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Characteristics of Changes in Gene Polymorphism in Community Acquisited Pneumonia in Children

U. R. Fayziyeva
MD, DMedSci Dots, Termez branch of Tashkent Medical Academy, Department of Propaedeutics of Children's Diseases and GP pediatrics

Abstract: This article describes the modern molecular genetic diagnosis of community-acquired pneumonia in children. The main points for improving the diagnosis and differential diagnosis of pneumonia in children is the timely identification of a sick child with complicated disease courses. According to the author of the article, the content of the IL1ß, TNFα and IL4 cytokine genes in the blood serum of sick children with community-acquired pneumonia depends on the prevalence and period of the disease, as well as the severity of pneumonia.

Key words: children, pneumonia, gene polymorphism region, cytokines.

Relevance of the work.

Pneumonia occupies a leading place in the structure of childhood morbidity and mortality. The incidence of pneumonia in the world is 15–20 per 1000 children in the first 3 years of life. Child mortality from pneumonia is about 1.1 million cases. Moreover, 99% of deaths from pneumonia in children under 5 years of age occur in under- and moderately developed countries of the world. According to WHO, the incidence of pneumonia in young children in economically developed countries does not exceed 3–4% and is no more than 8–9% among all other deaths. In countries with a low standard of living, the morbidity rate in children under the first 5 years of age exceeds 10–20%, and the share in the structure of causes of child mortality is 25% or more [1, p. 34; 2, p. 32].

The incidence of pneumonia in children of all age groups is still not decreasing, with a particularly high level of sick children and subsequent hospitalization occurring in early childhood and preschool age. In the Russian Federation, the incidence of pneumonia in children aged 1 month to 15 years ranges from 4 to 17 per 1000 per year. The maximum incidence was observed in children aged 1–3 years – from 465 to 1356 per 100,000 population. The reasons are: age-related features of the formation of the pulmonary, immune system, ENT organs of a growing organism, climatic and environmental living conditions of children, seasonality, social status of the family and living conditions, diseases of the mother and child, age up to 5 years, male gender, late application for medical care, late admission to hospital, gestational age at birth less than 28 weeks. Scientists highlight not only age-related, but also regional fluctuations in the incidence of community-acquired pneumonia [3, 4, 5].

The highest incidence and mortality due to pneumonia was observed in newborns and children of the first years of life. At the same time, the frequency and severity of the disease, and also his forecast in different countries of the world are not the same. Yes, according to According to WHO, the incidence of pneumonia in young children in economically developed regions are not exceeds 3-4% and is not more than 8-9% among all causes of mortality. IN same time at countries with low cultural and socio-economic level, unstable political situation and ongoing military conflicts, the incidence of pneumonia in similar age groups exceeds 10-20%, and its share in the structure of causes of child mortality is more than 25%.

Scientists in Uzbekistan have proven that long-term infections lead to secondary immunodeficiency, which causes activation of pathogens and frequent relapses of the disease. It has been shown that disturbances in the production, secretion and uptake of pro-inflammatory cytokines lead to profound defects in protection against infection, the development of "immunological paralysis", and increased direct damaging effects of microorganisms and their toxins on lung tissue. It has been established that secondary immunodeficiency, leading to exacerbation, closes the circle of pathological reactions with the development of chronic pneumonia (Bobomuratov T.A., Kamalov Z.S. et al., 2021). Despite the current changes in the diagnosis, treatment and rehabilitation of children with community-acquired pneumonia, there are many controversial issues regarding the use of new effective approaches in the diagnosis and treatment of these patients (Agzamova Sh.A., 2015, Shamsiev F.M. 2022, Fayzieva U.R., 2022).

Determining changes in clinical-anamnestic, biochemical, molecular-genetic analyzes of community-acquired pneumonia in young children, reducing the exacerbation of pneumonia by correcting methods of treating the disease taking into account the mechanisms of pathogenetic development of pneumonia, as well as reducing morbidity and mortality among young children, can provide the younger generation with a full-fledged active life.

The purpose of the study:

- to identify molecular genetic risk factors for the development of community-acquired pneumonia in children, taking into account the regional characteristics of the course of CAP in children.

The objectives of the study are as follows:

- to assess the prognostic significance of molecular genetic mechanisms (based on the study of IL1β gene polymorphisms in the development of community-acquired pneumonia in young children;
- to study the frequency of occurrence of TNFα, IL4 gene polymorphisms in CAP in children

The object of the study was 200 sick children with community-acquired pneumonia who were hospitalized in the department of pulmonology and pediatric intensive care of the clinical base of the Termez branch of the Tashkent Medical Academy.

The subject of the study was venous blood for biochemical and blood serum for immunological studies.

Research methods. The study used general clinical, biochemical, immunological (ELISA), functional, instrumental and statistical examination methods.

M molecular genetic The studies were carried out in the laboratories of the scientific diagnostic center at the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan. Methods of molecular genetic testing: IL1 β T-511C (rs 16944) and IL-4 (rs 2243250) of the C589T gene, a method for detecting polymorphism of the TNF α G308A gene by genotyping. DNA extraction. Analysis of gene polymorphism was carried out using the polymerase chain reaction of DNA synthesis (PCR).

The data obtained as a result of the study were subjected to statistical processing on an Acer computer using the Excel-2010 software package, which includes statistical processing functions. A correlation analysis was carried out using the correlation coefficient (r) to determine the relationships between the analyzed indicators and $\chi 2$ their significance according to the Student (t) and Pearson criteria $\chi 2$. Statistical processing of the results of molecular genetic analysis Microsoft Excel, SISA9.17® *SISA, Arlequin 3.5.2.* was carried out using practical mathematical and statistical analysis programs. Statistical methods have an average selection index (M), an average standard the error (m) is in determining the correlation coefficient (r). The reliability of differences in the statistical population was assessed by parametric methods for different variances using the Student's test (t).

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Criteria for inclusion of patients in scientific studies:

The age of the patients is from 3 months to 3 years 11 months 29 days ;

- X-ray examination of pulmonary tissue infiltrate iv determination of dead time;
- one of the following symptoms:

in the presence of severe cough , fever and local auscultatory symptoms typical of STP in the lungs;

Medical limited patients;

- patients with any immunodeficiency condition;
- Patients who were hospitalized within 4 weeks before the onset of this infection or who received antimicrobial chemotherapy drugs during the previous 3 months ;

Patients born with congenital anomalies

- children with suspected cancer
- patients are vaccinated against pneumococcal infection .

Research materials. The following research materials were used when writing the dissertation:

General blood analysis - blood taken from the patient's stomach

General urine analysis - patient's urine

General stool analysis - patient's feces

Biochemical tests (alanine transaminase (alt), aspartate the blood of sick children was taken for the translation of transaminases (ast), total protein, calcium, urea, nitrogen balance, creatinine.

For immunoassays - Blood serum from children with CAP was taken.

Research methods. General clinical studies, biochemical analysis, special research methods - molecular genetic, immunological research methods, statistical data processing was carried out using the Student's test.

The following methods were used to examine patients:

I. _ General clinical:

History of illness and life;

2. Physical examination;

3. Clinical blood test with leukocyte count ;

II. Instrumental research methods:

1. X- ray of the chest;

2. Pulse oximetry;

3 . Molecular genetic _ research:

Determination of the level of interleukins genes (IL-1β, TNFα , IL-4) in blood serum.

General clinical research methods:

Clinical and laboratory diagnosis - This was confirmed by a set of instrumental indicators. Clinical examination consisted of studying the complaints of sick children, collecting anamnesis data on death and life, physical examination, as well as monitoring the course of the disease over time . chest x-ray , The results of molecular genetic testing were taken into account. At the first stage, the examined patients were conditionally divided into 2 groups depending on the severity of VP , namely :

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moderate form of the disease and severe form . A severe form of CAP in patients was considered to have at least one of the following criteria:

- respiratory rate > 60 times per minute in children under 2 months, depending on the age of the patients;
- SpO2 < 90-92%;
- damage to two or more lobes of the lung;
- mental disorder of the patient;
- extrapulmonary source of infection (carditis, etc.);
- anuria;
- decrease in the number of leukocytes in the blood < 4 x $10^{9}/^{1}$;
- hypoxemia PaO_2 < 60 mm Hg;
- hemoglobin<100 g/l;
- hematocrit<30%;
- acute renal failure (blood creatinine >176.7 mmol /l , urea nitrogen >7.0 mmol /l).

Instrumental research _ For medical reasons Ultrasound examination (ultrasound) of internal organs (liver, kidneys) was performed.

X-ray examination of the chest organs. An X-ray examination of the chest organs was carried out according to medical instructions from the department (Korolyuk I.P., 2013).

Pulse oximetry examination was carried out in the emergency department of the Children's Medical Center, in the departments of pulmonology, pediatric intensive care, and pediatric pathology.

Pulse oximetry is a non-invasive method of measuring the percentage of oxyhemoglobin (oxygen saturation) in arterial blood. This method is based on the principle of spectrophotometry - measuring the absorption of light of a certain wavelength by hemoglobin contained in red blood cells of peripheral blood.

Results of the study and their discussion. "Analysis of a prospective study of clinical symptoms of CAP in children" shows the results of a study of the influence of risk factors and immunological studies on the course of CAP in children. The total number of patients in the prospective clinical study was 200 children aged 3 months to 3 years 11 months 29 days. From 2019 to December 2021, patients who were treated in the departments of pulmonology, pathology of infants and intensive care were monitored. The study included 15% of patients who were not vaccinated against pneumonia. During follow-up, all patients with CAP were analyzed for the presence of predominant clinical signs of pneumonia. Depending on the severity of the disease, patients were divided into the following groups depending on the severity of the disease.

Group 1: children with moderately severe CAP - 146 children, 80(55%) boys and 66(45%) girls.

Group 2, children with severe CAP - 54 children, 28 (52%) boys, 26 (48%) girls.

The distribution of children by gender who suffered from CAP shows that in the study the number of boys was 108 (54%), the number of girls was 92 (46%), but there was a statistically significant difference by gender (the number of boys was 8 (4%) more) was not observed ($p<0.05$).

Chest X-ray examination was performed on all 200 children with CAP.

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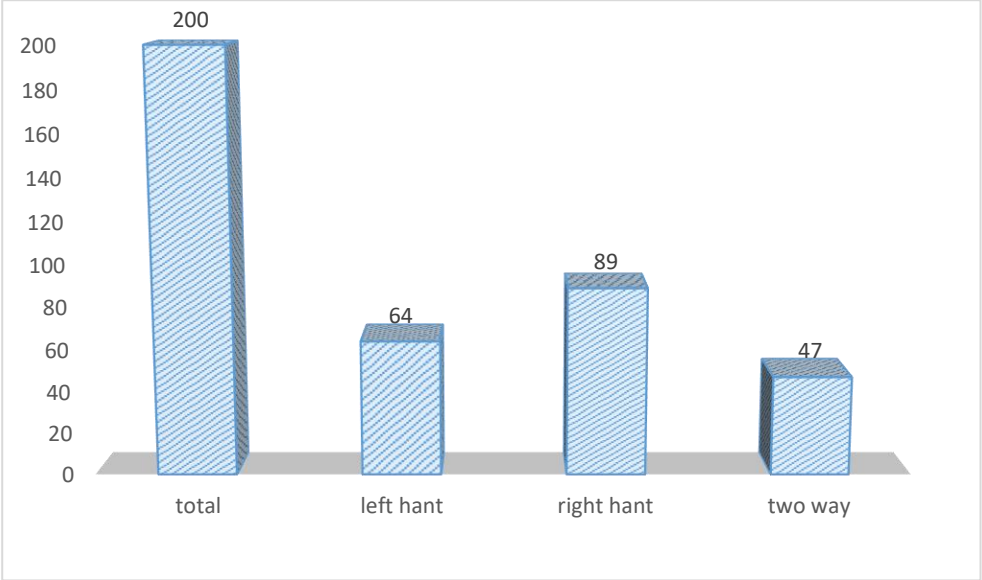

Fig-1 Chest X-ray results.

According to the analysis of Fig. 2 in moderate and severe forms of CAP, right-sided lesions were observed in 89(44.5%) patients, left-sided lesions in 64(32%), bilateral lung lesions in 47(23%).

"Features of molecular genetic indicators in community-acquired pneumonia" . A total of 72 children were taken for genetic testing, of which 38 were boys and 34 were girls. IL-1 β (rs 16944) gene T3954C, TNFα G308A, IL-4 gene polymorphism (rs2243250) C589T was studied in a special molecular genetic laboratory.

When analyzing the results obtained as part of genotyping, in the group of children with CAP living in the Surkhandarya region, compared with the control group in the group of patients with the allele OR = 1.946, 95% CI=1.119> 1.946> 3.386, x^2 = 5.63 (p=0.0176) were 1.57 times more common, Allele C OR = 0.514, 95% C I=0.295>0.514>0.894, x 2=5.63 (p=0.018) more common in the group of healthy children. When analyzing genotypes, the homozygous genotype TT IL 1β T-511C (rs 1143634) showed significant differences in frequency of occurrence, therefore for this genotype OR = 2.97, 95% CI = 0.93> 2.97> 9.489 2.6 times more common in the group of patients with x^2= 3.608 (p=0.057). Significant differences with O P parameters for the heterozygous CT IL genotype 1β (rs 16944) T-3954C not detected. However, along with the indicators OR = 0, 491, 95% СИ=0.234>0.49>1.031, x_2=3.578 (p=0.058) are registered as a protective genotype, and CC IL -1β. A clear trend of significance was noted for the T511C genotype (rs 1143634). An assessment of the total contribution of genotypes in the presence of the simultaneous occurrence of the mutant allele T - CT and TT revealed a high index OR = 2.037, 95% CI = 0.97 > 2.037> 4.278, x^2= 3.578 (p=0.058).

Table 1. IL-1β gene polymorphism (rs 16944) T3954C in genotypic groups and control groups

No.	Groups	Allele and genotype frequency distribution												χ2	OR (95% CI)
		C		T		T/T		T / S		S / S		TT +T C			
		n	%	n	%	n	%	n	%	n	%	n	%		
1.	General Main group (n= 72)	88	61	56	39	11	15.3	27	37.5	34	47.2	3 8	53	3.578 (p=0.06)	0.25 >0.50> 1.03
2.	Including: VP medium-heavy (n=47)	56	60	32	34	8	17	17	36	22	47	25	53	0.3 73 (p=0.50)	0.61 >1.30> 2.7
3.	Including: VP severe (n=25)	33	66	24	48	3	12	10	40	12	48	13	52	3.6 (p=0.057)	0.93 >2.97 > 9.5
4.	Control group (n=71)	106	75	3 6	25	5	7.0	26	37	40	56	31	4 4	3, 4 (p=0.0 5)	0.91 > 2.03 > 4.3

Note: χ^2 – Pearson *reliability index indicator;* OR – *relative risk*

Table 1 shows that IL1 β (rs 16944) T-3954 C gene polymorphism in genotype groups in severe form of CAP T/T was 3(12%), T/C 10(40%), C/C 12(48%) x^2= 3.6 (p=0.057) OR (95% CI) 0.93>2.97> was 9.5. Identification of heterozygous C/T and homozygous S/S allows one to predict the severity of CAP. In the control group it was χ 2 = 3.4 (p = 0.05), OR (95% CI) 0.91>2.03>4.3.

In conclusion, the data obtained show that in the Surkhandarya region, heterozygous T/C and C/C IL-1 β in the group of children infected with CAP homozygous genotype T-589C (rs 16944) and IL4 (rs 2243250) of the C589T gene in young children infected with CAP living in the Surkhandarya region is one of the unfavorable prognostic factors for the development of pathology.

Thus, both population selection and allele frequency in the group of patients with CAP indicate genetic variability in the determination of polymorphism of the IL-1β and IL-4 genes. Thus, the results obtained suggest that the C allele and CT+TT genotypes of IL1 β (rs 16944) T511C and IL4 (rs 2243250) C589T polymorphisms are significant predictors of a high risk of developing CAP in children in the Surkhandarya region (p <0.05) and allows us to predict the severity of the disease in children of this group. The actual values of allelic diversity in the tested groups are χ2 in the control group and χ2 = 0.66 among patients with VP = 0.84 from χ^2 = 0.86. The expected frequency of allelic diversity was found in all three genotyping groups.

Table 2. Distribution of IL-4 gene polymorphism (rs 2243250) in the group of patients with CAP S589T in genotypic groups and control groups

No.	Groups	Frequency distribution of alleles and genotypes												x 2	OR (95%
		C		T		CC		T / T		T / T		ST+TT			
		n	%	n	%	n	%	n	%	n	%	n	%		
1.	General main group (n=72)	97	67	47	33	37	51.4	29	40.3	6	8.3	35	48	0.041 (p =0.84)	0.51>1.08>2.25
2.	VP medium-heavy (n = 47)	63	67	31	33	22	47	16	34	2	4.2	18	38	0.029 (p =0.86)	0.45>0.94>1.95
3.	Severe form of CAP (n=25)	34	68	16	32	15	60	13	52	4	16	17	68	0.003 (p=0.088)	0.26 >0.97>3.7
4.	Control group (n=71)	97	68	45	32	32	45	33	46	6	8	39	5 5	0.041 (p=0.84)	0.45>0.93>1.9

Note: x^2 *– **Pearson*** reliability ***index;*** OR **–** ***relative risk***

In conclusion, our results indicate that IL1 β **(**rs 16944) T511C and И L 4 (rs 2243250) S589T S/T (rs 16944) polymorphism of the C allele and CT+TT genotypes allow us to estimate that it is a significant predictor of a high risk of developing CAP in the Surkhandarya region (p <0.05) and predicts the severe course of the disease in children of this group. IL-4 (rs 2243250), analysis of the C-589T gene polymorphism did not reveal allelic variants among the IL4 gene (rs 2243250), C-589T genotypes in the frequency of occurrence V P moderate S/S 22 (46%), S/T there were 16 (34%). C/C homozygosity was 15(60%), C/T 13(52%) in severe form of CAP. χ 2 = 0.041 (p = 0.84), O R (95% CI) was 0.51>1.08> 2.25. No significant differences in the frequency of occurrence of T/T homozygotes were found.

Table 3. Distribution of TNFα G308A gene polymorphism in genotypic and control groups

No.	Groups	Allele and genotype frequency distribution										χ2	OR (95% CI)
		G		A		G/G		G/A		A/A			
		n	%	n	%	n	%	n	%	n	%		
1.	General Main group (n= 72)	96	67	48	33	59	82	9	12.5	4	5.5	0.041 (p=0.8)	0.55>1.09>2.28
2.	Including: moderate CAP (n=47)	58	61	37	39	42	89	3	6	2	4	0.029 (p=0.86)	0.3 5>0.84> 1.95
3.	Including: CAP severe (n=25)	38	76	eleven	22	18	72	6	24	1	4	0.003(p= 0.089)	0, 4 5>0.92 > 3.8
4.	Control group (n=71)	85	60	57	40	35	49.3	33	46.4	3	4.3	0.041 (p=0.84)	0.51 >1.08> 2.25

Note. x^2 - Pearson reliability$_{index}$; *OR* - relative risk

TNFα gene polymorphism G308A G/G homozygote was 59(82%), and heterozygote G/A was 9(12.5) χ 2 0.041 (p=0.84) OR (95% CI) 0.55>1.09>2.28.

The data obtained show that in the Surkhandarya region the homozygous genotype TNFα G308A G/G in the group of children with CAP is one of the unfavorable prognostic factors for the occurrence of pathology.

In conclusion we can say, Regional genetic testing for the development of CAP in young children is the most modern method of scientific research, which shows the consequences of how pathology spreads across generations. The actual values of allelic diversity in the control groups are x 2 = 0.66 in the control group and x 2 = 60.20 among patients changed to 69.3.

Polymorphisms of the IL -1β gene T-511C (rs16944) and the IL -4 gene C-589T (rs 2243250) and the TNF-α G308A gene have pathogenetic significance in young children with CAP; the role of their interaction in the development of the severity and complications of CAP has been revealed. There was an association between the G/G genotype of the TNF-α gene and the risk of developing severe CAP (χ2=5.3 p=0.06; O R =0.45; 95% CI = 1.007-4.154).

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