ОПРЕДЕЛЕНИЕ МЕДИАТОРОВ ФИБРОЗИРОВАНИЯ И АНГИОГЕНЕЗА В СЫВОРОТКЕ КРОВИ НЕДОНОШЕННЫХ ДЕТЕЙ С БРОНХОЛЕГОЧНОЙ ДИСПЛАЗИЕЙ

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Резюме. При преждевременных родах и послеродовом повреждении развивающегося легкого нарушаются процессы роста легочных сосудов и формирования легочных альвеол, приводящие к формированию бронхолегочной дисплазии (БЛД). БЛД является многофакторным заболеванием, патогенез поражения тканей легкого до сих пор остается не до конца изученным. Исследования биомаркеров ангиогенеза могут быть информативны для оценки развития БЛД. Цель работы – определить уровень биомаркеров ангиогенеза в течении бронхолегочной дисплазии у недоношенных детей для совершенствования ранней диагностики БЛД.

Исследована сыворотка крови 65 недоношенных детей в возрасте от 6 до 180 дней жизни. При рождении гестационный возраст составлял от 23 до 33 недель, масса тела от 480 до 1840 г, оценка по APGAR 5-6. Все дети в раннем неонатальном периоде перенесли респираторный дистресс-синдром, после которого 46 детей сформировали и 19 не сформировали БЛД. Методом иммуноферментного анализа проведено определение концентрации комплекса факторов ангиогенеза и фиброзирования.

Не выявлено значимых различий в уровнях ангиопоэтинов 1 и 2, фактора роста сосудистого эндотелия VEGF-D, трансформирующего фактора роста бета TGF-β, тромбоспондина-1. Отмечена тенденция к повышению уровня фактора роста сосудистого эндотелия VEGF-A, являющегося регулятором ангиогенеза и созревания легких; нарушение его синтеза может привести к долгосрочному повреждению паренхимы легких. Тенденцию к повышению уровня VEGF-A у детей с БЛД мы расцениваем как благоприятный признак положительной динамики заболевания. Выявлены тенденции к повышению концентрации молекулы адгезии эндотелиальных клеток тромбоцитов PECAM-1, интерлейкина-8, фактора роста соединительной ткани CTGF. Экспрессия CTGF усиливается искусственной вентиляцией легких и воздействием высоких концентраций кислорода. Повышение уровня CTGF у детей с БЛД мы считаем неблагоприятным изменением, так как связывание CTGF с VEGF снижает доступность VEGF для его рецепторов, ингибируя индуцированный VEGF ангиогенез. У детей с БЛД отмечено статистически достоверное снижение уровня тромбоцитарного фактора роста PDGF-BB, медиана составила у детей с БЛД 3180 пг/мл против 4782 пг/мл у детей без БЛД ($p = 0,024$). PDGF является важным фактором регенерации тканей, рецепторы к нему имеются на фибробластах

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и гладкомышечные клетках сосудистой стенки. Стимулируя их пролиферацию, PDGF играет важную роль в формировании кровеносных сосудов.

Наиболее выраженным изменением у детей с БЛД явилось снижение уровня PDGF, которое может приводить к нарушению альвеоляризации, необходимой для формирования структуры здоровых легких. Исследования факторов ангиогенеза помогут лучше понять патогенез поражения легких при БЛД.

Ключевые слова: бронхолегочная дисплазия, медиаторы ангиогенеза, PDGF, CTGF, VEGF, PECAM, недоношенные дети

EVALUATION OF MEDIATORS OF FIBROSIS AND ANGIOGENESIS IN THE BLOOD SERUM OF PREMATURE INFANTS WITH BRONCHOPULMONARY DYSPLASIA

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Abstract. In premature birth and postpartum damage to the developing lung, the processes of the formation of pulmonary vessels and alveoli are disrupted, leading to bronchopulmonary dysplasia (BPD). BPD is a multifactorial disease and the pathogenesis of lung tissue damage is still not fully understood. Studies of angiogenesis biomarkers can be informative for assessing the development of BPD. In this study we examined the blood serum of 65 premature infants aged 6 to 180 days of life; gestational age at birth was 23-33 weeks, body weight 480-1840 g, APGAR score 5-6. All children in the early neonatal period had respiratory distress syndrome, then 46 children formed and 19 did not form bronchopulmonary dysplasia. The concentration of the factors of angiogenesis and fibrosis was determined in blood serum by ELISA. There were no differences in the levels of angiopoietins 1 and 2, vascular endothelial growth factor VEGF-D, transforming growth factor beta TGF-β, thrombospondin-1. We observed a tendency to increasing the level of VEGF-A, which is a key regulator of angiogenesis and lung maturation; we regard this tendency as a favorable sign of lung formation. We found tendencies to increase of the adhesion molecule of endothelial platelet cells PECAM-1, interleukin 8 and connective tissue growth factor CTGF. CTGF expression is enhanced by artificial lung ventilation and exposure to high oxygen concentrations. We consider an increase of CTGF in BPD to be an unfavorable change, since the binding of CTGF to VEGF inhibits VEGF-induced angiogenesis. In children with BPD, we found a decrease in the level of platelet derived growth factor PDGF-BB, the median concentration was 3180 pg/mL in BPD *versus* 4782 pg/mL without BPD ($p = 0.024$). PDGF is an important factor in tissue regeneration and plays an important role in the formation of blood vessels. We assume the decreasing of PDGF concentration in BPD can lead to a violation of the alveolarization necessary for the formation of the structure of healthy lungs. Studies of angiogenesis factors will help to better understand the pathogenesis of lung damage in BPD.

Keywords: bronchopulmonary dysplasia, mediators of angiogenesis, PDGF, CTGF, VEGF, PECAM, premature infants

Introduction

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that occurs in premature infants who required intensive respiratory support and high oxygen concentration therapy at birth. The main clinical manifestations of BPD are respiratory insufficiency, prolonged need for additional oxygen, intolerance to physical exertion, and the formation of pulmonary hypertension [7]. BPD is a multifactorial disease, the pathogenesis of which is still not fully understood [12]. With premature birth and postpartum damage to the developing lung, the processes of pulmonary vascular growth and the formation of pulmonary alveoli are disrupted [5, 12]. It is assumed that studies of angiogenesis biomarkers can be informative for assessing the development of BPD [13], however, the question of the diagnostic and prognostic significance of early changes in their levels requires further research.

The purpose of the study was to determine the level of some important biomarkers of angiogenesis in the formation and course of bronchopulmonary dysplasia in premature infants to improve the early diagnosis of this disease. Materials and methods of research: the work was carried out in 2022 at the Federal State Autonomous Institution "NMIC of Children's Health" of the Ministry of Health of the Russian Federation in the Laboratory of experimental immunology and virology (head of the department, PhD N.M. Alyabieva), the Laboratory of neonatology

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The study included 65 premature infants who were hospitalized in the Department of pathology of newborns and infants FSAU "NMIC of Children's Health" and in the department of resuscitation and intensive care of newborns of the GBUZ MO "MOPC" Balashikha. The age at the point of examination was 6 to 180 days of life. There were 23 children (35%) at the stage of respiratory distress syndrome of newborns (up to 28 days of life); and 42 children (65%) older than 28 days were examined. When analyzing the data, 2 groups were formed: children who formed BPD – 46 patients (71%) and those who did not form – 19 children (29%). The gestation period at birth of patients ranged from 23 to 33 weeks, including 32 children (49%) had gestation periods from 23 to 27.6 weeks and 33 children (51%) had gestation periods from 28 to 33 weeks. The birth weight ranged from 480 to 1840 grams (the average 1011±320 g). 43 children (66%) had an extremely low birth weight, 14 children (22%) had a very low birth weight, and 8 children (12%) had a low birth weight. The patients were examined according to clinical indications, taking an acceptable volume of blood (no more than 1 mL, taking into account the child's body weight). To determine the factors of angiogenesis, a residual amount of serum was used after performing a biochemical analysis in the amount of 100-150 μL. The work was approved by the local independent ethical committee of the FSAU "NMIC of Children's Health" of the Ministry of Health of the Russian Federation.

A complex of the most interesting factors from a modern point of view was selected for the study: angiopoietin 1 (ANGPT1), angiopoietin 2 (ANGPT2), vascular endothelial growth factor A (VEGF-A), vascular endothelial growth factor D (VEGF-D), platelet endothelial cell adhesion molecule (PECAM-1), thrombospondin 1 (TSP1), transforming growth factor beta-1 (TGF-β1), platelet derived growth factor BB (PDGF-BB), interleukin-8 (IL-8), and connective tissue growth factor (CTGF). The study was conducted by enzyme immunoassay. Aviscera Bioscience kits were used for CTGF, R&D Systems for thrombospondin, and for all other analytes – manufactured by RayBiotech (all – USA).

Results and discussion

When analyzing anamnestic factors, we confirmed known patterns: children with BPD compared to children without BPD had lower gestational age at birth (median 27 weeks *versus* 30), lower birth weight (920 g *versus* 1150 g), lower APGAR score (5 *vs* 6 at 1 minute and 6 *vs* 7 at 5 minute), as well as a significantly longer period artificial lung ventilation (13 days *vs* 3 days). There were no diagnostically significant changes in the number of leukocytes and leukocyte formula at the time of the examination; all indicators were within the age norm. At the time of the study, children with BPD had a slightly higher level of C-reactive protein – the median concentration in children with BPD was 0.825 mg/L, without BPD – 0.5 mg/L. This indicates the absence of laboratory signs of inflammatory reactions at the time of examination. The median concentrations of the angiogenesis factors determined are shown in Table 1.

Discussion of the results obtained: To date, it has been established that with premature birth and postpartum damage to the developing lung, the processes of growth of pulmonary vessels and the formation of pulmonary alveoli are disrupted [5, 7, 12]. The interaction of multidirectional factors seems to be important in the pathogenesis of BPD formation [12, 13]. Angiopoietins are important modulators of physiological and pathological neovascularization of the lungs [13]. It is known that experimental management of VEGF and ANGPT1 in laboratory animals stimulated lung growth and vascular maturation more effectively than VEGF therapy alone; the interaction of ANGPT2 with VEGF stimulated angiogenesis in hypoxia, while in the absence of sufficiently strong pro-angiogenic signals, ANGPT2 can cause endothelial cell death and vascular regression [14]. In our study, were no significant differences in the levels of angiopoietin 1 and 2 in children who formed BPD was slightly lower than in those who did not form.

VEGF has been identified as a key regulator of lung angiogenesis and maturation due to the coordination of the branching of the respiratory tract and microvascular bed, a violation of its synthesis can lead to long-term damage to the lung parenchyma. A decrease in VEGF levels in tracheal aspirates has been described in premature newborns born at 28-29 weeks of gestation who later developed BPD [2]. In the cohort we examined, the median concentration of VEGF-D in both groups of children was almost equal. However, the median concentration of VEGF-A in children with BPD was higher than in children without BPD – 109 and 78 pg/mL, respectively; this trend is statistically unreliable, but we can evaluate the data as a trend. A tendency to increase the level of vascular endothelial growth factor VEGF-A can be important for BPD pathogenesis. The violation of VEGF-A synthesis can lead to long-term damage to the lung parenchyma, and we regard the tendency to increase the level of VEGF-A in the examined cohort of children with BPD as a favorable sign of positive dynamics of the disease.

Thrombospondin-1 is an extracellular matrix glycoprotein that has an antiangiogenic effect. It was shown that the level of thrombospondin-1 in the lung tissue of premature newborns who were on a ventilator was 5.5 times higher than in the lungs of children of the same gestational age who did not have a

TABLE 1. CONCENTRATIONS OF MEDIATORS OF ANGIOGENESIS AND FIBROSIS IN THE BLOOD SERUM OF PREMATURE INFANTS WITH AND WITHOUT BPD, Me ($Q_{0.25}$-$Q_{0.75}$)

Mediator	BPD	No BPD	p
ANGPT1, pg/mL	11550 (7172-14037)	13300 (7537-19004)	p = 0.60
ANGPT2, pg/mL	7019 (5726-8700)	6624 (5877-9305)	p = 0.81
VEGF-A, pg/mL	109 (48-197)	78 (48-235)	p = 0.54
VEGF-D, ng/mL	1.8 (1.5-2.4)	1.9 (1.7-2.2)	p = 0.87
TSP1, ng/mL	25987 (16778-39173)	21022 (16323-40144)	p = 0.94
TGF-β1, pg/mL	132412 (119206-148262)	136544 (117180-160888)	p = 0.56
IL-8, pg/mL	62 (38-176)	48 (23-265)	p = 0.38
PECAM-1, pg/mL	3624 (1413-4845)	2724 (1171-3565)	p = 0.24
CTGF, pg/mL	167 (107-230)	117 (72-192)	p = 0.13
PDGF-BB, pg/mL	3180 (2503-5016)	4783 (3372-6170)	p = 0.024

ventilator [11]. In our study, the median concentration of thrombospondin-1 had no significant differences.

One of the well-known regulators of cell growth is TGF-β, which mediates interactions between cells and the extracellular matrix. Its level has been shown to increase with damage and inflammation in lung tissue; at the same time, the authors emphasize that TGF-β has antiangiogenic properties, inhibits inflammatory processes, is a mediator of lung repair and tissue remodeling [8]. There were no differences in the concentration of TGF-β in the groups of children we examined.

The role of inflammatory markers such as interleukin 6, 8, 10, tumor necrosis factor in the development of bronchopulmonary dysplasia has been proven in many studies [4]. Interleukin 8, a neutrophil migration factor, is one of the main pro-inflammatory chemokines produced by macrophages. In a published study in 2022, when assessing the levels of IL-6 and IL-8 in the blood serum of premature infants during the first week of life, it was shown that children with higher levels of these biomarkers were more often diagnosed with BPD in the first week of life [4]. We determined the median concentration of IL-8 in children with BPD of 62 pg/mL *versus* 48 pg/mL in children without BPD, so we can suppose a trend to an elevation in BPD, but the trend has not statistical significance.

PECAM-1 is a glycoprotein, a membrane protein from the immunoglobulin superfamily, belonging to the class of cell adhesion molecules. In infants with BPD, a decrease in the expression of VEGF and PECAM has been described, as well as a decrease in the staining density of alveolar capillaries, which is regarded as evidence of impaired lung development and the development of the pulmonary microcirculatory network [3]. In the groups of children we compared, the median concentrations of PECAM-1 were 3624 pg/mL in children with BPD and 2724 pg/mL without BPD. The differences are statistically unreliable, however, from our point of view, the data can be regarded as a definite trend towards an increase in the level of BPD.

As part of the scientific work carried out at the FSAU "Children's Health Research Center" of the Ministry of Health of the Russian Federation to determine the clinical and genetic features of the development of a new form of BPD in premature infants, full-exome sequencing was performed in 100 patients with BPD. As a result, 8 genetic variants significant for the pathogenesis of BPD were selected, in particular, the important role of the CTGF gene was established [1]. The molecular structure of CTGF allows it to interact with various growth factors – TGF , VEGF, etc. [10]. The important role of CTGF in the pathogenesis of various forms of pulmonary fibrosis and vascular diseases, including BPD, has been shown in many studies [6, 10, 15].

CTGF expression has been shown to be enhanced by artificial lung ventilation and exposure to high oxygen concentrations. Binding of CTGF to TGF-β provides dimerization of TGF-β with its receptors, thus facilitating the transmission of TGF-β signals [2]. On the contrary, binding of CTGF to VEGF reduces

the availability of VEGF for its receptors, inhibiting VEGF-induced angiogenesis [6]. We obtained data on a higher concentration of CTGF in children with BPD: the median was 167 pg/mL check units with an indicator of 117 pg/mL in children without BPD. The trend was not statistically reliable due to large data spread (p = 0,13); perhaps a larger volume of observations will give more reliable results. We consider an increase in CTGF levels in children with BPD to be an unfavorable change, since the binding of CTGF to VEGF reduces the availability of VEGF for its receptors, inhibiting VEGF-induced angiogenesis.

An important stimulator of tissue repair is PDGF, which is contained in the -granules of platelets. PDGF receptors have fibroblasts and smooth muscle cells of the vascular wall. By stimulating their proliferation, PDGF plays an important role in the formation of blood vessels. There is evidence that the PDGF level decreases with BPD, which leads to a violation of the alveolarization necessary for the formation of the structure of healthy lungs [8]. However, in other studies, when determining the levels of PDGF-AA and PDGF-BB in the aspiration fluid of the trachea, no differences were obtained between aspirates from children who developed BPD, compared with aspirates from children who did not develop BPD [10]. In the children with BPD examined by us, the median concentration of PDGF-BB was 3180 pg/mL, and in children without BPD – 4783 pg/mL (p = 0.024). The diagram of PDGF-BB concentration comparison is shown in Figure 1.

We assume the decreasing of PDGF concentration in infants with bronchopulmonary dysplasia can lead to a violation of alveolarization necessary for the formation of the structure of healthy lungs. Studies of

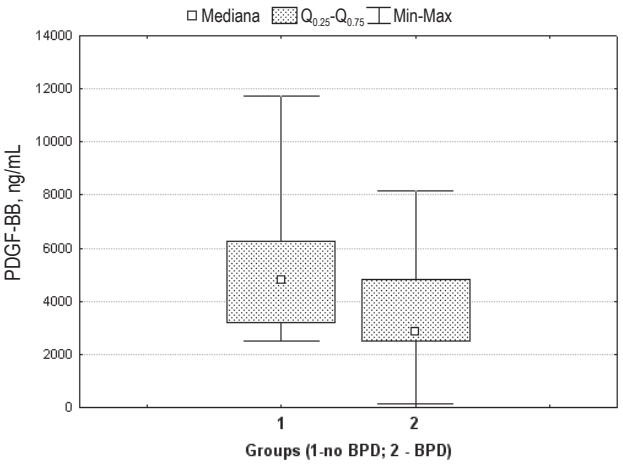

Figure 1. Medians and spread of serum levels of PDGF-BB in infants with and without BPD

angiogenesis factors will help to better understand the pathogenetic mechanisms of lung damage in BPD.

This study, conducted in limited groups of patients, revealed some trends. In this regard, we consider it appropriate to further study angiogenesis factors on more extensive and more diverse groups of patients, since it is these biomarkers that can help predict respiratory diseases in premature newborns during their initial hospitalization. Understanding the interaction of growth factors, transcription factors and inflammatory processes that regulate the normal development of the parenchyma and microvascular bed of the lungs, as well as their role in the pathogenesis of BPD, can help in the development of new treatment methods aimed at stimulating proper alveologenesis and angiogenesis, as well as the prevention of pulmonary hypertension in premature infants.

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