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EFFECT OF BSMI (283 G>A) POLYMORPHISM OF THE VDR GENE ON THE COURSE OF CHRONIC LUNG DISEASES IN CHILDREN

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ABSTRACT — The study was aimed to evaluate the effect of BSMI (283 G>A) polymorphism of the VDR gene on the course of the chronic nonspecific pulmonary diseases in children. In this study, it was proved that the A/A genotype is associated with the development of primary and secondary chronic lung diseases in children, has a predisposing effect on the development of secondary chronic bronchopulmonary conditions in males, is a preemptive genotype for the development of severe exacerbation in children with CNSLD and correlates with the chronic gram-negative infections in patients.

KEYWORDS — chronic nonspecific pulmonary diseases, children, BSMI polymorphism, VDR gene.

INTRODUCTION

In recent years, multiple studies on the genetic origin of lung diseases in children have confirmed the role of hereditary factors in the disease pathogenesis. [1]. A number of vitamin D receptor gene polymorphisms, particularly BSMI (283 G>A) polymorphism were identified by using bioinformatics methods as a result of the search for single-nuclear polymorphisms with the expected phenotypic effect [2]. The VDR gene regulates the activity of genes for mineral metabolism and parathyroid hormone secretion, thus controlling the homeostasis of calcium and phosphorus. At the same time, there is a similarity between sequences with steroid and thyroid hormone receptors. Upcoming targets of this nuclear hormone receptor are involved in the regulation of both immune response and metabolic processes [2, 3].

MATERIALS AND METHODS

In this study, 98 patients with non-allergic chronic lung diseases were examined. Patients were divided into 2 subgroups: the first (42 children) was consisted of children with chronic diseases formed on the initially intact lung (chronic bronchitis, obliterative bronchiolitis), the second was consisted of patients with genetically determined lung disease (cystic fibrosis, primary immunodeficiencies) and bronchopulmonary malformations. The control group was represented by conditionally healthy children (85 people). The molecular genetic study of the BSMI (283 G>A) polymorphism of the VDR gene was performed by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP). The following parameters of patients with various alleles and genotypes were analyzed: gender, frequency and severity of exacerbations, microbiota pattern, variations in lung function, frequency and pattern of comorbid conditions, morphological changes according to CT lung screening. Statistical analysis of the obtained data was performed using the Data Studio software, STATISTICA 6.0 application package.

RESULTS AND DISCUSSION

Statistically significant differences were found in the frequency of occurrence of the G\G, G\A and A\A genotypes ($\chi^2 = 18.556$ $p < 0.001$ $df = 4$) between patients and controls. According to the data, the genotype including the minor A allele in the homozygous condition was significantly more frequent in patients of the first and the second subgroups than in control group ($\chi^2 = 7.889$ $p = 0.020$ $df = 2$ and $\chi^2 = 18.028$ $p < 0.001$ $df = 2$) (Table 1, 2). Moreover, in our study, the assessment of the risk ratio revealed a positive association of the homozygous minor genotype with the development of chronic lung diseases in children in both groups (OR = 3.850 (CI 1.432–10.352 and OR = 5.347 (CI 2.151–13.290), respectively.

In the study, we analyzed the possibility of association of the effect of this polymorphism on the gender in various forms of chronic lung diseases in children. It was revealed that the A/A genotype of the BSMI polymorphism (283 G>A) of the VDR gene in patients of the second subgroup is significantly more frequent in males ($\chi^2 = 11{,}400$ $p = 0.004$, $df = 2$. OR = 5.347 (CI 2.151–13.290)).

When analyzing the severity of exacerbations with the focus on the Bsm1 VST7 G>A polymorphism of the VDR gene statistically significant differ-

Table 1. *Distribution of genotypes and variant alleles of BSMI polymorphism (283 G> A) of the VDR gene in the first subgroup and control group*

genotypes	control group (n=85)	first subgroup (n=42)	χ^2 ; p
G\G	28 (32,9%)	12 (23,8%)	$\chi^2 = 7,889$ p=0,020 df=2
G\A	49 (57,6%)	18 (42,8%)	
A\A	8 (9,5%)	12 (28,6%)	
alleles	n=134	n=60	
G	77 (57,4%)	30 (50,0%)	$\chi^2 = 0,933$ p=0,335 df=1
A	57 (42,6%)	30 (50,0%)	

Table 2. *Distribution of genotypes and variant alleles of BSMI polymorphism (283 G> A) of the VDR gene in the second subgroup and control group*

genotypes	control group (n=85)	second subgroup (n=56)	χ^2 ; p
G\G	28 (32,9%)	20 (35,7%)	$\chi^2 = 18,028$ p<0.001 df=2
G\A	49 (57,6%)	16 (28,6%)	
A\A	8 (9,5%)	20 (35,7%)	
alleles	n=134	n=72	
G	77 (57,4%)	36 (50,0%)	$\chi^2 = 1,053$ p=0,305 df=1
A	57 (42,6%)	36 (50,0%)	

Significant differences in the G\G, G\A and A\A genotypes, the types of respiratory failure (χ^2 = 3,792; p = 0,435 and χ^2 = 6,942; p = 0,140) and the frequency of exacerbations (χ^2 = 2,792; p = 0,673 and χ^2 = 5.984; p = 0.240) in patients of 1 and 2 subgroups were not found in our study.

When analyzing the influence of the studied genetic polymorphism, associations were revealed between the microbiota pattern of the respiratory tract in the examined patients of the second subgroups with variant genotypes for the BMSI VST7 G>A polymorphism of the VDR gene (χ^2 = 10.376: p = 0.035; df = 4). At the same time, a correlation was found between the A allele and the infection of gram bacteria in patients with cystic fibrosis (χ^2 = 7,000; p = 0.031 df = 2). According to statistics, the mutant A\A genotype is predisposing to chronic culturing of pathogenic flora in patients with chronic lung diseases (Table 4).

CONCLUSION

Our study has proved that the A/A genotype is associated with the development of primary and secondary chronic lung diseases in children, has a predisposing effect on the development of secondary chronic bronchopulmonary pathology in males, is a preemptive genotype for the development of severe exacerbation in children with CNSLD and correlates

Table 3. *Distribution of genotypes and variant alleles of BSMI polymorphism (283 G> A) of the VDR gene according to the severity of exacerbation in children with CNSLD*

genotypes	first subgroup (n=42)			second subgroup (n=56)		
	moderate exacerbation (n=32)	severe exacerbation (n=10)	χ^2 ; p	moderate exacerbation (n=40)	severe exacerbation (n=16)	χ^2 ; p
G\G	16 (50,0%) OR = 0,250 (CI 0,046-1,365)	2 (20,0%)	χ^2 = 6,475 p=0.040 df=2	20 (50,0%) OR = 0,143 (CI 0,029-0,712)	2 (12,5%)	χ^2 = 6,771 p=0.034 df=2
A\G	10 (31,25%)	2 (20,0%)		8 (20,0%)	6 (37,25%)	
A\A	6 (18,75%)	6 (60,0%) OR = 6,500 (CI 1,386-30,488)		12 (30,0%)	8 (50,0%) OR = 2,333 (CI 1,709-7,675)	
alleles	n=42	n=12		n=48	n=22	
G	24 (66,7%)	8 (40,0%)	χ^2= 2,724 p=0.099 df=1	16 (61,5%)	18 (39,1%)	χ^2 = 3,347 p=0.068 df=1
A	12 (33,3%)	12 (60,0%)		10 (38,5%)	28 (60,9%)	

ences were revealed between the genotypes in patients with primary and secondary chronic lung diseases (Table 3). It was proved that the A\A genotype is a predisposing factor for the development of severe exacerbation, while the G\G genotype is associated with moderate set of symptoms in both patients of the first and second subgroups.

with the presence of chronic gram-negative infection in patients. The results can be useful for predicting the course of CNSLD in children, studying the influence of molecular genetic factors on pathology, and also be used as the basis for a personalized approach to prescribing vitamin D in this category of patients.

Table 4. *Distribution of genotypes and variant alleles of BSMI polymorphism (283 G> A) of the VDR gene according to the duration of culturing pathogenic microflora in children with CNSLD*

genotypes	first subgroup (n=42)			second subgroup (n=56)		
	intermittent infection (n=26)	chronic culturing (n=16)	χ^2 ; p	intermittent infection (n=20)	chronic culturing (n=36)	χ^2 ; p
G\G	14 (53,8%)	4 (25,0%)	$\chi^2 = 9{,}908$ p=0,008 df=2	10 (50,0%)	8 (22,2%)	$\chi^2 = 6{,}054$ p=0.049 df=2
A\G	10 (38,5%)	4 (25,0%)		6 (30,0%)	10 (33,3%)	
A\A	2 (7,7%)	8 (50,0%)		4 (20,0%)	18 (44,4%)	
alleles	n=36	n=20		n=26	n=46	
G	24 (66,7%)	8 (40,0%)	$\chi^2 = 2{,}724$ p=0.099 df=1	16 (61,5%)	18 (39,1%)	$\chi^2 = 3{,}347$ p=0.068 df=1
A	12 (33,3%)	12 (60,0%)		10 (38,5%)	28 (60,9%)	

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