In middle-aged and elder children with pyelonephritis on congenital hydronephrosis background in the active stage of the disease a severe imbalance in cellular immunity was detected and characterized by a significant exceeding of the level of T-lymphocytes containing CD95+ receptors on their membrane surface versus reference values that indicates an activation of lymphocytes apoptosis. And elevated apoptosis leads to further profound changes and progression of existing T-lymphocyte deficiency, as well as imbalance of all immune system links.

At the same time, a decrease in the expression of the marker CD25+ on the surface of T cells was established. The revealed decrease in the level of immunoregulatory CD4+ and CD25+ T- regulating lymphocytes in the peripheral blood of children with pyelonephritis on congenital hydronephrosis background may indicate the development of autoimmune inflammation. Thus, the processes of activation of apoptosis in severe T-cell deficiency is an important pathogenetic aspect in pyelonephritis on congenital hydronephrosis background in middle-aged and elder children.

It should be noted that changes in cellular immune factors in children with pyelonephritis on congenital hydronephrosis background correspond to the inflammation processes of microbial origin in general, and are characterized by severe deficiency in absolute quantity of leukocytes, lymphocytes, cells with phenotypes CD3+, CD4+ CD8+, CD18+; decreased immunoregulatory index (CD4+ / CD8+), which is an important indicator of the harmonious function of the immune system.

**Discussion**

Disturbances in the composition of the cellular, humoral, phagocytic link and pro-inflammatory cytokine balance were noted, which were caused by antigenic factors of the leading pathogens of pyelonephritis on congenital hydronephrosis background. Therefore, it can be established that in such children a complex defect of the phagocytic link of the immune system took place, leading to insufficiency of this component of immunity. And also the high level in blood of pro-inflammatory IL-1β, IL-6, TNFα cytokines was found.

The formation of pyelonephritis on congenital hydronephrosis background is accompanied by a violation of adaptive immunity mechanisms, so the monitoring of immunological parameters showed a decrease in cellular immunity by functional activity of T-lymphocytes, absolute number of T-lymphocytes (CD3+), T-helpers (CD4+), natural regulatory cells for excluding of autoaggression (CD4+), T-cytotoxic cells (CD8+) in all age groups independently on the pathogen. According to the common view, after infecting of the urogenital tract an acute pyelonephritis is developing and in which T-lymphocytes actively migrate from the peripheral bloodstream to the area of primary inflammation. The strains of Enterococcus faecalis, Escherichia coli and Klebsiella pneumoniae have the most aggressive potential. In children with pyelonephritis on congenital hydronephrosis background such changes in the humoral immune system were detected and characterized by imbalance of CD22+, immunoglobulins A, M, G. Reduction in the absolute number of B-lymphocytes (CD22+), IgG and IgA levels in 2nd and 3rd groups, with normal IgM level in the 2nd group and a slight increase in the 3rd group. At the same time in the 1st group the rising in the number of B-lymphocytes, IgA, IgM and IgG levels in the active phase of the process was revealed.

An increase in the concentration of the circulating immune complexes is an indirect evidence of disease activity and severity. Thus, there is no doubt about the presence of immune mechanisms in children with pyelonephritis on congenital hydronephrosis background, autoimmune syndrome is developed by damage of own cells membranes and sensitization to cell components mimicking the infectious agent antigens. Post-infectious autoimmune syndrome in combination with secondary immunodeficiency is a more severe condition because it involves not only autoaggression, but also a lack of factors and components of various forms of immune response, manifested by severe course of pyelonephritis in children with congenital hydronephrosis. The existing immunodeficiency creates conditions for disease progression, stimulates other disease pathogenetic factors, and as the infectious inflammatory process is developing an immunological insufficiency is worsening and associated not only with the persistence of microorganisms, their toxins, but also with depletion of immune system reserves.

**Conclusion**

Thus, due to the etiological feature of secondary pyelonephritis on congenital hydronephrosis background, in the implementation of immune protection in this pathology innate immune factors participate greatly than the mechanisms of adaptive immunity, although, as in most diseases of infectious-inflammatory origin; the division is often quite conditional due to the close interaction and commonality of their mechanisms. Manifestation of innate immune functions in secondary pyelonephritis in children with congenital hydronephrosis in the active stage of the disease is carried out during an inflammatory reaction, which is a response to cell membranes damage by alteration and penetration of foreign agents, pathogenic or opportunistic bacteria.

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