ENGLISH VERSION: THE CONTENT OF INTERLEUKINS AT RESPIRATORY DISTRESS SYNDROME IN PREMATURE INFANTS

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The aim of this study is to analyze the contents of cytokines in preterm infants with respiratory distress syndrome. The child's gender plays an important role in the development of the disease (total patients - 38, boys-22 and girls-16). The different dynamics of IL-6 and TNF-α in the initial period of the high content of their ($p < 0.01$) was characterized for Neonatal respiratory distress syndrome. The indicators reduce on the background of the therapy ($p < 0.05$), full normalization is not achieved. Determination of IL-4 shows the authentic decrease in the initial stage of the disease ($p < 0.05$). Later in the blood content of IL-4 is changed - increased by improving but unreliable indicators are observed ($p>0.05$). IL-10 levels in the initial period rise, during therapy they are decreasing, but the results so far are reliable ($p < 0.01$). Identified violations testify to a great extent about the important role of these cytokines in the pathogenesis of respiratory disorders in premature infants with respiratory distress syndrome.

Key words: respiratory distress syndrome, pro-inflammatory interleukins, anti-inflammatory interleukins, premature infants

Introduction

It is known that neonatal period is one of the most critical in a child's life, when there is a major restructuring of its functional systems, especially breathing and circulation, starting with fetal life [4].

Among the respiratory disorders, respiratory distress syndrome is the most common cause of perinatal morbidity and mortality [7].

RDS is the most common cause of respiratory failure in the early neonatal period. The lower the gestational age and weight at birth are, the higher its occurrence is [2, 3, 10].

Respiratory disorders develop primarily in preterm infants. Development of neonatal RDS is promoted by morphofunctional features of the respiratory system in a premature infant [16, 20, 22, 24].

RDS is the cause of death in about 25% of all deceased infants and in infants born at 26-28 weeks of gestation, this figure rises to 80% [3, 11].

Due to the continuing high mortality from neonatal RDS, the study of this disease has received much attention during several decades [1, 5, 15].

Measures of antenatal prophylaxis of neonatal RDS have been developed, however, the incidence of the disease remains high [6, 12, 25]. Premature infants, who are characterized by this disorder, in the general population are 6-12% [3].

The disease is polygenic. In addition to the functions of oxygenation and ventilation, non-respiratory lung functions are impaired at RDS, in particular, the production of biologically active substances of cytokines [13]. Interleukins play the most important role among them. Currently, the increased production of pro-inflammatory interleukins in the mother's body with onset of labor has been proven. In addition, cytokines are one of the leading mechanisms to protect the newborn infant during the early adaptation [8, 21].

Cytokines are regulatory peptides produced by cells of the body. Cytokines are endogenous local mediators of intercellular communication. The secretion of cytokines is a short-term process. Regulation of the immune response at all stages of the disease is the main biological role of cytokines [8].

Therefore, cytokines may be distinguished as a new independent system of regulation of body functions, along with existing neural and hormonal regulation [13].

IL-6 is one of the main regulators of the immune response and hematopoiesis. Furthermore, it performs the function of mediator of protective processes against infection and tissue damage. Preterm birth is associated with a high synthesis of IL-6 [9, 19].

In response to the introduction of pathogens, a powerful expression of IL-6 by placental macrophages begins.

It is also known that TNF-α is a pluripotent cytokine which is produced mainly by monocytes and macrophages and it fulfills most important functions [18].

IL-4 is characterized by anti-inflammatory properties. It is a dimer with a certain molecular weight and a regulator of immune responses. Its products are regulated by other cytokines. It has an immunomodulatory effect [8]. The anti-inflammatory IL-10 is a key regulator of the immune response. It has a powerful anti-inflammatory effect.

The course of neonatal RDS is characterized by different dynamics of interleukins.

The role of pro-inflammatory and anti-inflammatory cytokines in the pathogenesis of respiratory distress syndrome in premature infants is of great interest, attracting the attention of clinicists and neonatologists [23].

The purpose of this study is to analyze the content of serum pro-inflammatory and anti-inflammatory cytokines in preterm infants with respiratory distress syndrome.

Material and methods

Information about ante- and intrapartum risk factors, information on the newborn, the results of clinical observation, laboratory data and instrumental methods have been included in thematic records.

The serum blood samples were stored at - 4° C no more than one month. Results of the study were recorded in the laboratory journal.

The inclusion criteria: preterm infants with respiratory distress syndrome.

The study included children with a gestational age from 27 weeks to 36 weeks and birth weight from 1120 to 2350 g (Table 1).

The quantitative determination of serum interleukin (TNF-α, IL-6 and IL-10, IL-4) was conducted by immunoenzyme method in 38 preterm infants. Sex of the infant plays an important role in the development of the disease (out of 38 infants 22 patients turned out to be boys, 16 – girls). Neonatal RDS is significantly more likely to develop in boys ($p <0.05$).

13% of infants with neonatal RDS were born from multiple pregnancies.

Static processing of the results was performed by variational statistics with calculation of the arithmetic mean value (M), standard error of the arithmetic mean (m), standard deviation (σ).

Table 1
General characteristic of the examined preterm infants at birth

Parameter	Values in groups	
	Neonatal RDS	Group of healthy preterm infants
Birth weight (grams)	1792±199.1	2065.2±432.1
Length (cm)	41.6±1.74	45.5±2.3
Term of gestation (weeks)	33.0±1.8	34.7±1.3
Evaluation according to the Apgar score at the 1st min. of life	5.2±1.3	6.7±0.6
At the 5th min. of life	6.3±0.9	7.3±0.4

Results and discussion

Clinical signs of neonatal RDS are manifested by respiratory failure in children of gestational age up to 36 weeks immediately after birth, or in 2-8 hours one can observe hurried respiration, swelling of the nose wings, participation of complaint regions of chest in the act of breathing, diffuse cyanosis.

Premature newborns from the subgroup without respiratory disorders after the stabilization in the NICU were transferred into the patient's management in the Department of pathology, mainly in connection with diet disorders: a low or very low body weight at birth.

Children from the subgroup with severe RF were in the NICU, and then were transferred to the NPD for aftercare and nursing. On the basis of clinical and survey data, all patients in this subgroup were diagnosed with respiratory distress syndrome. According to the clinical indications, all infants from this subgroup underwent infusion therapy and parenteral nutrition.

Gestational age, as well as body weight, is one of the prognostic parameters in newborns: the lesser GA, the higher is the likelihood of unfavorable outcome.

The distribution of premature newborns according to GA in our study was as follows (Table 2).

Table 2
*The distribution of subgroups of premature **newborn**s according to gestational age*

Gestational age (weeks)	Group of healthy preterm infants		Neonatal RDS	
	abs	%	abs	%
27-33 (early preterm birth)	12	60	21	55.3
34-37 (late premature birth)	8	40	17	44.7
Total	20	100	38	100

As can be seen from the table, the subgroup of preterm of healthy preterm infants patients and neonatal RDS was comparable to the distribution in the subgroups of early and late preterm birth, because the analysis showed no statistically significant differences ($p>0.05$).

In 90% of cases of acute respiratory failure, the symptoms appeared immediately after birth, in 10% of children – in the next few hours after birth. In the first day after birth, 33 patients (86.6%) had evidence of severe respiratory failure, which was an indication for AR.

In 5 (13.4%) of premature infants clinical symptoms of the disease were diagnosed in more than 24 hours after birth.

The obstetric history plays an important role in the assessment of the newborn condition: the data about the state of her health and characteristics of the pregnancy. Adverse conditions for antenatal fetal development entail the occurrence of preterm birth, which contributes to ante- and intrapartum-related damage to the lungs of the child and the development of neonatal respiratory distress syndrome.

The research results reveal the adverse factors affecting fetal development that contribute to premature birth.

The mothers of the "neonatal RDS" group had burdened obstetrical history: the present pregnancy was preceded by medical abortion, miscarriage, premature birth, that in the early stages created preconditions of threatened abortion, contributed to the development of severe gestosis of the second half of pregnancy, preterm birth. In this group gynecological and somatic diseases, chronic foci of infection were revealed significantly more often ($p<0.05$).

Condition of such factors as the threat of the abortion, a severe form of gestosis and operational labor adversely affect the condition of premature immediately after birth. Newborns are at high risk of developing acute intrapartum hypoxia and RF.

In most cases, children are born with low points at Apgar score (4.5 ± 0.9). Neonates had expressed symptoms of RF, manifested diffuse cyanosis, dyspnea with active participation of accessory muscles in the act of respiration.

Table 3
Parameters of respiratory function of the lungs at birth in preterm infants with neonatal RDS.

Parameter	Rates
pH	7.29±0.43
pCO_2 mm hg	50.5±11.8
pO_2 mm hg	53.5±13.2
% SO_2	78.9±9.61
blood saturation O_2 %	86.2±3.13

The absence of effective spontaneous respiration at birth is an important factor that disrupts the alteration of fetal blood circulation and normalization of pulmonary blood stream.

High content of IL-6 in rudimentary funicular blood is determined in 27.2% of premature newborns with neonatal RDS and in 18.3% of healthy premature newborns, which is related to its increased intrauterine output.

Morphological dismaturity of lungs, aspiration of amniotic fluid, contributing to the antenatal and intranatal trauma of alveolar and bronchial epithelium contribute the development of neonatal RDS.

In this context, in the group of neonata RDS, 82.2% of premature newborns develop RF at birth, which is an indication for AR. The laboratory criteria of lungs respiratory function correspond to the clinical signs of RF

For other children of neonatal RDS group (17.8%), the clinical signs of DN appear during the first 8 hours of life. As

we can see in the Table 4, the course of neonatal RDS was characterized by the dissimilar dynamics of IL-6.

Table 4
Content of IL-6 in blood of premature newborns with Neonatal RDS

Parameters	The values of parameters		
	Neonatal RDS		Group of healthy preterm infants
	At the beginning	At discharge	
IL-6 in pg/ml	21.30±0.05	14.21±3.18	5.19±0.16

High content of IL-6 ($p<0.01$) is registered at the initial period. Against the background of the complex therapy that was conducted, the decrease of this index ($p<0.05$) is observed, but it does not reach complete normalization.

From the data of literature it can be observed that the increased products of TNF-α cause regulation abnormalities of cellular energy exchange and metabolism, in premature newborns, the considerable increase of its level is noted on the first week of life, that is an unfavorable factor of bronchopulmonary dysplasia development. In this group of children the signs of RF are preserved and time of AR leading is considerably increased [14].

As Table 5 demonstrates, clinical course of neonatal RDS has been characterized by various dynamics of TNF-α. In the initial period, high levels of TNF-α ($p<0.001$) have been indicated. Against the background of complex therapy, this parameter has been decreasing ($p<0.01$), but has not reached full normalization.

Table 5
Content of TNF-α in blood of premature newborns with neonatal RDS

Parameters	The values of parameters		
	Neonatal RDS		Group of healthy preterm infants
	At the beginning	At discharge	
TNF-α pg/ml	40.6±0.51	23.1±0.47	4.50±1.57

In the investigation of the level of anti-inflammatory IL-4, the following changes have been revealed (Table 6).

Table 6
The content of IL-4 levels in preterm infants with neonatal RDS

Parameters	The values of parameters		
	Neonatal RDS		Group of healthy preterm infants
	At the beginning	At discharge	
IL-4 pg/ml	1.89±0.20	2.97±2.05	2.18±0.32

The investigation of the level of IL-4 (inhibiting differentiation of T-helper type 1 and synthesis of pro-inflammatory cytokines by macrophages) indicates a significant decrease in the initial period of the disease ($p<0.05$). Later levels of IL-4 in the blood have been changing – they are increasing while improving, but changes noted are unreliable ($p<0.05$).

As it can be seen, the content of IL-4 in the blood plasma of preterm infants with neonatal RDS did not have any statistically significant changes throughout the study period. Expression of interleukin has been stable and provided the necessary balance of the immune system.

Further, there is a full respiratory-hemodynamic adaptation of preterm infants.

In the investigation of the level of anti-inflammatory IL-10, the following changes have been revealed (Table 7).

Table 7
The content of IL-10 levels in preterm infants with neonatal RDS

Parameters	The values of parameters		
	Neonatal RDS		Group of healthy preterm infants
	At the beginning	At discharge	
IL-10pg/ml	14.02 ± 0.37	9.28± 0.38	5.51±1.06

As one can observe, there is an increase in this index ($p< 0.001$) during the investigation of IL-10 level in the first day of life in premature infants with respiratory distress syndrome. In future, the content of IL-10 level is changed and significantly decreased, but marked results are still reliable ($p < 0.01$). It indicates about important role of IL-10 in the development of pulmonary pathology in infants.

In that context, in the opinion of the authors [17], it plays an important role in the regulation of immunity, because it activates reactions of inflammation's interference.

Thus, considerable dominance of secretion of pro-inflammatory cytokines IL-6 led to the development of more serious inflammatory process in premature infants with respiratory distress syndrome.

The detected problems testify in a greater degree about important role of pro-inflammatory IL-6, anti-inflammatory cytokine (IL-4) in pathogenesis of respiratory problems in premature infants with respiratory distress syndrome.

Thus, the performed investigation detected special aspects of early postnatal immune acclimation in premature infants with neonatal RDS. The major changes are characteristic for TNF-alpha.

At first IL-10 level increased and kept overstated in the middle of pathological process. It testified about favorable course of the disease.

Conclusions

1. High levels of IL-6, TNF-α in the blood serum are detected, when there are respiratory disorders associated with RDS.
2. IL-4 level depends on fetal age. Amount of IL-4 decrease in the blood serum of premature infants is directly proportional to gestation period.
3. Changes in the blood of IL-10 level testify about important role of this indicant in the development of respiratory disorders when there is neonatal RDS.

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