

ASSOCIATION OF GLUTATHIONE S-TRANSFERASE GENES (GSTM1, GSTT1, GSTP1) POLYMORPHISMS WITH RISK FACTORS FOR BRONCHOPULMONARY DYSPLASIA IN PREMATURELY BORN INFANTS

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Received 06/28/2014; accepted for printing 08/22/2015

ABSTRACT

In recent years, there has been an increase in bronchopulmonary dysplasia morbidity in premature infants, which is associated with improved survival. We analyzed the risk factors for bronchopulmonary dysplasia. It is known that the most important factors are low gestational age and birth weight, as well as prolonged use of mechanical ventilation and late onset of neonatal infection. Genetic factors can alter the body's ability to withstand oxidative stress and infection. Many candidate genes may participate in the development of bronchopulmonary dysplasia, especially those related to the regulation of the growth of alveoli, the inflammatory response, antioxidant protection and recovery processes of cells.

For this study we selected glutathione-S-transferase family genes – GSTM1, GSTT1, GSTP1. We carried out a retrospective study on the basis of a case-control. The study included 21 prematurely born babies with bronchopulmonary dysplasia (main group) and 52 premature infants who did not have bronchopulmonary dysplasia (control group). All the children underwent clinical, instrumental and laboratory examination, as well as genetic testing. Polymorphism of the genes in question and various combinations of polymorphic variants do not affect the risk of bronchopulmonary dysplasia and its severity.

We have detected the effect of genetic polymorphisms on the indicators that characterize respiratory support, frequency of the use of mechanical ventilation, noninvasive ventilation, oxygen therapy, the duration of mechanical ventilation, the duration of non-invasive ventilation, maximum inspiratory pressure and the risk of bronchopulmonary dysplasia in the infants under study. We have found a similar indirect effect of genetic polymorphisms on other independent risk factor – late neonatal infections. For proper evaluation of the contribution of genetic polymorphism it is necessary to conduct a preliminary analysis of possible clinical and laboratory parameters to identify strong independent predictors, and then analyze the indirect effects of genetic factors. Further research and development of new approaches to the mechanical lung ventilation regimens in premature infants and consideration of the genetic polymorphisms will create a set of preventive measures and reduce the incidence of bronchopulmonary dysplasia.

KEYWORDS: *bronchopulmonary dysplasia, prematurely born children, risk factors, genetic polymorphisms, artificial lung ventilation.*

INTRODUCTION

The current advances in technology of premature infants nursing and applied prolonged respiratory therapy boosted the incidence of bronchopulmonary dysplasia among patients in the neonatal intensive care unit. According to literature data there is a tendency to reduce the severity of clinical

symptoms, but the problem of the disease pathogenesis study is still great and the development of preventive measures is very important [Bhandari A, Panitch HB 2006; Matthew M et al., 2011; Ali Z et al., 2013].

As of today the main pathogenetic mechanisms of bronchopulmonary dysplasia development, in particular the imbalance between the release of pro-inflammatory and anti-inflammatory cytokines due to baro- or volutrauma, hyperoxia, pulmonary edema and septicemia has been identified. It is known that

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the central role in the development of BPD belongs to infection. The works of Bhandari V. (2009, 2014) indicate the key role of infection, as well as hyperoxia and invasive mechanical ventilation in the pathogenesis of bronchopulmonary dysplasia. According to the work of Woynarowska M. (2008), there is association between the severe form of bronchopulmonary dysplasia and late infections. The presence of prenatal infection may increase the risk of chronic lung disease, and the number of late infections affects the severity of bronchopulmonary dysplasia. Long-term use of antibiotics and extraction of multidrug-resistant strains from the endotracheal tube is confirmation of the role of late infection in the pathogenesis of bronchopulmonary dysplasia. So, it can be concluded that there are several factors leading up to the development of bronchopulmonary dysplasia, among which premature birth is the leading one, and the others, such as pulmonary baro- and volumotrauma, hyperoxia and inflammation are triggering ones. The multiple morphoregulatory molecules with a wide margin of activity, which depends on the genetic variability of a single nucleotide polymorphism in an individual, are involved in these processes. Those genetic factors may alter the body's ability to resist oxidative stress and infection. Many candidate genes may participate in the development of bronchopulmonary dysplasia, especially those associated with the regulation of alveoli growth, inflammatory response, antioxidant protection and cellular recovery processes [Van Marter L et al., 2002; Woynarowska M et al., 2008; Danileviciute A et al., 2012; Lopez E, Jarreau P, 2013; Bhandari V, 2014; Novitsky A et al., 2014].

Glutathione S-transferase (GSTs) is a family of cytosolic proteins that are involved in detoxification and conversion of various active exogenous and endogenous substances, including products of lipid peroxidation and medicines. In biological human tissues the expression of different classes of GSTs occurs in different periods of the ontogenetic development, which determines the state of the metabolic conversion of foreign compounds and endogenous toxic metabolites. The concentration of enzymes isomer, identified in liver, placenta, lung, brain, kidney, intestine and other organs and tissues depends on age features and anthropogenic load, since the inducible system of regulation is characteristic for these enzymes [Hayes J, Strange R, 2000].

Synthesis of isomer enzymes is encoded by the

family of glutathione S-transferase genes. In humans five major subfamilies of cytosolic GSTs are distinguished, which are designated as GST α , GST μ , GST τ , GST π and GST ζ [Hayes J, Strange R, 2000].

The most studied gene among the GST μ subfamily is GSTM1 (chr 1: 110,031,965-110,037,890), which may have a deletion polymorphism, if the deletion is present in the homozygous state, the synthesis of the respective enzyme-isomer does not occur. Due to the broad cross substrate specificity for the entire family of enzymes in GSTs, the absence of this isomer does not affect the viability and survival of individuals with this genetic defect. The rate of the deletion polymorphisms in the homozygous state for individuals of white race composes from 40 to 60%, for the different age groups of Ukrainian population – 50% in average [Bolt H, Thier R, 2006; Znamenskaya T et al., 2009].

GSTT1 gene (chr 22: 22,706,142-22,714,271) is the member of the τ family. If the deletion polymorphism of the gene GSTT1 is present in the homozygous state the enzyme-isomer synthesis does not takes place. The rate of homozygous deletion polymorphism in white races is 10 to 20%, in Asian population – 40%, in the different age groups of Ukrainian population – 20% in average [Znamenskaya T et al., 2009].

GSTP1 gene (chr 11: 67,108,171-67,110,701) is encoding the corresponding enzyme-isomer, and can have several polymorphisms that determine the catalytic activity. Replacement of the nucleotides adenine to guanine in position 313 of the gene results in the changes to the protein molecules, specifically, a substitution of valine for isoleucine at position 105. Among individuals with guanine instead of adenine in homozygous and heterozygous state the enzymatic activity of GSTP1 is decreasing [Frank D et al., 2002].

At present time the following features of GST genes are known: biotransformation of a large amount of drugs and industrial chemicals, for example, cytostatics, and halogenated hydrocarbons; metabolic detoxification of various carcinogens; deactivation of oxygen free radicals, which can be involved in cellular inflammation, aging and development of degenerative changes; activity in the antioxidant defense mechanisms; control of the antioxidant system and the inflammatory response in allergies; impact on the development of the lungs

[Hayes J, Strange R, 1995; Hayes J, Pulford D, 1995; Strange R et al., 2001; Gilliland F et al., 2002; An J, Blackwell T, 2003; Allocati N et al., 2003; Habdous M et al., 2004; Bolt H, Thier R, 2006; Melén E et al., 2008].

Recently there has been a lot of evidence that GSTM1 and GSTP1 are responsible for the reduction of lipid oxidation products in the lungs and modulation of eicosanoid synthesis and other pro-inflammatory mediators. Furthermore, GST act as modulators of signal transduction pathways that control cell proliferation and death, can therefore be assumed that these genes can be programmed in prematurely born children development of the lungs, which can go on the road of recovery or repair depending on interaction of genetic factors and the environment [Hayes J, Strange R, 2000; Lo H, Ali-Osman, 2007; Laborde E, 2010; Sau A et al., 2010].

In confirmation of the above, scientific literature provides evidence about associations between the glutathione S-transferases genes polymorphism and the increased demand in the use of mechanical ventilation in prematurely born infants, the increased rate of pneumonia, respiratory infections, perinatal pathology, chronic obstructive lung disease and asthma. There are studies that confirm the impact of glutathione S-transferase family genes (GSTT1, GSTM1 and GSTP1) polymorphism on the formation of the pulmonary system in infants and young children, starting from the prenatal period of life, as well as the presence of expressed genetically mediated differences in the functional lung parameters in preschool children. Insufficient attention has been paid to the issue of studying the genetic polymorphisms effect on the risk of bronchopulmonary dysplasia in pre-term children, and available literature data indicate that the glutathione S-transferase family genes can be considered as candidate genes for the risk of bronchopulmonary dysplasia [Horovenko N et al., 2007; Rossoha Z, 2007; Saadat M, Ansari-Lari M, 2007; Lavoie P et al., 2008; Horovenko et al., 2009; Znamenskaya T et al., 2009; Liang M, 2010; Danileviciute A et al., 2012; Ali Z et al., 2013; Hadchouel A, Delacourt C, 2013; Esposito S, 2014; Liu Y, 2014].

The objective of this work was to study the possible associations between GSTT1, GSTM1, GSTP1 genes polymorphism and the risk of bronchopulmonary dysplasia, its severity, and the need for respiratory support within neonatal period.

MATERIALS AND METHODS

We conducted a retrospective study on the basis of a case-control. The study was approved by the Institutional bioethics committee and conforms to the principles outlined in the Declaration of Helsinki (Br. Med. J. 1964; p.177). The study included 21 prematurely born babies with BPD (main group) and 52 premature born babies who did not have bronchopulmonary dysplasia (control group). Clinical and laboratory-instrumental examination and genetic testing were conducted for all infants. The following criteria were used for inclusion in the control group: body weight at birth less than 1500 g, gestation age less than 32 weeks and absence of the first clinical manifestations of bronchopulmonary dysplasia starting from the 36th week of gestation and subsequent follow-up. Significant differences in main clinical parameters in patients of both groups have not been identified (Table 1).

The material for conducting the study was peripheral venous blood of newborns, collected into tubes with ethylene diamine tetraacetic acid in the amount of 1.2 ml. Blood samples were collected in sterile tubes of closed system Monovett, SARSTEDT AG&Co, Germany. Before analysis the samples were stored at a temperature of -20°C. After the procedure of DNA samples extraction from the collected material using a commercial reagent kit DNA-sorb-B, AmpliPrime Company, Russia, molecular genetic study was performed using polymerase chain reaction and restriction fragment length polymorphism methods. Analysis of deletion polymorphism of

TABLE 1.

The main characteristics
of the newborns under study

| Clinical parameters | Indicators | Main group (n=21) | Control group (n=52) | p* |
|-------------------------|--------------------------------|-------------------|----------------------|--------|
| Gestational age (weeks) | M | 27.66 | 28.92 | 0.1184 |
| | Me | 27 | 28 | |
| | Q ₁ -Q ₃ | 26-29 | 27-31 | |
| Weight at birth (g) | M | 1093.81 | 1142.78 | 0.2469 |
| | Me | 990 | 1180 | |
| | Q ₁ -Q ₃ | 850-1330 | 975-1315 | |
| Number of neonates | n | 12 | 26 | 0.580 |
| | % | 57.14 | 50.0 | |

NOTE: * – significant difference between the main and control groups.

GSTT1, GSTM1 genes was conducted using the multiple polymerase chain reaction method. To determine polymorphic variants of A313G 5 of the GSTP1 gene exon polymerase chain reaction was also performed using the amplification reaction products. Detection of the polymerase chain reaction products and restriction analysis was performed using agarose gel. Amplification of extracted DNA was performed in a reaction mixture using M. Arand. The amplification products of the GSTP1 gene site were subjected to hydrolytic decomposition with the help of Alw261 restriction endonuclease. The amplified fragments were subdivided using horizontal electrophoresis in 1.5% agarose gel by staining with ethidium bromide [Arand M et al., 1996].

Processing of quantitative variables involved traditional methods of parametric and non-parametric statistical analysis. The analysis of qualitative features, which were displayed mainly in percent, involved non-parametric methods. Using parametric statistics, normal distribution of quantitative traits conducted via Kolmogorov-Smirnov test was verified; equality of the population variance was checked using Fisher's exact test.

In a normal distribution of data main statistical characteristics were used, specifically: main value (M) to determine the central tendency, standard mean error (m) for the accuracy of estimates of the mean, confidence interval (CI) – to determine the 95% range of the mean.

Determination of the *t*-test allowed us to find the probability that the average values of quantitative traits calculated for different groups belong to one and the same set. If this is probability, like $p < 0.05$ then those traits belong to different sets, because their averages differ significantly. Conversely, if the probability found above 0.05, the samples belong to one set, because there is no significant difference between their average values.

When the distribution of central tendency was abnormal we used median (Me) and the first and the third quartiles (Q_1 - Q_3).

Comparison of relative values expressed in percentage was performed using the test χ^2 (xi-square test), and comparison of the quantitative values with abnormal distribution for unrelated samples was performed using the Mann-Whitney test (*U*-test).

In order to evaluate the differences in the compared groups we used the method of logistic regression (SPSS software).

RESULTS

In 2012 in the Poltava area of bronchopulmonary dysplasia was observed at an increased rate of 29.6%. It should be noted that 100% of the identified cases were prematurely born children with gestational age of 25-27 weeks. On the one hand, this indicates the improvement of survival rates in preterm children, and on the other, it shows the need for a comprehensive analysis of known genetic risk factors for reducing morbidity rates.

We analyzed the influence of well-known risk factors of the perinatal and neonatal period on the development of bronchopulmonary dysplasia in the neonates under study. We also took into account the emergency medical attendance provided to prematurely born infants beginning from the delivery room until 36 weeks of postconception age. The retrospective analysis of risk factors conducted by stages - on the 1st, 7th, 28th day in 36 weeks of post conceptional age.

We have revealed the significant impact of gestational age and weight at birth on the increased risk of BPD developing. The children from the main group significantly more often demanded the artificial lung ventilation in the delivery room, at the same time no differences were found in the groups in the case of oxygen therapy. The beginning time of the respiratory support for both groups did not differ significantly. The analysis of the neonatal course revealed the significant increase in the number of the arterial hypotension episodes in newborns from the main group during the first 7 days. Other important risk factors are mechanical ventilation and respiratory support. A statistical analysis of the results showed that on the 7th day of life each gram of newborn's weight reduces the risk of bronchopulmonary dysplasia by 0,005; each week of gestational age does it by 0.48, and in the presence of mechanical ventilation in the early neonatal period the risk of bronchopulmonary dysplasia increases by 4.04.

We revealed that the newborns from the main groups on the 28th day had significant increase in the degree of late infections and recanalization of open *ductus arteriosus* as well as the rate in the required long-term mechanical ventilation.

At the second stage, we analyzed the polymorphic GSTT1, GSTM1 and GSTP1 gene variations (Figure 1), as well as their combinations in the

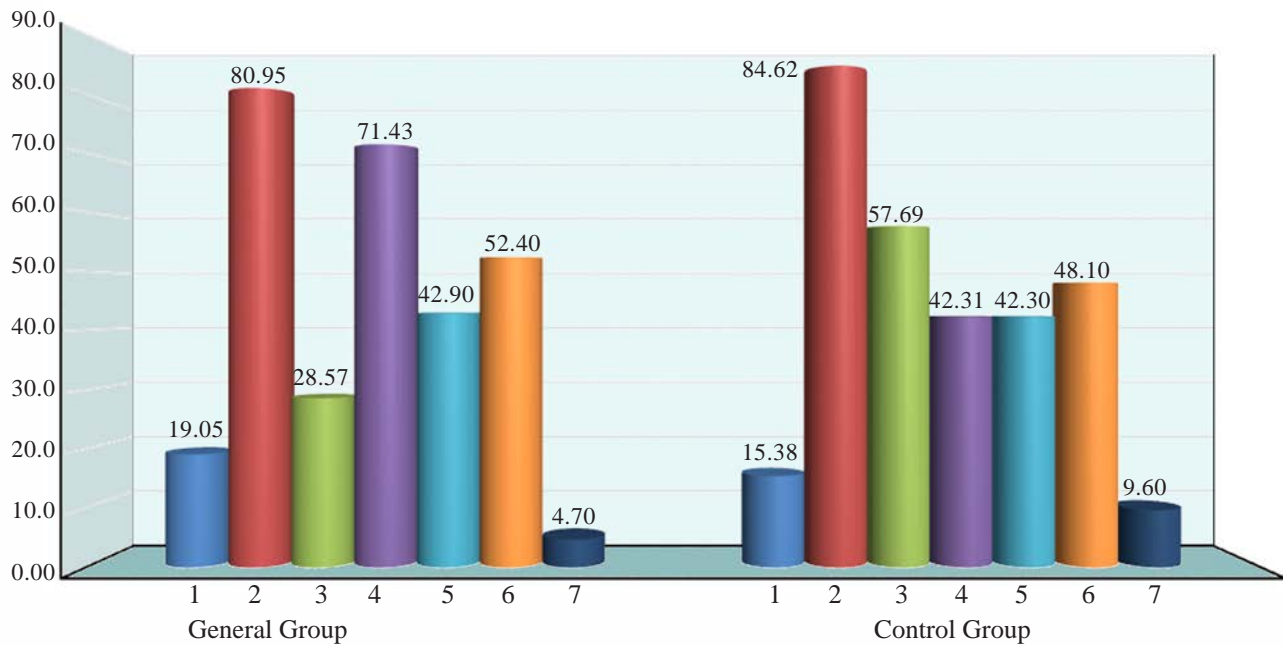


FIGURE 1. Distribution of polymorphic GSTT1, GSTM1 and GSTP1 genes variants in the comparison groups.
NOTES: 1 - GSTT1 deletion, 2 - GSTT1 allele, 3 - GSTM1 deletion, 4 - GSTM1 allele, 5 - GSTP1 AA, 6 - GSTP1 AG, 7 - GSTP1 GG

comparison groups. Insignificant increase in the rate of GSTM1 gene deletion polymorphism was observed in main group compared with the control. The rate of the deletion GSTT1 gene polymorphism does not significantly differ in the comparison groups. Distribution polymorphic variants of GSTP1 gene were not statistically different in the main and control groups as well.

Therefore, the polymorphic variants of genes of the glutathione-S-transferase family did not affect the risk of bronchopulmonary dysplasia in premature infants. Also, we found no effect of these genes on the severity of the disease. Since we were determined that the important risk factors for the development of bronchopulmonary dysplasia are mechanical ventilation and respiratory support, in the following analysis, we analyzed the effect of

polymorphic variants of these genes on the need for respiratory support.

Several authors have shown that genetic polymorphisms can be used to predict the need for respiratory support and artificial lung ventilation in prematurely born children. We evaluated the effect of genetic polymorphisms on the indicators that characterize respiratory support, the frequency of use of ventilation, continuous positive airway pressure (CPAP) and oxygen therapy, the duration of mechanical ventilation, continuous positive airway pressure and peak inspiratory pressure. The polymorphic variants of genes we studied did not affect the need for artificial lung ventilation in premature infants, but as can be seen from table 2 they conclusively determined its duration.

The mean duration of artificial lung ventilation

TABLE 2.

Respiratory support parameters in neonates, depending on the GSTT1, GSTM1 genes polymorphism

| Health intervention | GSTT1 genotype | | | GSTM1 genotype | | |
|--|---------------------|---------------------|-------|---------------------|---------------------|-------|
| | GSTT1 (+) (n=37) | GSTT1 (-) (n=11) | P | GSTM1 (+) (n=27) | GSTM1 (-) (n=21) | P |
| Mean duration of mechanical ventilation in days (Me/Q ₁ -Q ₃) | 7 (4-10) | 16 (8-28) | 0.017 | 7 (4-10) | 9 (7-19) | 0.069 |
| Mean duration of CPAP in days (Me/Q ₁ -Q ₃) | 5.5 (2-7) | 20 (12-32.5) | 0,001 | 11 (6-23) | 6 (2-16) | 0.221 |

in premature infants, who had the GSTT1 (-) genotype was significantly higher than in newborns with the GSTT1(+) genotype, $p=0.017$. These differences were also found when we were evaluating the impact of these genes on the average duration of continuous positive airway pressure, in newborns with the genotype GSTT1 (-) the mean duration of CPAP was significantly higher. Polymorphic variants of GSTM1 gene did not affect the parameters of respiratory support in the premature infants under study. We have identified the impact of GSTR1 gene polymorphism on the respiratory support parameters (Table 3).

In newborns with the GG genotype the duration of mechanical ventilation was significantly higher compared to children with genotype AA and AG (respectively, Me / Q_1-Q_3 26.5 [25-28] days compared with 7 [5-8] days, $p=0.000$ and 9 [3.5-17.5] days, $p=0.0236$). The average duration of continuous positive airway pressure therapy in the presence of genotype AA GSTP1 gene was less than in children with genotype AA and AG, but these data were not significantly different. These data indicate a need for increase sampling and further studies to obtain reliable results.

In carrying out this work we analyzed the impact of combinations of genotypes on mechanical ventilation options. The children with the combination of GSTT1(-) and GSTM1 (-) had a significantly longer mean duration of artificial lung ventilation, than the children with the functional variants of these genes (16 [8-28] days versus 7 [4-10] days, $p=0.0021$). The children, who had combination of the GSTT1 (-) and the GG genotype of the GSTP1 gene had a significantly longer mean dura-

tion of artificial lung ventilation (17.5 [8-28] days) compared to the children who had the functional variants of these genes and the mean duration of artificial lung ventilation for them was 7 [5-8.5] days, $p=0.0149$. Similar results were obtained for children with non-functional versions of the genes GSTM1 and GSTP1 compared to children with functional variants of these genes (13 [7-28] days and 7 [5-8] days, respectively, $p=0.0325$). The results of statistical analysis revealed no significant differences in the mean duration of continuous positive airway pressure depending on various combinations of genotypes. Therefore, we have identified a significant impact of genes data and combinations of their unfavorable variants on an increase in the duration of mechanical ventilation.

This indirect effect of genetic polymorphisms on the risk of bronchopulmonary dysplasia has been revealed during the analysis of its impact on another independent risk factor – late neonatal infection. In children who had the GSTM1 (-) variant the risk of late infections increased (OR 3.71 [95% CI 1.4-9.82]), $p=0.008$, compared to genotype GSTM1(+). Similar results were found for genotype AG of GSTP1 gene, in particular a relative risk to have a recent infection in children with this gene variant was 3.71 (95% CI 1.04-9.82), $p=0.008$. The relative risk of later infection in premature infants increased with a combination of these unfavorable polymorphisms AG and GG by 4.2 times (OR 4.22 [95% CI 1.53-11.65]), $p=0.005$. Our findings are of no little interest, because they show that genetic polymorphism may indirectly contribute to the development of the disease, affecting its other significant risk factors.

TABLE 3.

| Parameters of respiratory support in newborns depending on the GSTP1 gene polymorphism | | | | |
|--|-------------------|-----------------|-----------------|--|
| Health intervention | GSTP1 genotypes | | | P |
| | AA1 (n=21) | AG2 (n=24) | GG3 (n=4) | |
| Mean duration of mechanical ventilation in days (Me/ Q_1-Q_3) | 7 (5-8) | 9 (3.5-17.5) | 26,5 (25-28) | $p_1=0,136$ $p_2=0,0001$ $p_3=0,0236$ |
| Mean duration of CPAP in days (Me/ Q_1-Q_3) | 2.5 (1.5-11.5) | 11 (4-22) | 7 (6.5-20.5) | $p_1=0,1189$ $p_2=0,2998$ $p_3=0,5974$ |

DISCUSSION OF RESULTS

Our study found no significant direct association between GSTM1, GSTT1, GSTP1 genes polymorphism and the development of bronchopulmonary dysplasia as well as its severity. We investigated the mediating impact of the polymorphism of these genes on the development of bronchopulmonary dysplasia by identifying significant associations with known risk factors for this disease – the duration of mechanical ventilation and late-onset infections.

We have proved a significantly longer duration of mechanical ventilation in children with:

- GSTT1 deletion polymorphism versus the children with its functional genotype
- GSTP1 deletion versus the children with its functional genotype
- GSTT1 (-) / GSTM1(-) genotypes versus the children with GSTT1(+) / GSTM1 (+) genotypes
- GSTT1 (-) / GSTP1 (AG+GG) genotypes versus the children with GSTT1 (+) / GSTP1 AA genotypes
- GSTM1 (-) / GSTP1 (AG+GG) genotypes versus the children with GSTM1 (+) / GSTP1 AA genotypes.

The associations between polymorphisms of these genes and late-onset infections are proved to be strong, as confirmed by strong links:

- between the development of late-onset infections and the presence of a polymorphic gene GSTM1 (OR 3.71 [95% CI 1.4-9.82], p=0.008.
- between the development of late-onset infections and the presence of a GSTP1 AG or GSTP1 GG genotype (OR 4.22 [95% CI 1.53-11.65], p=0.005.

This result agrees with the data of foreign researchers: Dillon M. et al (2013) shows that null GSTM1 genotype is a risk factor for exacerbation of inflammation in individuals after inhalation of endotoxin.

The combination of polymorphic genes variants significantly increases the risk of having a late-onset infection that is confirmed by strong links between:

- development of late-onset infection and the presence of GSTT1 (-) and GSTM1 (-) genotypes (OR 4.88 [95% CI 0.75-31.59], p=0.096.
- development of late-onset infection and the presence of the GSTM1 (-) and GSTP1 AG/GG genotypes (OR 22.67 [95% CI 3.8-132.1], p=0.001.

Therefore, we have identified a significant impact of these genes and combinations of their unfav-

orable variants to increase the duration of mechanical ventilation. Such long-term mechanical ventilation is undoubtedly a risk factor for volu-motrauma and barotrauma, which can later cause damage to the immature lungs.

Literature demonstrates that there are few data about the effect of unfavorable gene variants on an increase in the duration of mechanical ventilation in preterm infants, but analysis of the impact of genetic markers on the risk and severity of dysplasia has not been conducted. Obtained findings indicate that the influence of genes on the risk of bronchopulmonary dysplasia is mediated, that is, it is implemented due to the change in the parameters of mechanical ventilation, whose duration, in its turn, is an independent risk factor for the development of bronchopulmonary dysplasia.

These data may indicate genetic susceptibility of prematurely born children for prolonged mechanical ventilation and late infections, which are the risk factors for bronchopulmonary dysplasia.

Literature data presented the influence of glutathione S-transferase genes polymorphism on premature birth, perinatal pathology, delay of the morphological lung development in infants and preschool children. The results and data presented by other authors had some controversies. From our point of view, in order to properly assess the contribution of genetic polymorphism it is necessary to conduct preliminary analysis of possible clinical and laboratory parameters to identify strong independent predictors, and then to analyze the indirect effects of genetic factors on the significant predictors. Obviously, the gestational age of the newborn, weight and duration of mechanical ventilation, late neonatal infections are the most powerful predictors of bronchopulmonary dysplasia. However, as shown by our results, the polymorphism of the genes we studied contributes to the need for prolonged mechanical ventilation and the occurrence of late-onset infections [Minelli C et al., 2010].

Thus, bronchopulmonary dysplasia is a disease that impairs the program of lung development due to the interaction of genetic and environmental factors, with invasive mechanical ventilation, infection and hyperoxia being important among them. The course of lungs development – restoration or reparation – depends on the balance of proinflammatory cytokines and antiinflammatory cytokines. As a

consequence of reparation there occurs impairment of alveolar function and deregulated vascularization that constitute the morphological substrate of architectonics in chronic lung disease.

There are many developed clinical prediction models of bronchopulmonary dysplasia, but they do not have the popularity in clinical practice due to their low validity. Another problem is the lack of information about the risk factors for bronchopulmonary dysplasia in infants within postmenstrual age changes. It is the development of valid risk predictor models for bronchopulmonary dysplasia, based on available clinical information, that will enable clinicians to promptly undertake preventive measures, parents to introduce psychological adaptation and psychological support, and scientists to plan and organize a study to examine the effectiveness of those or other prophylactics. [Agashkov V, 2011].

The research of scientists from developed countries, including Ukraine present the adverse early and long-term results of bronchopulmonary dysplasia treatment, especially the high morbidity rate in prematurely born children with bronchopulmonary dysplasia, the delay in physical and psychological development, but the risk factors including GST genes polymorphisms, which are significantly associated with the development of these effects

has not yet been identified [Anderson P, Doyle L, 2006; Bhandari A, Panitch H, 2006; Taylor J et al., 2013; Collaco J et al., 2014].

Bronchopulmonary dysplasia treatment is the subject of many works, but prescription of inhaled bronchodilators and steroids is still debatable, primarily because of the lack of clear diagnostic criteria of the presence of airflow obstruction in infants. The number of scientific works related to the development of a phased comprehensive model of newborn care aimed at the prevention in-hospital and organizing multidisciplinary post-hospital surveillance is limited [Wilkie R, Bryan M, 1987; Brundage K et al., 1990; Yuksel B, Greenough A, 1991; Holt W et al., 1995; Lister P et al., 2000; Shah V et al., 2000; Ng G et al., 2001].

Thus, the study of the mechanisms that is necessary for the protection of immature lungs from damage in the course of providing intensive care and during the growth of the child remains extremely important and urgent task. Identification of glutathione S-transferase genes polymorphism and other clinical factors could help with early identification of infants with increased risk for bronchopulmonary dysplasia, timely development of individualized preventive and treatment programs, and reduction of the incidence of bronchopulmonary dysplasia.

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