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Effectiveness of bronchial asthma treatment in accordance with the genotype of the bcl1 polymorphism of glucocorticoid receptor gene and body mass

Key words: *bronchial asthma, Bcl1 polymorphism, glucocorticoid receptor gene, body mass index, treatment.*

Obesity as a risk factor for bronchial asthma (BA) contributes not only to a more severe BA clinical course, but also to worse asthma control. It is known that obese people with BA demonstrate reduced sensitivity to inhaled corticosteroids (inhaled GCs) and acquire resistance to background therapy drugs [4, 11]. This is confirmed by: lower growth of forced expiratory volume in 1 second (FEV1) in response to treatment; low chance to acquire BA control by means of inhaled corticosteroids and long-acting β^2-agonists [4]; reduced response to systemic glucocorticosteroids and albuterol; more frequent hospitalizations [16]. It has been also established that increased body mass index (BMI) leads to reduced response to inhaled corticosteroids, but doesn't influence response to antileukotriene drugs [5, 18]. Asthma control and spirometric parameters were reported to improve along with weight reduction in women, who have been operated for obesity, and due to dietary treatment [17]. More severe clinical course and worse asthma control in obese individuals are probably caused by multifactorial causes. Increased BMI is associated with suppressed in-vitro response to dexamethasone [18] as well as with the budesonide-induced inhibition of cortisol that is responsible for poor peripheral deposition and absorption of these medications [3].

Besides, it has been established that the lack of adequate response to asthma drugs results from genetic peculiarities approximately in half of patients. Several single nucleotide polymorphisms were described in literature and reported to have association with decreased pulmonary function, poor response to pharmacotherapy, uncontrolled BA risk [1, 5] and obesity occurrence [7, 19]. In many scientists' opinion, the association between bronchial asthma and obesity is partly induced by common genetic factors. Bronchial asthma is associated with the genes, which encode β-adrenergic receptor (locus 5q, ADRB2 gene), insulin-like growth factor (locus 12q, IGF1 gene), IL-1α (locus 12q, IL-1α gene), leukotriene A4 hydroxylase (locus 12q, LTA4H gene), GR (locus 5q, NR3C1 gene), signal transducers and activators of transcription (locus 12q), TNF (locus 6p, TNF gene), uncoupling protein (locus 11q13, gene UCP2 and 3); the connection between these genes and BMI has been also found out [7, 8, 10, 12, 13].

Considering the proven association of BCL1 polymorphism in glucocorticoid receptor gene (GR) with obesity occurrence [19], BA occurrence [15] and response to glucocorticosteroids [14, 19], we determined our **research objective** as assessment of treatment effectiveness in BA patients according to genotype of GR gene polymorphism and BMI.

Materials and methods

188 patients with BA have been examined. The control group consisted of 95 apparently healthy adult individuals. The level of asthma control was assessed according to the GINA recommendations (2011), BMI was assessed according to the WHO recommendations. The respiratory function was studied with the help of KardioPlus diagnostic suite (Ukraine).

The determination of allelic polymorphism in exon 2 of Bcl1 GR gene (C647G; rs41423247) was performed by means of polymerase chain reaction with subsequent analysis of restriction fragment length polymorphism (according to Fleury I. et al.) with modifications. Statistical analysis of the results was performed using SPSS-17 program.

Results

Asthma control analysis performed without reference to genetic factors revealed that 8.5 % of patients had controlled asthma, 68.6 % – partially controlled asthma and 22.9 % – uncontrolled asthma. Comparison of control level in patients with different genotypes of BCL1 polymorphism of GR gene demonstrated statistically significant difference in the distribution of gene allelic variations according to Pearson's chi-squared test ($\chi 2$) (p=0,001) (table 1). Thus, 27,9 % of patients with C/C genotype had well-controlled asthma, 55,8 % – had partially asthma and 16,3 % – had uncontrolled asthma. Among the patients with C/G genotype, 85 % had partially controlled asthma and 15 % had uncontrolled asthma. 6,2 % of G/G homozygotes demonstrated well-controlled asthma, 56,9 % – partially controlled and 36,9 % – uncontrolled asthma.

Table 1

Distribution of genotypes of Bcl1 GR gene polymorphism according to bronchial asthma control level

Control level	Genotypes					
	C/C		C/G		G/G	
	Absol. number	%	Absol. number	%	Absol. number	%
controlled	12	75	0	0	4	25
partially controlled	24	18,6	68	52,7	37	28,7
uncontrolled	7	16,3	12	27,9	24	55,8
χ^2=40,3; p=0,001						

On the other hand, 75 % of patients with controlled asthma had C/C genotype, while every second patient with partial control had C/G and every third one – G/G genotype. Among the patients with uncontrolled asthma, 48,8 % had G/G genotype. These results confirm that C/C genotype was associated with well-controlled asthma and G/G genotype – with uncontrolled BA.

Genotypes distribution for BCL1 polymorphism of GR gene was analyzed in BA patients in relation to inhaled GCs doses. This analysis showed that low doses were taken mostly by patients with C/G genotype (52,3 %), while subjects with G/G genotype took mostly medium doses (p=0,001). 74,4 % of patients with C/C genotype, 98,8 % – with C/G genotype and 61,5 % – with G/G genotype took low doses of inhaled corticosteroids; low doses were taken by 16,3 %, 1,3 % and 35,4 % of patients with C/C genotype, C/G genotype and G/G genotype, respectively (table 2).

Table 2

Genotype frequency of Bcl1 GR gene polymorphism in relation to the doses of inhaled glucocorticosteroids

Inhaled GCs dose, mcg	Genotypes					
	C/C		C/G		G/G	
Zero dose	3	60	0	0	2	40
Low dose	32	21,2	79	52,3	40	26,5
Medium dose	7	22.6	1	3,2	23	74,2
High dose	1	100	0	0	0	0

Table 3 represents genotype distribution for BCL1 polymorphism of GR gene in BA patients in relation to BMI and control level.

62,5 % of patients with controlled asthma had healthy weight, 83,3 % of these patients demonstrated C/C genotype. We have identified significant differences in genotypes distribution of BclI polymorphism of GR gene in patients with partial asthma control, depending on BMI (p<0,001). The results indicate that 58,1 % of patients had healthy weight, 14,4 % – overweight and 27,1 % were obese. On the other hand, C/C and C/G genotypes prevailed in the patients with healthy weight and equaled to 62,5 % and 70,6%, respectively, while G/G genotype was mostly present in obese subjects (51,4 %). It was found out that 23,3 % of patients with healthy weight, 14 % – with overweight and 62,8 % of obese patients had uncontrolled bronchial asthma. It should be also noted that 87,5 % of subjects with G/G genotype and uncontrolled course had obesity.

Discussion

Analysis of population data indicated that obese patients had worse asthma control and more severe disease course [2, 3, 10, 11, 18]. The results of our research also showed that obesity can determine asthma control, since 62,5 % of patients with controlled asthma had healthy weight, 25 % – had overweight and 12,5 % were obese. Among the patients with partially controlled and uncontrolled bronchial asthma, 27,1 % and 62,8 % of patients suffered from obesity, respectively.

We have found out that asthma control also depends on the genotype of BCL1 polymorphism of GR gene. This is confirmed by the fact that C/C genotype prevailed in the patients with controlled asthma, and G/G genotype was mostly found in the subjects with uncontrolled BA. These data are consistent with the results of M.V. Zhdanov (2008), which demonstrated association between different genotypes of Bcl1 polymorphism and BA control in children: well-controlled asthma was characteristic of C/C and C/G genotypes; uncontrolled asthma – of G/G genotype. Besides, the patients, who were homozygous or heterozygous for G allele, required more intensive treatment of asthma exacerbations that corresponded to lower FEV1 values [20]. We have identified statistically significant difference in dose-dependent genotypes distribution of BclI polymorphism of GR gene in the control group and in patients with asthma (p<0,001). Thereat, patients with C/G genotype mostly took lower doses of inhaled corticosteroids, while patients with

Table 3

Distribution of the genotypes for Bcl1 polymorphism of glucocorticoid receptor (GCR) gene in patients with bronchial asthma, depending on body mass index and control level

Controlled						
Genotypes	**Body mass index**					
	≤24,9		**25–29,9**		**30≤**	
	Absol. number	**%**	**Absol. number**	**%**	**Absol. number**	**%**
C/C	10	83,3	1	8,3	1	8,3
G/G	0	0	3	75	1	25
Total	10	62,5	4	25	2	12,5
χ^2=9.3; p=0,009						
Partially controlled						
Genotypes	**Body mass index**					
	≤24,9		**25–29,9**		**30≤**	
	Absol. number	**%**	**Absol. number**	**%**	**Absol. number**	**%**
C/C	15	62,5	4	16,7	5	20,8
C/G	48	70,6	9	13,2	11	16,2
G/G	12	32,4	6	16,2	19	51,4
Total	75	58,1	19	14,7	35	27,1
χ^2=17,7; p=0,001						
Uncontrolled						
Genotypes	**Body mass index**					
	≤24,9		**25–29,9**		**30≤**	
	Absol. number	**%**	**Absol. number**	**%**	**Absol. number**	**%**
C/C	2	28,6	4	57,1	1	14,3
C/G	7	58,3	0	0	5	41,7
G/G	1	4,2	2	8,3	21	87,5
Total	10	23,3	6	14	27	62,8
χ^2=27,6; p=0,001						

G/G genotype – medium doses. Despite this fact, uncontrolled course was observed in G/G genotype carriers twice as often as in C/G genotype carriers, and three times as often as in C/C genotype carriers.

Therefore, the minor allele was associated with controlled asthma and BMI in BA patients. The latter, in its turn, was a determining factor for control level of BA. So, we can speak of association between obesity in BA patients and BCL1 polymorphism, which influences course control of asthma. However, further researches are required to determine the main mechanisms, which induce inadequate asthma control in obese subjects in relation to Bcl1 polymorphism of GR gene, in order to assess patients' response to steroids or other anti-inflammatory drugs.

Conclusions

1. C/C genotype was associated with controlled and partially controlled asthma, while G/G genotype – with partially controlled and poorly controlled BA. Uncontrolled course was observed in G/G genotype carriers twice as often as in C/G genotype carriers, and three times as often as in C/C genotype carriers.

2. Patients with C/G genotype mostly took low doses of inhaled corticosteroids, while patients with G/G genotype were prescribed medium doses.

3. C/C genotype was mostly frequent in patients with healthy weight and controlled asthma, while G/G genotype was typical for obese subjects with partial and poor asthma control.

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ЭФФЕКТИВНОСТЬ ЛЕЧЕНИЯ БРОНХИАЛЬНОЙ АСТМЫ В ЗАВИСИМОСТИ ОТ ГЕНОТИПА BCL1 ПОЛИМОРФИЗМА ГЕНА ГЛЮКОКОРТИКОИДНОГО РЕЦЕПТОРА И МАССЫ ТЕЛА

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Резюме

Целью исследования *была оценка эффективности лечения больных бронхиальной астмой (БА) в зависимости от генотипа по bcl1 полиморфизму гена глюкокортикоидного рецептора и индекса массы тела (ИМТ).*

Материал и методы исследования. *Обследовано 188 пациентов с БА и 95 практически здоровых лиц. Уровень контроля БА оценивали согласно рекомендациям GINA (2011), ИМТ – согласно критериям ВОЗ. Bcl1 полиморфизм определяли по методу Fleury I. Статистическую обработку результатов проводили с использованием программы SPSS-17.*

Результаты исследования. *Установлено, что неконтролируемое течение БА вдвое чаще встречалось при наличии G/G генотипа в сравнении с C/G генотипом и втрое чаще – в сравнении с C/C генотипом. Анализ распределения генотипов в зависимости от дозы ингаляционных глюкокортикоидов показал, что низкую дозу получали преимущественно пациентыс C/G генотипом, а среднюю – с G/G (p=0,001). Частота C/C генотипов была наивысшей у пациентов с нормальной массой тела и контролем БА, а G/G – с ожирением и частичным или отсутствующим контролем заболевания.*

Выводы. *Установлено, что bcl1 полиморфизм гена глюкокортикоидного рецептора ассоциирован с контролем БА и ИМТ.*

Ключевые слова: *бронхиальная астма, bcl1 полиморфизм, глюкокортикоидный рецептор, индекс массы тела, лечение.*

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EFFECTIVENESS OF BRONCHIAL ASTHMATREATMENT DEPENDING ON THE GENOTYPE OF BCL1 GLUCOCORTICOID RECEPTOR GENE POLYMORPHISM AND BODY WEIGHT

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Summary

The aim *of the study was to evaluate the effectiveness of bronchial asthma treatment depending on the genotype of bcl1 glucocorticoid receptor gene polymorphism and body mass index.*

Material and methods. *188 patients with bronchial asthma and 95 healthy individuals have been examined. The level of asthma control was assessed according to the recommendations of GINA (2011), BMI – according to the WHO criteria. Bcl1 polymorphism was determined by the method of Fleury I. Statistical analysis was performed using SPSS-17 program.*

The results of the study. *It was established that during uncontrolled asthma course G/G genotype occurs twice more often compare to C/G genotype and three times – in comparison with C/C genotype. Analysis of genotypes distribution depending on the dosage of inhaled glucocorticoids showed that patients with C/G genotype preferably were treated with low dose and patients with G/G genotype – middle dose (p=0,001). The frequency of C/C genotype was highest in patients with normal body weight and controlled bronchial asthma, and G / G – with obesity and partial or lack of control of the disease.*

Conclusions. *It was found that bcl1 glucocorticoid receptor gene polymorphism is associated with bronchial asthma control and body mass index.*

Key words: *bronchial asthma, bcl1 polymorphism, glucocorticoid receptor, body mass index, treatment.*

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