Том 16, № 3(47), вересень – грудень 2019 р.
<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original research</td>
<td>308</td>
</tr>
<tr>
<td>Kolesnyk Yu. M., Isachenko M. I., Melnïkova O. V.</td>
<td>The features of the nitric oxide system in the left ventricle myocardium in the rats with experimental intermittent hypoxia of different duration</td>
</tr>
<tr>
<td>Kuryata O. V., Semenov V. V.</td>
<td>Myocardial remodeling and arterial stiffness depending on aldosterone level in patients with chronic kidney disease and arterial hypertension</td>
</tr>
<tr>
<td>Hrushka N. H., Podlovych S. I., Kondratska O. A., Pilkoych N. O., Yanclil R. I.</td>
<td>Inhibition of poly(ADP-ribose)polymerase contributes to the reduction of oxidative stress in murine liver under the conditions of experimental endotoxemia</td>
</tr>
<tr>
<td>Kuryata O. V., Semenov V. V.</td>
<td>Myocardial remodeling and arterial stiffness depending on aldosterone level in patients with chronic kidney disease and arterial hypertension</td>
</tr>
<tr>
<td>Abramova N. O., Pashkovska N. V.</td>
<td>Peculiarities of carbohydrate metabolism in patients with metabolic syndrome depending on C/T polymorphism in the DIO 1 gene</td>
</tr>
<tr>
<td>Abramova T. V., Ivanenko T. V., Melnykova O. V.</td>
<td>Features of Bcl2 and p53 proteins synthesis in pancreatic islets of normotensive and hypertensive rats with streptozotocin-induced diabetes</td>
</tr>
<tr>
<td>Kuzyk Yu. I.</td>
<td>Features of the pathomorphological structure of the atherosclerotic plaques of carotid atherosclerosis</td>
</tr>
<tr>
<td>Fushtei I. M., Tkachenko O. V., Podsevakhina S. L., Palamarchuk O. I.</td>
<td>Subclinical features of atherosclerotic remodeling of arteries in patients with rheumatoid arthritis</td>
</tr>
<tr>
<td>Deinichenko O. V., Krut Yu. Ya.</td>
<td>Factors of angiogenesis and placental hormones in pregnant women with arterial hypertension</td>
</tr>
<tr>
<td>Khomenko I. P., Korol S. O., Kozhokara A. A., Matviychuk B. V., Cinâeva R. M.</td>
<td>Functional status of the cardiovascular system in the wounded with limb injuries at the levels of health care according to tetrapolar rheography</td>
</tr>
<tr>
<td>Haidash D. I., Haidash I. S., Bondar O. O., Yevtushenker Yu. O., Haidash O. I.</td>
<td>Activity of matrix metalloproteinases and their tissue inhibitors in serum in chronic granulating periodontitis</td>
</tr>
</tbody>
</table>
Крайдашенко О. В., Тягла О. С.
Клінічна ефективність екзогеного L-аргініну у хворих на гіпертонічну хворобу на тлі хронічного обструктивного захворювання легень

Троїн В. І., Сінайко І. О., Лобова О. В., Костровський О. М.
Частота метастазування у сторожовий лімфовузол і його предиктори у хворих на рак гортані $T_{1-2}N_{0}M_{0}$

Шумна Т. Є., Недельська С. М., Федосєєва О. С.
Дослідження асоціації розподілу генотипів поліморфізму C/A гена колагену COL1A1_1 (rs1107946) із показниками функції зовнішнього дихання в дітей із бронхіальною астмою

Ащеулова Т. В., Компанієць К. М., Герасимчук Н. М.
Надмолекулярний комплекс сакубітрил/валсартан – перший представник нового класу препаратів для лікування хронічної серцевої недостатності

Теремецький В. І., Матвійчук А. В., Музичук О. М., Щербаковський М. Г., Одерій О. В.
Особливості правової охорони медичних винаходів: сучасність і перспективи

Разнатовська О. М., Федорець А. В., Фурик О. О., Макуріна Г. І., Грекова Т. А., Ромашченко В. В.
Клінічний випадок поєднаного перебігу туберкульозу з широкою лікарською стійкістю з ВІЛ-інфекцією та третинним сифілісом

Ашечулова Т. В., Компаниятс К. М., Herasymchuk N. M.
Supramolecular complex sacubitril/valsartan – the first representative of a new class of drugs for the treatment of chronic heart failure

Teremetskyi V. I., Matvyiuch A. V., Muzychuk O. M., Shcherbakovskyi M. H., Oderii O. V.
Features of legal protection of medical inventions: present and future

Raznatovska O. M., Fedorets A. V., Furyk O. O., Makurina H. I., Hrekova T. O., Romashchenko V. V.
Clinical course of extensively drug-resistant tuberculosis with HIV infection and tertiary syphilis: a case report

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Index Copernicus (Польща): http://www.indexcopernicus.com/Pathologia,p5665,3.html
DOAJ (Великобританія): https://doaj.org/toc/2310-1237

Патологія. Том 16. № 3, Серпень – Декабрь 2019
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307
Study of the association of distribution pattern of genotypes of C/A polymorphism of COL1A1_1 collagen gene (RS1107946) with indicators of external breathing in children with bronchial asthma

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Zaporizhzhia State Medical University, Ukraine

Purpose. The study of the distribution patterns of allelic genes and genotypes of the C/A polymorphism of the collagen COL1A1_1 gene (rs1107946) in children with bronchial asthma, taking into account the indicators of external respiration function.

Materials and methods. Molecular-genetic study to determine the C/A polymorphism of the collagen COL1A1_1 gene (rs1107946) was conducted in 125 children from 6 to 18 years, 100 of them with bronchial asthma who were hospitalized in the Allergic Department of the Municipal Non-Profit Enterprise “City Children Hospital No 5 of Zaporizhzhia City Council” and 25 healthy children (control group). There were no differences in age and sex in the comparison groups (P > 0.05). Genotype determination was performed by polymerase chain reaction method according to the instruction (Applied Biosystems, USA) using the samples of total DNA received from whole venous blood using SNP-Screen reagents (manufactured by “Syntol”) on amplifier CFX96TM Real-Time PCR Detection Systems (“Bio-Rad laboratories, Inc.”, USA). The ventilation function of the lungs was studied by conducting a spirometric study on a computer spirograph “PULMOREM” TU U 33.1-02066769-005-2002 (Kharkiv, Ukraine). To compare the frequencies of alleles and genotypes in different groups, the non-parametric statistical method “2 × 2 Table”, the Chi-square (df = 1) was used. Medians and interquartile intervals were also calculated, the two independent groups were compared by the Mann-Whitney criterion, the χ² criterion. Non-parametric statistics methods for the licensed software package Statistica for Windows 6.1.RU, serial number AXXR712D83214SANS, were used to process the obtained study data.

Results. Molecular-genetic study of distribution patterns of allelic genes of the C/A polymorphism of the COL1A1_1 collagen gene (rs1107946) in patients with bronchial asthma and in practically healthy children, showed that the allele C was registered with a frequency of 69.5 % and 84.0 %, allele A – 30.5 % and 16.0 %; dominant genotype C/C – 58 % and 76 %; heterozygous genotype C/A – 23 % and 16 %; homozygous genotype A/A – 19 % and 8 %, respectively. Children with bronchial asthma with genotype A/A had significantly lower FVC values up to 2.32 (1.55; 3.29), VCmax up to 1.89 (1.40; 2.98), FEV1 up to 1.82 (1.43; 2.98), with genotype C/C – MEF50 up to 2.34 (1.87; 3.14) when compared with patients with heterozygous genotype A/C, and very low rates of FVC were recorded in 68.75 % of children with bronchial asthma with the A/A genotype against 30.77 % of patients with the A/C genotype and 36.17 % with the C/C genotype (P < 0.05).

Conclusion. Homozygous genotype A/A of C/A polymorphism of the COL1A1_1 collagen gene (rs1107946), was associated with more pronounced disorders of ventilatory function of lungs with obstructive breathing type due to impaired collagen formation in the bronchi, which may have prognostic significance both for early diagnosis and prediction of clinical course severity of this disease as well as for prevention and treatment of bronchial obstruction in patients.
Результати. Молекулярно-генетичне дослідження закономірностей розподілу алегних генів поліморфізму С/А гена колагену COL1A1_1 (rs1107946) у дітей з бронхіальною астмою та у практично здорових показало, що алегель С рєсєрували з частотою 69,5 % та 84,0 %, алегель А – 30,5 % та 16,0 %; домінуючий генотип С/С – 58 % та 76 %; гетерозозитний генотип С/А – 23 % та 16 %; гомозозитний генотип А/А – 19 % та 8 % відповідно. У дітей з бронхіальною астмою з генотипом А/А був вірогідно нижчим показниками ФЖЕЛ до 2,32 (1,55; 3,29), ЖЕЛ до 1,69 (1,40; 2,98), ОФВ до 1,92 (1,43; 2,98), із генотипом С/С – МОСдо до 2,34 (1,87; 3,14) порівняно з пацієнтами з гетерозозитним генотипомА/С, а дуже низькі показники ФЖЕЛ зареєстровані у 68,75 % дітей із бронхіальною астмою з генотипом А/А проти 30,77 % пацієнтів із генотипом А/С і 36,17 % із генотипом С/С (р < 0,05).

Висновки. Гомозозитний генотип А/А поліморфізму С/А гена колагену COL1A1_1 (rs1107946) асоціюється з вираженішими порушеннями вентиляційної функції легенів за обструктивним типом дихання, залежно від порушення вентиляції у бронхах, що може мати прогностичне значення для ранньої діагностики та прогнозування тяжкості клінічного перебігу цього захворювання та профілактики й лікування бронхіальної обструкції у пацієнтів.

Исследование ассоциации распределения генотипов полиморфизма С/А гена коллагена COL1A1_1 (rs1107946) с показателями функции внешнего дыхания у детей с бронхиальной астмой

Т. Е. Шумная, С. Н. Недельская, Е. С. Федосеева

Цель работы – исследование закономерностей распределения алегелей генов и генотипов полиморфизма С/А гена коллагена COL1A1_1 (rs1107946) у детей с бронхиальной астмой, учитывая показатели функции внешнего дыхания.

Материалы и методы. Молекулярно-генетическое исследование для определения полиморфизма С/А гена коллагена COL1A1_1 (rs1107946) проведено у 125 детей в возрасте от 6 до 18 лет, из них 100 детей с бронхиальной астмой, которые находились на стационарном лечении в аллергологическом отделении НПО «Городская детская больница № 5» ГФС и 25 здоровых детей (контрольная группа). Дети по возрасту и полу в группах наблюдения не отличались (р > 0,05). Определение генотипа проводили методом полимеразной цепной реакции согласно инструкции (Applied Biosystems, USA) с использованием мультиплексной праймерной схемы. Амплификацию проводили на амплификаторе CFX96TM Real-Time PCR Detection Systems (Bio-Rad laboratories, Inc., USA). Вентиляционную функцию легких изучали путем проведения спирометрического исследования на компьютерном спирографе «PULMOREM» ТУ У 33.1-02066769-005-2002 (г. Харьков, Украина). Использовали непараметрический статистический тест 2×2 Table, the Chi-square (df = 1), вычисляли медианы и интерквартильные интервалы, две независимые группы сравнивали с использованием критерия Манна-Уитни, критерий χ².

Результаты. Молекулярно-генетическое исследование закономерностей распределения алегелей генов полиморфизма С/А гена коллагена COL1A1_1 (rs1107946) у детей с бронхиальной астмой и у практически здоровых показало, что алегель С регистрировали с частотой 69,5 % и 84,0 %, алегель А – 30,5 % и 16,0 %, доминирующий генотип С/С – 58 % и 76 %, гетерозозитный генотип С/А – 23 % и 16 %; гомозозитный генотип А/А – 19 % и 8 % соответственно. У детей с бронхиальной астмой с генотипом А/А зарегистрированы достоверно сниженные показатели ФЖЕЛ до 2,32 (1,55; 3,29), ЖЕЛ до 1,69 (1,40; 2,98), ОФВ до 1,92 (1,43; 2,98), МОС до 2,34 (1,87; 3,14) при сравнении с пациентами с гетерозозитным генотипом А/С, а очень низкие показатели ФЖЕЛ зарегистрированы у 68,75 % детей с бронхиальной астмой с генотипом А/А против 30,77 % пациентов с генотипом А/С и 36,17 % с генотипом С/С (р < 0,05).

Выводы. Гомозозитный генотип А/А полиморфизма С/А гена коллагена COL1A1_1 (rs1107946) ассоциировался с более выраженными нарушениями вентиляционной функции легких по обструктивному типу дыхания: вследствие нарушения клапанообразования в бронках, что может иметь прогностическое значение для ранней диагностики и прогнозирования тяжести клинического течения этого заболевания, профилактики и лечения бронхиальной обструкции у пациентов.
According to the latest data, up to 27 types of collagen are strength and elasticity under mechanical loading [11].

Collagen is the main insoluble fibrillar protein that under the risk of pathology and to prevent the risk of pathology. Metabolism genes (COL1A1), which will allow to predict in order to determine the polymorphism of collagen and asthma, taking into account the indicators of external respiration function.

Purpose

The study of the distribution patterns of allelic genes and genotypes of the C/A polymorphism of the collagen COL1A1_1 gene (rs1107946) in children with bronchial asthma, taking into account the indicators of external respiration function.

Materials and methods

Molecular-genetic study to determine the C/A polymorphism of the collagen COL1A1_1 gene (rs1107946) was conducted in 125 children from 6 to 18 years, 100 of them with bronchial asthma who were hospitalized in the Allergic Department of the Municipal Non-Profit Enterprise City Children Hospital No. 5 of Zaporizhzhia City Council and 25 healthy children (control group). There were no differences in age and sex in the comparison groups (P > 0.05).

Genotype determination was performed by polymerase chain reaction method according to the instruction (Applied Biosystems, USA) using the samples of total DNA received from whole venous blood using SNP-Screen reagents (manufactured by “Syntol”) on amplifier CFX96TM Real-Time PCR Detection Systems (“Bio-Rad laboratories, Inc.”, USA). The study was carried out in the Department of Molecular and Genetic Studies of the Research Medical-Laboratory Center at the Department of Microbiology, Virology and Immunology of Zaporizhzhia State Medical University.
The ventilation function of the lungs was studied by conducting a spirometric study on a computer spirometer “PULMOREM” TU U 33.1-02066769-005-2002 (Kharkiv, Ukraine). The forced expiratory maneuver has been performed three times, with the following indicators: vital capacity maximal (V_{C_{max}}), forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), FEV_1/FEV_{max} ratio, maximum expiratory flow at 25%, 50% and 75% FVC (MEF_{25}, MEF_{50} and MEF_{75})

To compare the frequencies of alleles and genotypes in different groups, the non-parametric statistical method "2 × 2 Table", the Chi-square (df = 1) was used. Medians and interquartile intervals were also calculated, the two independent groups were compared by the Mann-Whitney criterion, the χ² criterion. Non-parametric statistics methods for the licensed software package Statistica for Windows 6.1.RU, serial number AXKR712D833214SAN5, were used to process the obtained study data.

**Results**

Molecular and genetic study of C/A polymorphism of collagen gene COL1A1_1 (rs1107946) in children with bronchial asthma has detected that the incidence of allelic gene A was 30.5%, allele C – 69.5%, and in healthy children 16% and 84%, respectively.

Studies have found that in children with bronchial asthma, the homozygous genotype C/C was most frequently registered and was equal to 58%. The heterozygous genotype C/A and the homozygous genotype A/A were significantly less frequently reported; the incidence of bridging among children with bronchial asthma was only 23% and 19%, respectively (Fig. 1).

In the comparison control group, that is, in healthy children, homozygous C/C genotype (76%) was also significantly more frequently registered compared with the incidence of homozygous A/A genotype (8%) and heterozygous C/A genotype (16%) respectively (Fig. 2).

Depending on the presence or absence of pathology such as bronchial asthma, a comparative analysis of the genotype distribution of C/A polymorphism of the collagen COL1A1_1 gene (rs1107946) was also performed. Although in healthy children only a tendency for the prevalence of homozygous genotype C/C and a tendency for a decrease in the incidence of homozygous genotype A/A and heterozygous genotype C/A than in patients with bronchial asthma was observed, but there was no significant difference between these parameters.

Therefore, we further analyzed the association of genotype distribution of the C/A polymorphism of the collagen COL1A1_1 gene (rs1107946) with indicators of external respiratory function in children with bronchial asthma. In the study of ventilatory function of the lungs, obstructive breathing with a decrease in external respiration, at the time of examination, was recorded in 76 children with bronchial asthma. All 25 practically healthy children and 24 children with controlled bronchial asthma during sustained remission had all indicators of external respiration within the age range.

Indicators of external respiratory function in children with bronchial asthma, depending on their genotypes of C/A polymorphism of COL1A1_1 collagen gene (rs1107946) are presented in **Table 1**.

Concurrently children with bronchial asthma and homozygous A/A genotype, when compared with patients with heterozygous A/C genotype, had significantly lower rates of forced vital lung capacity (2.32 (1.55; 3.29) versus 3.20 (2.51; 3.77)), P < 0.05; vital lung capacity (1.69 (1.40; 2.98) vs. 2.37 (1.97; 2.88)), P < 0.05; forced expiratory volume in the first second (1.82 (1.43; 2.98) vs. 2.40 (1.83; 3.08)), P < 0.05. At the same time, in children with bronchial asthma and homozygous C/C genotype, the maximum exhalation volume rate at 75% of FVC was significantly lower than in children with A/C genotype (2.34 (1.87; 3.14) vs. 2.46 (1.95; 3.24)), P < 0.05.

The distribution of genotypes of the C/A polymorphism of COL1A1_1 collagen gene (rs1107946) in children with bronchial asthma and with impaired ventilatory function of the lung, characterized by very low rates of external respiration during spirometry, are presented in **Table 2**

Concurrently 68.75% of children with bronchial asthma with A/A genotype were significantly more likely to have very low rates of forced vital lung capacity, compared to 30.77% of patients with A/C genotype and 36.17% with C/C genotype.

According to our hypothesis, these data can be explained by the fact that in children with bronchial asthma with the A/A genotype of C/A polymorphism of the collagen gene COL1A1_1 (rs1107946) the violation of collagen formation in the bronchi is observed, which causes more pronounced disorders of lung ventilatory function with obstruction respiratory type while patients with genotypes C/A and C/C have bronchial obstruction due to the well-known heterogeneous chronic inflammation of the respiratory tract.
Table 1. Indicators of external respiratory function, depending on their genotypes of C/A polymorphism of COL1A1_1 collagen gene (rs1107946) in children with bronchial asthma (Me (Q25; Q75))

<table>
<thead>
<tr>
<th>Indicators</th>
<th>FVC</th>
<th>VC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>FEV₁</th>
<th>FEV₁ %F</th>
<th>MEF&lt;sub&gt;25&lt;/sub&gt;</th>
<th>MEF&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MEF&lt;sub&gt;75&lt;/sub&gt;</th>
</tr>
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<tbody>
<tr>
<td>Genotype A/A (n = 16)</td>
<td>2.32 (1.51; 3.29)</td>
<td>1.69 (1.40; 2.98)</td>
<td>1.82 (1.43; 2.98)</td>
<td>0.62 (0.72; 0.90)</td>
<td>4.46 (3.59; 5.12)</td>
<td>3.41 (2.27; 3.90)</td>
<td>1.87 (1.20; 2.29)</td>
</tr>
<tr>
<td>Genotype A/C (n = 13)</td>
<td>3.20 (2.51; 3.77)</td>
<td>2.37 (1.97; 2.88)</td>
<td>2.40 (1.89; 3.08)</td>
<td>0.83 (0.62; 0.90)</td>
<td>5.23 (4.76; 5.57)</td>
<td>3.79 (2.64; 4.43)</td>
<td>2.46 (1.95; 3.24)</td>
</tr>
<tr>
<td>Genotype C/C (n = 47)</td>
<td>3.16 (2.64; 3.75)</td>
<td>3.10 (2.64; 3.75)</td>
<td>2.67 (2.07; 3.32)</td>
<td>0.81 (0.73; 0.92)</td>
<td>5.27 (3.98; 6.66)</td>
<td>4.06 (2.95; 5.38)</td>
<td>2.34 (1.87; 3.14)</td>
</tr>
</tbody>
</table>

Table 2. Genotype distribution of collagen gene C/A polymorphism of COL1A1_1 collagen gene (rs1107946) in children with bronchial asthma with very low ventilatory function (abs/%)

<table>
<thead>
<tr>
<th>Indicators</th>
<th>FVC</th>
<th>VC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>FEV₁</th>
<th>FEV₁ %F</th>
<th>MEF&lt;sub&gt;25&lt;/sub&gt;</th>
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<tr>
<td>Genotype A/A (n = 6)</td>
<td>11/68.75</td>
<td>9/56.25</td>
<td>3/18.75</td>
<td>5/31.25</td>
<td>0/0</td>
<td>4/25.00</td>
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<td>Genotype A/C (n = 13)</td>
<td>4/30.77</td>
<td>6/46.15</td>
<td>3/23.08</td>
<td>2/15.38</td>
<td>2/15.38</td>
<td>1/7.69</td>
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<tr>
<td>Genotype C/C (n = 47)</td>
<td>17/36.17</td>
<td>25/53.19</td>
<td>9/19.15</td>
<td>15/31.91</td>
<td>5/10.84</td>
<td>10/21.28</td>
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</table>

Discussion

Other scientific works that we analyzed in the course of our study are dedicated as well to the identification of genotypic and associated with it phenotypic features of bronchial asthma. Thus, three subgroups of patients participated in the study of the association of the rs510432 polymorphism of the ATG5 gene with indicators of forced expiratory volume in the first second (FEV1). The first subgroup included 18 patients (18.37 %) with the major (homozygous) genotype, the second – 51 children (52.04 %) with the heterozygous genotype, the third – 29 persons (29.59 %) with minor (homozygous) genotype. At the same time, no statistically significant differences between the average values of FEV1 in patients with major and heterozygous genotype, heterozygous and minor genotype were found (P < 0.05). However, average FEV1 values in patients with a minor genotype were significantly lower than with the major genotype (P < 0.05). Thus, the rs510432 polymorphism of ATG5 gene is also considered to be a predictor of decreased respiratory function in children, allowing individually prescription of prophylactic measures and / or treatment to prevent the development or exacerbation of bronchial asthma [13–15].

Fedortsev O. Y. also studied the function of external respiration in children with bronchial asthma; but according to his conclusions, the changes in spirometric parameters in patients are informative only during the attacks allowing distinguishing the types of disorders of the function of external respiration – mixed with obstruction predominance and purely obstructive. During exacerbation of bronchial asthma, priority indicators are violated that are dependent allergic pathology, the Gly16Gly genotype registered with a frequency of 53.33 %, occupies a leading place [17].

Banadyha N. V. has put forward an assumption that the polymorphism of the rs1042713 Arg16Gly of the ADRβ2 gene in children with bronchial asthma is represented by the predominance of the Arg16Gly variant in all phenotypes, as well as in the case of early debut disease. Late manifestation of the disease is associated with the homozygous variant Gly16GlyADRβ2 [18]. It has also been shown that among patients with bronchial asthma with a difficult hereditary history of atopy, the Arg16Gly genotype of ADRβ2 gene prevails. At that time, in families with no cases of allergic pathology, the Gly16Gly genotype registered with a frequency of 53.33 %, occupies a leading place [19].

According to the results of genotyping, Ivanova L. A. states that the genotype T1delM1 + is registered in eosinophilic bronchial asthma in 15.5 % of cases, that is more frequent than in the neutrophilic type of airway inflammation (11.6 %). The T1 + M1del genotype was more frequently reported in children with a non-eosinophilic disease phenotype of disease (32.6 %) than in their peers with eosinophilic bronchial asthma (28.9 %). Severe form of disease was detected in 4 of 5 carriers of the T1delM1del genotype (80 %) in patients with eosinophilic asthma and in 2 of 5 carriers (40 %) with neutrophilic type of respiratory passages inflammation. At the same time, carriers of the T1 + M1 + genotype were diagnosed with severe form of disease in 12 of 21 (57.1 %) patients with eosinophilic asthma and in 8 of 19 (42.1 %) with non-eosinophilic type of respiratory passages inflammation. Thus, in patients with an eosinophilic phenotype of bronchial asthma who have the T1delM1del genotype, the disease more often passed...
in the severe forms. In general, it should be noted that in patients with eosinophilic asthma, which are carriers of defective alleles of GSTT1 and M1 genes in the homozygous state, there was a tendency to increased bronchial lability due to a more pronounced bronchospasm, and the index of hyper-reactivity of the bronchi was significantly higher than in children with functionally complete alleles of these genes. Therefore, genetically caused lack of activity of individual enzymes of the biotransformation system of xenobiotics, in particular GSTT1 and M1, may be a cause of higher lability of the bronchi [20].

In recent years, children with chronic somatic pathology have been increasingly diagnosed with signs of undifferentiated connective tissue dysplasia [21]. It is known that the development of both bronchial asthma and undifferentiated connective tissue dysplasia is caused by the interaction of genetic and external factors, which, in turn, leads to changes in the functional activity of the hereditary apparatus of somatic cells [22,23].

Changes from the side of the bronchopulmonary system occupy a significant place among patients with undifferentiated connective tissue dysplasia, complicating the course of the underlying disease [24].

There are morphological changes of the respiratory tract of inflammatory nature. These is thickening of the sub-mucosal layer, infiltration of the respiratory passages walls by eosinophils and lymphocytes with damage to the epithelium, smooth muscle hypertrophy, redistribution of interstitial collagen as a mechanism of respiratory passages remodeling. These changes occur with the participation of the same cytokines as in classical bronchial asthma – histamine, prostaglandins, leukotrienes [25].

Scientific articles have also highlighted studies aimed at studying the collagen gene COL1A1_1, phenotypic and clinical manifestations of other diseases in children [26–29].

Peigen Xie, Bin Liu, Liang Ming Zhang suggested that type I collagen is the most common protein and is a component of the bone matrix. The collagen COL1A1_1 gene is considered to be a strong candidate gene, which may be important for the regulation and function of connective tissue, therefore, potential associations between polymorphism within collagen 1 alpha 1 (COL-1A1) in the examined patients lead to abnormalities in bone matrix structure and connective tissues [30].

Victor A. Mc Kusick’s article discusses that COL3A1 gene mutations are life-threatening for a person, and leads to enlargement, rupture of the arterioles, and risk of damage to internal organs such as the lungs [31].

Malachkova N. V. studied the value of the rs1107946 polymorphism of the COL1A1 gene in children and states that the average population frequency of the A SNP rs1107946 variant allele in the world is 0.26–0.27, and the average genotype distribution indicators according to various data are: C/C – 55.5–66.0 %, A/C – 27.0–37.5 %, A/A – 5–7 %. However, there is considerable geographical variability in the frequency of allelic variants of the SNP rs1107946 of the COL1A1 gene in different populations of the world. It should be noted that the population of Europe is characterized by a very low incidence of homozygous AA SNP rs1107946 carriers – in average 0.8 %, which coincides with the data obtained in our studies and explains the absence of homozygous with variant alleles in the sample of persons who participated in genotyping by this polymorphism. A more detailed analysis of the above studies conducted in Ukraine allows the assumption that the most probable cause of such significant differences in the frequency of allelic variants of the SNP rs1107946 of the COL1A1 gene may be the differences in the size of the sampling at genotyping. Thus, the studies which showed the high frequency of the SNPs rs1107946 variant allele, the number of persons in the control groups was 20 and 30, respectively. Thus, the results of genotyping SNPsrs1107946 of the COL1A1 gene among children obtained in our study do not differ from the European average population data and coincide with the data of prevalence of allelic variants in Ukraine obtained in large samplings [32].

Conclusions

1. Molecular-genetic study of distribution patterns of allelic genes of the C/A polymorphism of the COL1A1_1 collagen gene (rs1107946) in patients with bronchial asthma and in practically healthy children showed, that the allele C was registered with a frequency of 69.5 % and 84.0 %, allele A – 30.5 % and 16.0 %; dominant genotype C/C – 58 % and 76 %; heterozygous genotype C/A – 23 % and 16 %; homozygous genotype A/A – 19 % and 8 %, respectively.

2. Children with bronchial asthma with genotype A/A had significantly lower FVC values up to 2.32 (1.55; 3.29), VCmax up to 1.69 (1.40; 2.98), FEV1 up to 1.82 (1.43; 2.98), with genotype C/C – MEF1 up to 2.34 (1.87; 3.14) when compared with patients with heterozygous genotype A/C, and very low rates of FVC were recorded in 68.75 % of children with bronchial asthma with the A/A genotype against 30.77 % of patients with the A/C genotype and 36.17 % with the C/C genotype (P < 0.05).

3. Homozygous genotype A/A of C/A polymorphism of the COL1A1_1 collagen gene (rs1107946), was associated with more pronounced disorders of ventilatory function of lungs with obstructive breathing type due to impaired collagen formation in the bronchi, which may have prognostic significance both for early diagnosis and prediction of clinical course severity of this disease as well as for prevention and treatment of bronchial obstruction in patients.

Prospects for further studies. In the future, we are planning to study the occurrence frequency of the presented genotypes depending on the clinical and laboratory data in children with bronchial asthma.

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