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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

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რეზიუმე

პაციენტების სადიაგნოსტიკო და სამკურნალო ღონისიებების კომპლექსის დასაბუთება პაციენტებისათვის ყბა-კბილთა დეფორმაციებით და ფონეტიკური დარღვევებით

პ.ფლისი, ლ.იაკოვენკო, ვ.ფილონენკო, ა.მელნიკი

ა.ბოგომოლცის სახელობის ეროვნული სამედიცინო უნივერსიტეტი, კიევი, უკრაინა

კვლევის მიზანს წარმოადგენდა ყბა-კბილთა დეფორმაციების და თანხვედრილი ფონეტიკური დარღვევების ორთოდონტიული მკურნალობის ეფექტურობის გაუმჯობესება სადიაგოსტიკო და სამკურნალო ღონისძიებების კომპლექსის მულტიდისციპლინური მიდგომით შემუშავებისა და დასაბუთების საშუალებით.

ყელ-ყურ-ცხვირის ორგანოთა მდგომარეობის გავლენა ყბა-კბილთა დეფორმაციების და თანხვედრილი ფონეტიკური დარღვევების განვითარებაზე შესწავლილია 155 ბავშვზე. კლინიკური სტომატოლოგიური გამოკვლევა და ორთოდონტიული მკურნალობა ჩაუტარდა 6-12 წლის ასაკის 82 პაციენტს. მეტყველების ფონოლოგიური ნაწილის დეფექტების აღმოფხვრისათვის ჩატარებულია ინდივიდური მაკორეგირებელი ლოგოპედიური სამუშაო.

სადიაგნოსტიკო და სამკურნალო ღონისძიებების შეთავაზებული კომპლექსი იძლევა ყბა-კბილთა დეფორმაციების და თანხვედრილი მეტყველების დარღვევების მქონე ბავშვების ორთოდონტიული მკურნალობის ეფექტურობის გაუმჯობესების საშუალებას თანკბილვის ტიპის გათვალისწინებით და ინტერდისციპლინური გუნდის მონაწილეობით – ოტორინოლარინგოლოგი, ლოგოპედი, პედიატრი და ქირურგი, რაც დასტურდება პაციენტების 86,6%-ში ელექტრომიოგრაფიის, ყბების მოდელების ანთროპომეტრიული გაზომვების სკანირების და ცეფალომეტრიის მაჩვენებლების გაუმჯობესებით; კონუსურ-სხივური კომპიუტერული ტომოგრაფიის მონაცემების ანალიზმა აჩვენა ზედა სასუნთქი გზების მოცულობის გაზრდა 53,8 4,2%-ით.

EVALUATION OF GENE POLYMORPHISM OF IL-1β AND IL-10 IN CHILDREN WITH NEPHROTIC SYNDROME

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Estimating the prevalence of chronic kidney disease (CKD) in children and investigating markers of the prognosis and progression are the priority for public health. Approximately 9 in every 1 million children in the developed world require renal replacement therapy treating end-stage renal disease of CKD. The prevalence of CKD and end-stage renal disease is growing worldwide [5,13]. Taking into account the considerable prevalence and progression of CKD in children, findings effective methods of the prevention of this disease is important goal of all pediatric nephrologists. The issue of early onset of prophylaxis, the individual factors of progression of CKD not completely understood [15].

Traditional risk factors of the progression of CKD are arterial hypertension, persistent proteinuria, anemia, congenital anomalies, progressive course of the disease and resistance to pathogenetic treatment, hereditary history, and acute renal failure [4]. Nephrologists have good results in decreasing of both progression of disease and number of patients with end-stage renal disease by avoiding or correction of risk factors of CKD, and widely using renoprotective therapy. However, despite the results, the improving of quality of life and reducing the number of patients with progressive CKD is still unresolved. Genetic factors may also influence the incidence and/or the progression of CKD and its complications. Studies of genetic factors are now interesting in this population. The goal of identifying genetic factors that contribute to the outcome of CKD is to gain further understanding of the disease pathogenesis and underlying causes and, possibly, to use this knowledge to predict disease or its complications. Furthermore, by identifying patients' genetic backgrounds, it is possible that a more individualized therapy could be performed [1,3].

Progression of CKD in children with chronic glomerulonephritis also connected with immune inflammation which is known to be a marker of unfavorable prognosis. Chronic glomerulonephritis is considered as immunocomplex disease in which monocytes are activated and secreted a wide variety of biologically active compounds into the blood.

The immune inflammation is a cascade of biochemical and immunological reactions regulated by a large number of mediators, among which a special place is belonged to cytokines – low-molecular weight proteins. Each cytokine has cross-linked, synergistic or inhibitor activity in relation to other cytokines.

It is known that in the development of glomerular injury and nephrosclerosis great role belongs to pro-inflammatory cytokine IL-1β [10]. It has been shown that IL-1β is a key cytokine that induces the development of a cascade of other proinflammatory cytokines. This leads to glomerular and tubulointerstitial damage and stimulates the fibrogenesis of nephrons. IL -1β is considered to be one of the factors of progression of chronic glomerulonephritis. Balance between the production, expression and inhibition of the synthesis of proteins of the IL-1 family play the main role in the development of any inflammatory process. It was known that a higher level of IL-1 was determined in part of the patients, even before identifying the association of increased

IL-1 production with certain alleles. It has also been shown that the duration and intensity of the inflammatory process in different individuals may be different [4].

The predisposition to multifactorial diseases, especially their course, the effectiveness and safety of their treatment are largely determined by a specific set of polymorphic variants of genes.

The aim of our work was to determine the gene polymorphism of cytokines IL-1β (-511) and IL-10 (-1082) in children with nephrotic syndrome.

Material and methods. 20 patients with nephrotic syndrome were recruited into the study from 2017 to 2018 years in single center (Vinnytsya regional clinical children's hospital), in Ukraine. Mean age of the patients was 11,73±3,63 years. Boys and girls were met with the same frequency among them. All patients were diagnosed with nephrotic syndrome and received subsequent medical care at Vinnytsya regional clinical children's hospital.

All the children were carefully clinically and laboratory examined. Blood and urine samples were collected after 8 h of overnight fast. Our study included children with levels of glomerular filtration rate >90 ml/min. Estimated glomerular filtration rate (eGFR) was calculated using the Schwarz formula.

Genetic polymorphism of IL-1β (-511) and IL-10 (-1082) and serum IL1β were evaluated. The variants of IL-1β and IL-10 genes were determined from whole blood samples. Polymorphic analysis for IL-1β and IL-10 was performed by polymerase chain reaction (PCR) and subsequent restriction fragment length polymorphism (RFLP) methods. The level of IL-1β was determined by the ELISA method using standard reagent kits.

Statistical analysis was performed using the SPSS software. Difference between different groups of patients was analyzed by Mann-Whitney U-test. P values < 0.05 were considered to be statistically significant.

The study was performed in accordance with the Declaration of Helsinki and was approved by local ethics committees at the individual study center. All patients and their parents gave written informed consent before undergoing any study related procedures.

Results and their discussion. Of the 20 patients, 4 were diagnosed as nonrelapsers or infrequent relapsers of nephrotic syndrome, 12 patients as frequent relapsers, and 4 with steroid resistant nephrotic syndrome according to the diagnostic criteria of the KDIGO recommendations. All the children had I stage of CKD without renal insufficiency. There were 12 children in remission of disease during examination, 8 children had active stage of nephrotic syndrome.

We determined the variants of IL-1β (-511) and IL-10 (-1082) genes in children with nephrotic syndrome (Table 1).

We found the prevalence of the genotype CT (16 patients – 80%) of allelic polymorphism of IL-1β (-511) gene. Among the patients with nephrotic syndrome 4 had the genotype CC of the gene IL-1β (-511) (20 %).

Preliminary evidence primarily from adult CKD studies indicates that gene polymorphisms of IL-1β CT (-511) was associated with the progressive course of CKD. Presence of the C/T allelic polymorphism of the gene IL-1β (-511) in children with glomerulonephritis in the human genome can be one of the factors of the progression of CKD.

We analyzed allelic polymorphism of IL-10 as one of the important anti-inflammatory interleukins. IL-10 attenuates the inflammatory response. Decreased production of IL-10 is associated with increased CRP. Checking the polymorphism of SNP -1082 of IL-10, we determined that in 50% of children with nephrotic syndrome there was G/A genotype, in 40% - G/G genotype, and genotype A/A was only in 10% of patients. The low producer genotype A/A of the gene -1082 G>A SNP is associated with increased cardio-vascular mortality in end-stage renal disease patients.

Analyzing the contents of IL -1β in serum of children with chronic glomerulonephritis, nephrotic syndrome, we found that IL -1β was significantly increased in children with steroid-resistant nephrotic syndrome and with progression of glomerulonephritis compared with remission and with healthy children ($p<0.05$). The presence of C/T genotype is associated with twice increased production of interleukin-1β in serum, compared with children with genotype C/C ($p<0.05$) (Table 2).

A strong direct relationship between the level of IL-1β in serum and C/T allelic polymorphism of the gene IL-1β (-511) was found ($r=+0,56$) ($p<0.05$). This indicate an increased level of secretion of this interleukin in the presence of C/T genotype of IL -1β.

We analyzed connection between allelic polymorphism of gene of IL-1β and the course of the disease in our patients. Patients were divided into 3 groups: nonrelapsers or infrequent relapsers of nephrotic syndrome, frequent relapsers, and with steroid resistant nephrotic syndrome in remission and in active stage. 4 children with steroid resistant nephrotic syndrome had C/T allelic polymorphism of the gene IL-1β (-511). C/C allelic polymorphism of the gene IL-1β (-511) mostly was found in children in remission of glomerulonephritis. Our data suggest that genetic association studies have the potential to provide new insights into the factors responsible for CKD progression in case of nephrotic syndrome.

Recently, several studies have reported that polymorphisms of cytokine genes were associated with the development and severity of inflammatory diseases. Many researchers have evaluated the association with genetic polymorphisms in the IL-1b, IL-1ra, and TNF-a genes in patients with various inflammatory diseases, including IgA nephropathy, ankylosing spondylitis, and multiple sclerosis [7,9,11,13]

Interleukin genes have an extremely high degree of polymorphism, and the number of sites of this polymorphism in one gene can reach several dozen and they can be located both in encoding exons and introns, and, most importantly, in the promoter

Table 1. Allele frequencies of IL-1b and IL-10

Group of investigation	IL-1β (-511)		IL-10 (-1082)		
Children with nephrotic syndrome	CT	CC	GA	GG	AA
	16(80%)	4(20%)	10(50%)	8(40%)	2(10%)

Table 2 Levels of IL-1β according to gene polymorphism

	Genotype CC	Genotyp CT	Healthy children
IL-1β(pg/ml)	4,65±0,27	10,66±0,96*	3,16±0,25

regulatory regions of the gene structure. These DNA regions contain zones of binding of regulatory factors that determine not the reading structure, but the intensity of the end-product protein production, that is, the molecules of interleukins itself. The presence of allelic polymorphism in the promoter regions of the genes of interleukins provides a variety of individuals according to the cytokine production.

It is known that each gene is located in one of 23 pairs of chromosomes. The two alleles may be the same or differ from each other. Polymorphism represents variants of alleles that are relatively common in the population and are generally associated with a deviation in the expression or function of enzymes. Genetic polymorphism is a nucleotide variation in a particular genomic sequence, including insertions, deletions, single nucleotide polymorphism (SNP), which account for about 90% of all variations in the genome.

The genes encoding IL-1β are localized on the chromosome 2q 13-21. Among the allelic polymorphisms of IL-1β, the most studied are changes in the positions -511, -31, +3953, representing the replacement of one nucleotide. Analysis of transcriptional activity showed that at position -511 cytosine is replaced by thymine (C→T), and at position-31 thymine is replaced by cytosine (T→C). There are studies about the relation of polymorphism in the position -511 C → T with a progressive and more severe course of nephropathy. It is proved that polymorphic variants of the IL-1β gene are highly productive. Persons who are homozygous for the high-producing IL-1β allele are produced 4 or 2 times more of this cytokine, respectively, in comparing the homozygous individuals with non-mutant allele of this gene. It has also been proven that the IL-1β gene polymorphism has a close relationship with such effects as hypertension, atherosclerosis, cardiovascular complications, progression of nephropathy [2,6].

Violation of the synthesis of IL-10 may play an important role in the pathogenesis of glomerulonephritis. IL-10, as one of the anti-inflammatory cytokines, reduces inflammatory reaction. Pathological decline in the production of this interleukin leads to an increase in C-reactive protein. The genes encoding IL-10 are localized on the chromosome 1q 31-32. Among the polymorphisms of the gene most studied are -592 C→A, -819 C→T and -1082 G→A. In different studies, changes -1082 G→A are associated with mortality from cardiovascular complications in patients with an end-stage renal disease. In a number of studies, it has been established that the genotype A/A in the allelic polymorphism -1082 G→A leads to decreased production of IL-10 and increased levels of cardiovascular morbidity.

Resent study with investigating of the association between single nucleotide polymorphisms of the IL-1 gene cluster and childhood IgA nephropathy suggested that the IL1 β and IL1RN genes are associated with increased susceptibility to IgAN in children. They also suggested that the development of proteinuria in IgAN is related to IL1A and that podocyte foot process effacement is associated with IL1 β [8,13].

In another study, they investigated whether genetic polymorphisms of TNF-α, IL-1β, IL-6, and IL-10 genes leading to a more intense inflammatory response might predispose very low birth weight infants to the development of acute renal failure in severe infection. The single presence of TNF-α, IL-1β, IL-6, and IL-10 variants does not influence the development of acute renal failure, but the constellation of TNF-α and IL-6 genetic variants is associated with acute renal failure [14].

Unfortunately, studies of IL-1b, IL-1ra, and TNF-a gene polymorphism are limited in children with nephrotic syndrome [12].

Conclusions. Our data suggest the prevalence of the genotype C/T of allelic polymorphism of IL-1β (-511) gene in children with nephrotic syndrome. In our study, we demonstrated that pro-inflammatory cytokine IL-1β is independently associated with C/T allelic polymorphism of the gene IL-1β (-511) in children with steroid-resistant nephrotic syndrome and with possible progression of glomerulonephritis. Polymorphism of SNP -1082 of IL-10 consists of 50% of children with G/A genotype, 40% - G/G genotype, and 10% genotype A/A.

Genetic testing has increasingly become a valuable tool in the identification of genetic variations associated with nephrotic syndrome and may decrease the need for biopsies in the future.

Genetic screening of paediatric CKD patients may enhance the impact of preventive measures that could have a positive effect on outcome. Further studies are needed to confirm our findings and to elucidate the role of the IL-1β gene polymorphism in the progression of CKD in children with nephrotic syndrome.

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SUMMARY

EVALUATION OF GENE POLYMORPHISM OF IL-1β AND IL-10 IN CHILDREN WITH NEPHROTIC SYNDROME

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The aim of our work was to determine the gene polymorphism of cytokines IL-1β (-511) and IL-10 (-1082) in children with nephrotic syndrome.

20 patients with nephrotic syndrome were recruited into the study from 2017 to 2018 years in single center. Our study included children with levels of glomerular filtration rate >90 ml/min. Genetic polymorphism of IL-1β (-511) and IL-10 (-1082) and serum IL1β were evaluated.

Analyzing the contents of IL-1β in serum of children with nephrotic syndrome, we found that IL-1β was significantly increased in children with steroid-resistant nephrotic syndrome and with progression of glomerulonephritis compared with remission and with healthy children ($p<0.05$). The presence of C/T genotype is associated with increased production of interleukin-1β in serum, compared with children with genotype C/C ($p<0.05$). Checking the polymorphism of SNP -1082 of IL-10 we determined that in 50% of children with nephrotic syndrome there was G/A genotype, in 40% - G/G genotype, and genotype A/A was only in 10% of patients. A strong direct relationship between the level of IL-1β in serum and C/T allelic polymorphism of the gene IL-1β (-511) was found ($r=+0,56$) ($p<0.05$).

Gene polymorphism of IL-1β (-511) can be used as a marker of progression of glomerulonephritis, nephrotic syndrome but more studies are needed.

Keywords: children, nephrotic syndrome, cytokines IL-1β, IL-10, gene polymorphism.

РЕЗЮМЕ

ПОЛИМОРФИЗМ ГЕНОВ ИЛ-1β И ИЛ-10 У ДЕТЕЙ С НЕФРОТИЧЕСКИМ СИНДРОМОМ

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Целью исследования явилось определение полиморфизма генов цитокинов ИЛ-1β (-511) и ИЛ-10 (-1082) у детей с нефротическим синдромом.

20 пациентов с нефротическим синдромом включены в исследование с 2017 по 2018 гг. В исследование были включены детей с уровнем скорости клубочковой фильтрации >90 мл/мин. Оценивали генетический полиморфизм ИЛ-1β (-511), ИЛ-10 (-1082) и уровень сывороточного IL1β.

Анализ содержания ИЛ-1β в сыворотке у детей с нефротическим синдромом выявил, что ИЛ-1β значительно повышен у детей с стероид-резистентным нефротическим синдромом и детей с прогрессированием гломерулонефрита в сравнении с ремиссией и здоровыми детьми ($p<0,05$). Наличие C/T генотипа связано с повышенной продукцией ИЛ-1β в сыворотке в сравнении с детьми с генотипом C/C ($p<0,05$). Изучая полиморфизм SNP-1082 ИЛ-10, определено, что у 50% детей с нефротическим синдромом имеется G/A генотип, у 40% - G/G генотип, а генотип A/A - у 10% пациентов. Обнаружена сильная прямая связь между уровнем ИЛ-1β в сыворотке и C/T аллельным полиморфизмом гена ИЛ-1β (-511) ($r=+0,56$) ($p<0,05$).

Результаты проведенного исследования позволяют заключить, что генный полиморфизм ИЛ-1β (-511) можно использовать в качестве маркера прогрессирования гломерулонефрита и нефротического синдрома.

რეზიუმე

ინტერლეიკინ-1β-ს და ინტერლეიკინ-10-ის გენების პოლიმორფიზმი ბავშვებში ნეფროზული სინდრომით

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კვლევის მიზანს წარმოადგენდა ინტერლეიკინი-1β-ს (-511) და ინტერლეიკინი -10-ის (-1082) გენების პოლიმორფიზმის განსაზღვრა ბავშვებში ნეფროზული სინდრომით.

კვლევაში 2017-2019 წწ. ჩართული იყო 20 პაციენტი ნეფროზული სინდრომით, გორგლოვანი ფილტრაციის სიჩქარით >90 მლ/წთ. ფასდებოდა ინტერლეიკინი-1β-ს (-511) და ინტერლეიკინი-10-ის (-1082) გენების პოლიმორფიზმი და შრატისმიერი ინტერლეიკინი-1β.

ინტერლეიკინი-1β-ს შემცველობის ანალიზის საფუძველზე ნეფროზული სინდრომის მქონე ბავშვებში გამოავლდა ინტერლეიკინი-1β მნიშვნელოვანი მატება ბავშვებში სტეროიდ-რეზისტენტული ნეფროზული სინდრომით და ბავშვებში გლომერულონეფრიტის პროგრესირებით რემისიაში მყოფ და ჯანმრთელ ბავშვებთან შედარებით ($p<0,05$). C/T გენოტიპის არსებობა დაკავშირებულია ინტერლეიკინი-1β-ს მომატებულ პროდუქციასთან C/C გენოტიპის მქონე ბავშვებთან შედარებით ($p<0,05$). ინტერლეიკინი -10 -ის SNP-1082 პოლიმორფიზმის კვლევით დადგენილია, რომ ნეფროზული სინდრომით ბავშვების 50%-ს აქვს G/A გენოტიპი, 40%-ს - G/ G გენოტიპი, 10%-ს კი - A/A გენოტიპი. დადგენილია ძლიერი პირდაპირი კავშირი სისხლის შრატში ინტერლეიკინი-1β-ს და ინტერლეიკინი-1β-ს (-511) გენის C/T ალელურ პოლიმორფოზმს შორის ($r=+0,56$) ($p<0,05$).

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