**Features immunity in children with bronchopulmonary dysplasia**G.S. Senatorova, О.L. Logvinovа
Department of pediatrics and neonatology №1 Kharkiv national medical university
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**Resume:** the inspected state of the immune system in a 131 child with bronchopulmonary dysplasiaduring a remission and intensifying of disease. It is educed that for children with bronchopulmonary dysplasiainherent low level of absolute amount of lymphocyte, on a background the increase of cytotoxic lymphocyte (CD8, CD16), oxygen dependent ability of granulocyte, and activating of immunoproteins of sharp phase (Ig M), in default of clinical signs of intensifying of disease.

At acute respiratory infection there is a paradoxical reaction of cellular immunity with the decline of lymphocyte on a background activating of cytotoxic cages. Equally with that dynamics of increase of cytotoxic markers at sharp respiratory infection unsatisfactory, that testifies to exhaustion of reactivity of cellular chain of immunity.

Bronchopulmonary dysplasia(BPD) is severe chronic bronchopulmonary diseases that arises up mainly for the prematurely born children. For today, classic BPD, the basic etiologic factors of that is a hyperoxya, volumotrauma and barotrauma, goes away to the past. Improvement of methods of artificial ventilation of lungs, assisted survivability of new-born with small and extremely small mass bodies сакулах lungs had born that to the terms of appearance of septal tissue [1].

Necessity of respiratory support prematurely born can be accompanied by the mechanical defeat of lungs and hyperoxya. They are often joined by pre-, postnatal infection, hyper-, or hypovolume of small circle of circulation of blood, that brake alveolarisation. For such children, at present depend of oxygen on 28 time of life, the "new" form of bronchopulmonary dysplasiais diagnosed [2, 9].

Phatomorphology of forming of bronchopulmonary dysplasia, includes inflammation and fibrosis. For children with the "new" form of BPD fibrosis is minimum. Triggers at the "new" form of bronchopulmonary dysplasia more influence on alveolarisation and angiogenesis of pulmonary system [1]. Next to it, intensifying of BPD passes through an only mechanism - inflammation, with the further programed transformation in fibrosis through activating of cytokines (TNFα, IL1 β,- 6, - 8) and inducible enzymes [7].

At the bronchopulmonary dysplasia acute inflammation always arises up on a background chronic, that stipulates duration and weight of intensifying. Equally with that for a patient on BPD of 3th [7]. Alveolarisation proceeds and predominance of destructive or processes of reparation in shallow bronchial tubes, bronchioles and teeth ridges determine the prognosis of disease. Thus, at slave child with formed BPD it is important warning of activating of inflammation in the distal departments of respiratory highway.

Triggers of intensifying of bronchopulmonary dysplasia pathogens are considered, from them there are 80-90 % are viruses. In the aspect of features of immunity of child with bronchopulmonary dysplasia, as prematurely born with a chronic bronchopulmonary disease, in a period, becoming of the immune system is remembered expression of L.Paster "Microbe - nothing, substrate – all”.

The features of the immune system of child that was born prematurely born. Yes, the prematurely born do not have a sufficient amount of granulocytic predecessors in marrow and the reserve pool of granulocytes is sharply decreased. Therefore at the case of considerable requirement in granulocytes more often there is a neutropenia. Granulocytes and monocytes of child born prematurely differ in chemotaxis activity and increase adhesive.

The capacity is decreased of phagocytes for tranasendotelium migration is bound to the presence of more "hard" impoverished by the unesteritied fatty acids of membrane. Certain insufficient secretion of liposomal-cationic proteins equally with a high capacity for the generation of oxygen by phagocytes. A function of phagocytosis differs in the incompleteness of processing and violation of HLA- of presentation for forming of the purchased immune answer [10].

Maybe that the protective role of phagocytosis is limited by imperfectness of mechanisms of opsonization, in particular by the excalation of the system of complement. In umbilical cord blood at the general level of haemolytical activity of complement, content of components of С3, С4, is born, factor In folds 50 level of adults, and components of attacks membrane complex С5, С8 and С9 all in prematurely born prolonged the grows products of complement, while in worn 2 to life.

In the conditions of insufficiency of a bear immunity, the basic loading is on the alternative way of activating of complement, but in prematurely born he remains inferior due to the deficit of factor B and properdine [5,10]. In blood of prematurely born subzero content of NК- of cages (is marked 0,3 in comparing to worn (0,77 NК- of cage differ cytotoxice and by the capacity of lymphocytes for the synthesis γ-INF) [6]. Squirrel of sharp phase, namely CRP, α-macroglobuline, antitrypsin is decrease.

A bear immunity is compensated by mainly plenty of lysocime and far of lymphocytes, that equally with IgG of mother protects from massive expansion of antigens. The T-cell show a high capacity for spontaneous proliferation, but a capacity for proliferation on ordinary mitogens and bacterial antigens is decrease. Except that, at lymphocytes prematurely born can appear both the marker of CD4 and CD8 [10]. It testifies to the exit in circulation of blood of fully ripe not cell of thymus.

The feature of T-cell prematurely born is absence of expression on them receptors to IL- 2 and weak synthesis of IL- 2, that influences on differentiation of cages and products γ-INF[6]. Next to it, researches are show rapid growth of levels of cytokines and С-reaction protein in blood of new-born children at development of sepsis that testifies to the early ripening of mechanisms of products and secretion of separate cytokines and proteins of sharp phase. To the level of adults of helpers function of lymphocytes arrive at after the second year.

Level of Ig G in new-born to 32 weeks gestation an about 0,4 g/л. From 32 to 38 week is an active transport of Ig G through a placenta and in worn new-born content of Ig G in blood does not differ from indexes adult. Child that was born it is to 32 weeks had very low level of Ig G, physiology weakness in relation to the synthesis of this immunoprotein. On the first year of life on various antigens the immune system can valuably answer only the products of IgМ.

Taking into account appearance of capacity for the products of Ig G only after 2 months for children to this age, especially prematurely born beside the purpose to determine propulsion MODULE of class of Ig G to the that or other infection. Large probability of by-negative results. Level of IgM higher after 0,02г/л for the prematurely born children can testify to intrauterine antigen stimulation of the immune system. Level of Ig But not anymore 0,01г/л, secretory Ig and are absent in prematurely born.

The difference of В-lymphocytes is antibody formation only Ig of M equally with satisfactory prolifaration and absence of differentiation in the cages of memory [10]. Thus, bronchopulmonary dysplasia is a disease that develops for children with the vulnerable system of local immunity of mucous membranes, by the presence of defects in cellular and humoral chains, that gives possible persist of the chronic inflammation induced as infection so by the dysregulation of immune answer.

At consideration of clinical presentation of intensifying of BPD it follows to distinguish two important aspects, needing fundamentally different going near treatment. Firstly, it is necessary to take into account ability of all viruses, some bacteria and microorganisms to persistent and avoidance of immune answer. Secondly, in most cases, feature of immune answer of child, where viruses acted part only starting factor, with further by maintenance of pathological process, due to inadequate activity of immunoregulatory mechanisms [8].

Acute infectious disease, it is considered the strong factor of activating of immunocompetency cages and products of heterospecific цитокінів of ФНО-α and ІЛ- 1, that can be produced by prematurely born at sufficient level for sharp inflammation. Through a week after the debut of disease main value specific immunoreactions begin to acquire: В-cell activating with appearance of propulsion module to the concrete causative agents, products of cytotoxic T-cell. The second phase of immune answer stipulates final eliminated of causative agent.

At the defects of activating of elements of the second phase, that characteristically, both for prematurely born and for the children of с by the chronic diseases of lungs, eliminated to the antigen is not completed. There is storage of causative agent in the organism of owner on a background establishment of new, near to the neutral mutual relations, unapparent infection or form that runs across with the effaced symptomatology [9].

All viruses are capable to persistent. Persistent of flu virus can last to 2-3,5 months, and sometimes to 17 months [4]. A parainfluenza can be in the epithelium of bronchial tubes to 3 months. Adenovirus kept in a faces of children of early age to 515 days. Persistent of RS- of virus is possible from 3 months 1 to [3]. The viruses of group of herpes, in a unapparent form, can for years be kept in neuroganglions, epithelium, lymphatic system. Obviously, that protracted persistent of microflora needs the refined tactics of avoidance of control of the immune system of owner.

This tactics include strategies: to the "presence", that allows to avoid instantaneous recognition the immune system of owner; "sabotage" - defeat of mechanisms of immune defense; "exploitations" are the use of mechanisms of immunity in the interests. Underline that exactly defects of reactivity of immune homoeostasis, can consist in basis of the heavy, complicated intensifying of BPD protracted [10].

Thus, a high risk of exacerbation of bronchopulmonary dysplasia, persistence of the pathogen on the background of dysregulation of the immune response may cause the severity of BPD, duration of exacerbation and inhibition of reparative processes in the lungs, the child born prematurely. Along the same time, work on the immunological characteristics of preterm infants is not enough. As for bronchopulmonary dysplasia - did not match at all.

The goal: to improve the diagnosis of immune status in children with bronchopulmonary dysplasia by means of first and second level of immunological studies in acute and remission.

Materials and Methods: The study was conducted at the Department of Pediatrics and Neonatology №1 Kharkiv National Medical University (Head. Department - G.S.Senatorova) in the regional center for diagnosis and treatment of bronchopulmonary dysplasia in children Kharkiv Regional Children's Hospital (chief doctor – G.R. Muratov).

The observation was located 131 child from 1 month to 3 years of age with a diagnosis of bronchopulmonary dysplasia. The diagnosis of bronchopulmonary dysplasia was established by the International Classification of Diseases 10 view (code R27.0). In the comparison group consisted of 36 children aged from 1 month to 3 year olds born prematurely who had respiratory disorders in the newborn period and is not formed BPD. Informed consent of the parents of children signed up to the beginning of the study.

Taken into account a history on the incidence of respiratory illness during the year: the relative number of patients, who are sick with respiratory diseases, respiratory diseases rate in a year, the duration of the disease.

To assess the immune status was performed first and second levels of immunological research in remission of BPD in the study group and the background health in the comparison group. Immune reactivity in both groups was determined during disease acute respiratory infections (ARI), 2-5 day acute illness (an average of 3.11 + 1.78 day ARI).

The first level of immunological studies included calculation of the absolute number of leukocytes after staining with Romanovsky-Himze;

The second level of immunological studies in each child was assessed:

Congenital immunity:

• phagocytic ability of the neutrophils, and in particular the definition of phagocytic number and phagocytic index used technique proposed D.V. Belokrinitskaya (1987);

• metabolic activity of neutrophils was assessed by a test of NBT-test (spontaneous and induced) - by G. Stuart (1983) as modified V.S. Nahoyeva (1983).

Acquired immunity:

The concentration of immunoglobulin (Ig) class A, M, G in serum by enzyme immunoassay;
• determine the number of populations and subpopulations of lymphocytes using monoclonal antibodies (T-lymphocytes (CD3), B lymphocytes (CD19), T-helper (CD4), T-suppressor (CD8)).

When analyzing the age of the patients, in order to optimize the representativeness of corrected age was calculated using the formula:

A (k) = - 40 + (A (g) + A (t)) / 4.

Where, A (k) - adjusted age in months, and (A (g) - the gestational age of the child in the week, and A (t) - chronological age in weeks.

With the purpose of research, under different ratios of immunological parameters in each category was determined percentage deviations of the formula:
% P = P PAC / P among

P% -% rejection rate; P abs - absolute value of the index in each patient; Of P - the average rate for this age

  Comparison of the samples was carried out by means of parametric and nonparametric statistics.

**Results and discussion.**

From the data history of children in both groups were transferred respiratory disease (Table. 1). Drawn attention to a large number of cases of acute respiratory illness in both groups studied. Thus, from 95,6-99,9% of children born prematurely had 1-5 episodes of ARI during the year. The presence of bronchopulmonary dysplasia did not affect the rate (r = -0,038) and duration (r = -0,112) acute nasopharyngitis, resulting ARI.

The incidence of obstructive bronchitis predominated in patients with BPD (p <0.001), whereas in the comparison group children often suffered from simple bronchitis (p <0.001). The presence of BPD was significantly correlated with the incidence (r = + 0,885) and duration of obstructive bronchitis (r = + 0,899). The course of bronchiolitis was longer in children with BPD (p <0.001). In our opinion, the prevalence of obstruction in children with bronchopulmonary dysplasia caused morphological changes that are characteristic for this disease, as a reduction of the diameter of the bronchial metaplasia of the bronchial epithelium, hypertrophy and hyperplasia of smooth muscles of the bronchioles and bronchi, bronchial hyperplastic infiltration, interstitial edema and persistent fibrosis.

Table 1.

Structure of respiratory diseases of children with bronchopulmonary dysplasia (study group) and patients who were born prematurely and did not form BPD (comparator group)

|  |  |  |  |
| --- | --- | --- | --- |
| Forms | **Study****group****n=131** | Compilation group**n=36** | **р** |
| Acute respiratory infection(nasopharyngitis) | Number of children who are sick | 125 (95,6%) | 36 (99,9%) | >0,05 |
| Incidence per year | 2,12+1,23 | 1,84+1,14 | >0,05 |
| Duration of illness (days) | 4,49+0,86 | 4,07+0,56 | >0,05 |
| Simple bronchitis | Number of children who are sick | 3 (2,9%) | 18 (50%) | <0,001 |
| Incidence per year | 0,29+0,03 | 0,84+0,22 | <0,001 |
| Duration of illness (days) | 7,87+1,87 | 6,07+0,59 | >0,05 |
| Obstructive bronchitis | Number of children who are sick | 115(87,8%) | 23 (63,8%) | <0,001 |
| Incidence per year | 2,90+1,67 | 1,38+1,14 | <0,025 |
| Duration of illness (days) | 11,8+3,02 | 7,15+1,11 | <0,025 |
| Bronchiolitis | Number of children who are sick | 11(8,39%) | 2 (5,5%) | >0,05 |
| Incidence per year | 0,67+0,43 | 0,42+0,12 | >0,05 |
| Duration of illness (days) | 18,98+1,42  | 7,34+1,26  | <0,001 |
| Pneumonia | Number of children who are sick | 52 (39,6%)  | 21 (58,3%) | <0,05 |
| Incidence per year | 1,36+1,28 | 0,76+1,14  | >0,05 |
| Duration of illness (days) | 12,98+2,42  | 9,77+1,87  | <0,05 |

In data morphologic changes superimposed edema, bronchospasm, mechanical obstruction of the bronchi and bronchioles. Ran across Pneumonia in children with bronchopulmonary dysplasia 1.5 times longer than in the comparison group (p <0.001).

In both groups revealed low absolute number of lymphocytes, along with significant individual variation (tabl..2). Perhaps this is due to inhibition of production thymocytes against a background of prematurity.

Table 2.
Percentage deviation from the norm of the absolute number of lymphocytes, cellular and humoral immunity in children chains of the main group (with BPD) and comparison group (children born prematurely)

|  |  |  |  |
| --- | --- | --- | --- |
| Indicators | **Study****group****n=131****М+m%** | Comparison group **n=36****М+m%** | **Р\*** |
| The absolute number of lymphocytes | 69,06+35,18% | 61,55+24,9% | >0,05 |
| CD3 | 88,01+43,49%  | 75,03+33,8% | >0,05 |
| CD4 | 97,76+33,43%  | 77,9+11,4% | >0,05 |
| CD8 | 108,8+34,43%  | 71,5+14,2% | <0,01 |
| CD16 | 154+117,11%  | 71,25+12,7% | <0,05 |
| CD22 | 91,43+4,62%  | 99,4+23,54%  | >0,05 |
| IgA | 86,51+57,8%  | 42,3+19,4%  | <0,001 |
| IgM | 172,47+31,2%  | 58,1+24,6%  | <0,001 |
| IgG | 98,5+58,1%  | 106+42,4%  | >0,05 |

Criteria significant at p <0.05

Significant activation killers cells (CD8, CD16) on a background of remission bronchopulmonary dysplasia, which may be regarded as higher reactivity immunity. Сhanges may be caused by a virus persistent and activation of cytotoxicity due to the specific HLA expression on the membrane of phagocytes and epithelial cells of the bronchi. Thus the term remission in children with BPD kept activating cellular immunity, indicating that long-term cytotoxic activity.

Significantly elevated levels of antibodies were acute phase and IgA. These changes confirm the theory sluggish running across inflammation of the bronchial mucosa. High (1.7 times) the level of IgM necessitates a thorough study of children with BPD at persistence of infection even in remission.

Amid ARI determined a significant inhibition of lymphocyte levels (p <0.025) (Fig.1.).

Fig.1. Figure distributions of cellular and humoral immunity in children surveyed the main group and the comparison group on the background of ARI.

Maintained activation of T-killers and NK-cells. The observed regular immune response to viral infection in children with BPD, due to activation of cytotoxic lymphocytes and immunoglobulins acute phase. We believe that reducing the absolute number of lymphocytes in the background ARI demonstrates the suppression of cellular immunity by a virus, and on the background of chronic inflammation. This phenomenon can be considered as a marker of acquired immunity deficiency components that can cause insufficient elimination of pathogens.

Indicators of phagocytosis, namely phagocytic index, phagocytic number and spontaneous and induced NBT - test were higher than in the study group and in the comparison group (Fig. 2).

Figure 2. Diagram of distribution parameters of phagocytosis in children, the main group and the comparison group on the background of the ARI.

In the presence of ARI observed the greatest increase NST - test in both groups (study group 23.2 + 12.4%, comparison group 10.05 + 11.14%). So NST - test in patients with BPD during the ARI increased in 0.8 times, which was significantly (p <0.025) indicates significant activation oxygen dependent function of neutrophils during ARI.

**Conclusions:**
1. For all preterm infants aged 1 month to 3 years exposed to low levels of absolute number of lymphocytes, as evidenced by the high incidence of respiratory disease in this category of patients.

2. For children with BPD escalated cytotoxic lymphocytes (CD8, CD16), oxygen dependent enhance the ability of granulocytes, and activation of acute phase immunoglobulin (Ig M), in the absence of clinical signs of disease exacerbation. These changes indicate a continuing inflammation with selective activation of cellular and humoral, phagocytosis in remission BPD. In monitoring of children with BPD need to consider this phenomenon to determine the persistence of inflammation and preventive measures to prevent recurrence of BPD.

3. When playing a paradoxical reaction occurs with decreased cellular immunity against a background of lymphocytes activated cytotoxic cells. Along with the increasing dynamics of cytotoxic markers when playing poor, indicating that depletion of cellular reactivity circuit immunity.

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