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Influence of Prematurity and Glutation S-Transferase Gene Polymorphisms on the Degree of Asthma Control in Children

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Abstract

Introduction: asthma is the most common chronic inflammatory disease of the respiratory tract in children. The clinical manifestation of asthma is closely related to the pathomorphological changes presenting the basis of the disease, and it concerns the difficult air flow through the lower airways during the expiratory phase of breathing. Inadequate treatment of children who have asthma affects the appearance of remodeling of the lower airways and, in the most severe cases, permanent reduction of the lung function values.

The Aim is to determine the influence of prematurity and GSTT1 and GSTM1 gene polymorphisms on the degree of asthma control.

Materials and Methods: The research was designed as a clinical, cohort, observational, retrospective-prospective study. It included 200 patients divided into two groups of one hundred respondents each. The first group of respondents consisted of premature children hospitalized at the Department of Neonatal Intensive Care of the CCUS Pediatric Clinic due to respiratory problems caused by immaturity. In contrast, the second group consisted of at-term-born children monitored through the Pulmonary Counselling of the Pediatric Clinic.

Results: The male and female genders were equally represented. In the premature children group, respiratory support was used in 60/100 (60%) cases. GSTT1 polymorphism was proven in 150 respondents, and GSTM1 polymorphism in 98. Fisher's test showed that gestational age at birth significantly influenced asthma control: the test value was 11.281, p=0.019.

Conclusion: gestation weeks at birth have a statistically significant effect on the degree of asthma control at older age. Although poorly controlled asthma and uncontrolled asthma were more prevalent in children with positive GSTT1 and GSM1 gene polymorphisms, we could not demonstrate a statistically significant influence of the mentioned polymorphisms on the degree of asthma control.

Keywords: prematurity, asthma, GST gene polymorphisms

Introduction

Asthma is the most common chronic inflammatory disease of the respiratory tract of children. The incidence of the disease varies from region to region, ranging from 1-18% [1]. It is considered that 14% of the pediatric population suffers from asthma, with a mortality rate of 0.7/100,000 [2]. The clinical manifestation of asthma is closely related to the pathomorphological changes presenting the basis of the disease, and it concerns the difficult air flow through the lower airways during the expiratory phase of breathing. Inadequate treatment of children who have asthma affects the appearance of remodeling of the lower airways and, in the most severe cases, permanent reduction of the lung function values. Wang R, et al. have proven that there is a significant correlation - the difference in lung function values in asthmatic children who use adequate therapy and have reasonable disease control compared to children who are not under treatment [3].

Asthma is a heterogeneous disease occurring due to the interaction of environmental factors and genetic material

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specific to each person, but recently, prenatal factors have emerged as a specific group of factors. The lifestyle habits of the mother during pregnancy, premature birth, and the method of delivery are now also considered important factors influencing the clinical expression of the disease [4]. Retrospective studies and meta-analyses indicate that prematurity is a significant risk factor for the possible development of asthma. Leps C, et al., observed children from infancy to 11. They concluded that premature birth (<37 GW) was a risk factor for difficulty breathing attacks, wheezing, and asthma in later life [5].

The pathophysiology of asthma is complex and still needs to be fully understood. Nowadays, it is considered that the basis of the disease is the oxidative stress process. Reactive oxygen and nitrogen species (RONS) contribute to the development of airway inflammation, mucus hypersecretion, airway hyperreactivity, and thickening and remodeling, which are the essential characteristics of the pathomorphological changes in asthma [6]. Oxidative stress reduces the response to corticosteroid therapy by altering glucocorticoid receptor expression and signaling [7]. Oxidative stress control implies a better response to therapy and better asthma control. Genes from the glutathione S-transferase family encode enzymes that affect oxidative stress by detoxifying ROS and RNS, thus protecting tissue from the unwanted effects of oxidative stress. There are seven subgroups of glutathione S-transferase genes, with the genes glutathione S-transferase Pi (GSTP), gene glutathione S-transferase Mi (GSTM), and gene glutathione S-transferase Teta (GSTT) being specifically examined, and considered essential for pathological processes in the respiratory tract.

Bowatte G. et al. found a close connection between glutathione S-transferase gene polymorphisms and obstructive lung diseases in persons exposed to adverse environmental factors (air pollution) [8]. The research aimed to determine the influence of prematurity and GSTT1 and GSTM1 gene polymorphisms on the degree of asthma control.

Materials and Methods

The research was designed as a clinical, cohort, observational, retrospective-prospective study. It included 200 respondents divided into two groups of one hundred subjects each. The first group of respondents consisted of premature children hospitalized at the Department of Neonatal Intensive Care of the CCUS Pediatric Clinic in the period from 2007 to 2009, requiring various forms of respiratory support due to respiratory difficulties. The second group of respondents - the control group - consisted of term children who did not have breathing difficulties at birth and did not require any form of respiratory support. The second group of respondents was monitored through the Pulmonary Counselling of the Pediatric Clinic due to breathing difficulty. All respondents were children aged 8 to 10 who could cooperate adequately when performing the planned tests.

Asthma was classified based on the application of the asthma control test (ACT) evaluated by GINA, measurement of FEV1 value, measurement of nitric oxide value in exhaled air, and also based on auscultatory findings of the lungs (presence of wheezing). Genetic testing was performed from a blood sample and was carried out at the Institute of Genetics of the Faculty of Medicine, University of Sarajevo.

The Asthma Control Test (ACT) contains four questions concerning daily asthma symptoms, physical limitations, use of additional medications, and night awakenings during the observed four weeks. The answers were scored with 0 and 1. Based on the sum of values, asthma was classified in the following way: Well-controlled asthma - score 0, partly controlled asthma - score 1-2, Uncontrolled asthma - score 3-4.

FEV1 was measured using a Jaeger Master Scope spirometer (Jaeger GmbH, Germany) in a standardized procedure. The results were expressed as a percentage (%) of the predicted values for height and gender.

A value ≥ 80% was considered a proper finding. FeNO was measured with a chemiluminescent analyzer (NIOX, Aerocrine, Sweden) using the single exhalation technique according to the ERS/ATS recommendations for measuring FeNO in children.

Values are expressed in ppb (parts per billion).

The physical examination included a general pediatric examination with auscultation of the lungs.

The presence of sound phenomena such as wheezing favored the presence of lower airway obstruction and poorer asthma control.

QIAGEN kits were used for DNA extraction from blood. A multiplex PCR test was used to determine the absence/null or presence of GSTT1 (480 bp) and GSTM1 (215 bp) genes. The β-globin (268 bp) gene was used as a control gene.

Statistical Analysis

The normality of continuous variable distribution values was analysed with the Kolmogorov-Smirnov Goodness of Fit Test. Continuous variables with normal distributions of their values were described by mean value as a central tendency measure and standard deviation as a variability measure.

Continuous variables whose values did not follow a normal distribution were described by the median as a central tendency measure and the interquartile range as a variability measure.

Categorical variables were described through the frequency and percentage representation of individual categories. In the case of categorical variables, the Chi-square Test or the Exact Fisher Test was used to test the difference between the study groups if the frequency of one of the combinations of categories of the variables being compared was less than 5. The strength of the statistical relationship between categorical variables was assessed

using Kramer's V coefficient. To compare the values of continuous variables between the study groups, Student's T-test for independent samples and one-factor analysis of variance (when there were more than two groups) were used in the case of normal data distribution, i.e., Mann-Whitney U test or the Kruskal-Wallis non-parametric analysis variance (when there were more than two groups), in case the data were not normally distributed. The results of all used statistical tests were considered statistically significant if the probability of the null hypothesis was less than 0.05.

Results

The study included 200 respondents, with an equal representation of premature and term-born children. In the group of preterm-born children, 89 (89/100) related to the group of 32-36 gestation weeks prematurity, while 11 (11/100) related to the group of 28-32 gestation weeks prematurity. Male and female genders were equally represented. In the premature group, respiratory support was used in 60/100 (60%) cases. One child was on complete mechanical ventilation, 22 (22%) were on NCPAP support, and 37 (37%) required only oxygen support. The minimum weight in both groups of respondents was 1,870 grams, while the maximum weight was 4,800 grams.

In the group of term-born children (100), 44 had well-controlled asthma, 39 had poorly controlled asthma, and 17 had uncontrolled asthma. Out of the total of 89 respondents for premature children born between 32 and 36 gestation weeks, 48 had good asthma control, 36 had poor asthma control, and 5 had uncontrolled asthma.

Out of the respondents born between 28-32 gestation weeks [11], 2 had reasonable asthma control, 6 had poor asthma control, and 3 had uncontrolled asthma (Table 1)**.** Fisher's test showed a significant influence of gestational age at birth on asthma control: the test value was 11.281, p=0.019. Accordingly, premature-born children had poorly

controlled asthma or uncontrolled asthma more frequently, and the lower the week of gestation at birth, the lower the degree of asthma control.

Out of the 150 children with proven GSTT1 gene polymorphism, 74 were born at term and 76 before the planned term. Sixty-six respondents had reasonable asthma control compared to the remaining 84, who had poor and uncontrolled asthma. Using the Fisher test, it was found that in children with positive TT1 polymorphism, the gestational age at birth significantly influenced asthma control. Fisher's test was 10.109, p=0.030 (Table 2).

Poorly controlled and uncontrolled asthma was more prevalent in the group of asthmatic children with the TT1 gene polymorphism compared to the group of asthmatic children in whom we did not prove the presence of this gene polymorphism. However, the Fisher test showed that the TT1 gene polymorphism had no significant influence on asthma control: the test value was 4.886, p=0.083 (Table 3).

Out of the 200 respondents, the GSTM1 polymorphism was confirmed in 98.

Of the 40 respondents with a positive GSTM1 polymorphism with reasonable asthma control, 25 were born before the planned term.

Out of the 14 respondents in the uncontrolled asthma group, nine were delivered at term.

Fisher's test determined that in the group of respondents with a positive TM1 polymorphism, gestational age at birth did NOT significantly influence asthma control. Fisher's test was 4.895, p=0.276 (Table 4).

Poorly controlled asthma and uncontrolled asthma were more prevalent in the group of asthmatic infants with the TM1 gene polymorphism than in the group of asthmatic children without this gene polymorphism. However, the Chi-square test showed no significant influence of the TM1 gene polymorphism on asthma control: the test value was 2.738, the number of degrees of freedom df=2, and the probability of the null hypothesis p=0.254 (Table 5).

Weeks of gestation at birth * Asthma control Cross tabulation						
		Asthma control	*Asthma control*	*Asthma control*	*Asthma control*	
			Good asthma control	*Poor asthma control*	*Uncontrolled asthma*	*Total*
Week of gestation at birth	**Delivery at term**	No.	43	40	17	100
		%	46.2%	48.1%	68.0%	49.7%
	from 32 to 36 weeks of gestation	No.	48	36	5	89
		%	51.6%	44.4%	20.0%	44.7%
	from 28 to 32 weeks of gestation	No.	2	6	3	11
		%	2.2%	7.4%	12.0%	5.5%
Total		No.	93	82	25	200
		%	100.0%	100.0%	100.0%	100.0%

Table 1 - The influence of gestation weeks at birth on the degree of asthma control in both groups of respondents.

*Weeks of gestation at birth * Asthma control Cross tabulation*						
		Asthma control	**Asthma control**			**Total**
			Good asthma control	**Poor asthma control**	**Uncontrolled asthma**	
Week of gestation at birth	**Delivery at term**	No.	27	32	15	74
		%	40.9%	52.5%	65.2%	49.3%
	from 32 to 36 weeks of gestation	No.	37	25	5	**67**
		%	56.1%	41.0%	21.7%	44.7%
	from 28 to 32 weeks of gestation	No.	2	4	3	**9**
		%	3.0%	6.6%	13.0%	6.0%
Total		No.	66	61	23	150
		%	100.0%	100.0%	100.0%	100.0%

Table 2. Influence of gestation weeks on the degree of asthma control in children with a positive GSTT1 polymorphism.

		Asthma control	**Asthma control**			**Total**
			Good asthma control	**Poor asthma control**	**Uncontrolled asthma**	
TT1 gene polymorphism	**YES**	No.	66	61	23	150
		%	71.0%	75.3%	92.0%	75.4%
	NO	No.	27	21	2	50
		%	29.0%	24.7%	8.0%	24.6%
		%	3.0%	6.6%	13.0%	6.0%
Total		No.	93	82	25	200
		%	100.0%	100.0%	100.0%	100.0%

Table 3. The effect of GSTT1 gene polymorphism on the degree of asthma control was assessed with ACT.

Asthma control * Week of gestation at birth Crosstabulation						
		Weeks of gestation at birth	**Weeks of gestation at birth**			**Total**
			Delivery at term	**from 32 to 36 weeks of gestation**	**from 28 to 32 weeks of gestation**	
Asthma control	**Good asthma control**	No.	15	24	1	40
		%	34.9%	48.0%	20.0%	40.8%
	Poor asthma control	No.	19	22	3	44
		%	44.2%	44.0%	60.0%	44.9%
	Non-controlled asthma	No.	9	4	1	14
		%	20.9%	8.0%	20.0%	14.3%
Total		No.	43	50	5	98
		%	100.0%	100.0%	100.0%	100.0%

Table 4. The effect of gestation weeks on the degree of asthma control in children with a positive GSTM1 polymorphism

	Asthma control		Asthma control			
			Good asthma control	Poor asthma control	Uncontrolled asthma	Total
TM1 gene polymorphism	YES	No.	40	44	14	98
		%	43.0%	54.3%	56.0%	49.2%
	NO	No.	53	37	11	101
		%	57.0%	45.7%	44.0%	50.8%
Total		No.	93	81	25	199
		%	100.0%	100.0%	100.0%	100.0%

Table 5. The effect of GSTM1 gene polymorphism on the degree of asthma control was assessed with ACT.

Discussion

Asthma is a significant health problem worldwide. It is the most common chronic inflammatory disease of childhood. Based on the World Health Organization (WHO) data, 262 million people had asthma in 2019, and asthma caused 455,000 deaths [9].

It is well known that boys have asthma more often than girls at a younger age, but at an older age, this relationship is reversed. After the age of 23, women get sick more often than men.

Lee A. et al. defend this finding by pointing to minimal differences in fetal and postnatal lung development and the influence of sex hormones. This study included 200 subjects, with equal representation of men and women [10].

In 2010, 1722 children were examined through Pulmonary Counselling at the CCUS Pediatric Clinic.

From Jan 1 to Dec 31, 2021, 2,950 children were examined. In more than 60% of cases, the children were examined for repeated attacks of breathing difficulty, followed by an auscultatory lung finding, which revealed wheezing.

Ferrante G. et al. stated that the incidence of respiratory diseases is constantly increasing, which supports the presented data concerning the increased influx of patients with respiratory symptoms [11].

Numerous factors influence the increased incidence of respiratory diseases, one of them being prematurity.

Numerous studies have shown a significant impact of prematurity on the occurrence of wheezing and asthma attacks in children.

In their follow-up study, Thunqvist P et al. analyzed 350 preterm children, and at the age 7, they performed spirometric and other measurements. The results of the study showed that the forced vital capacity (FVC) and forced expiratory volume (FVC1) in the group of premature infants were significantly lower compared to full-term infants [12].

Leps C et al. established that children between 32 and 36 gestation weeks had a higher frequency of school-age asthma than term-born children [13]. In their prospective study, Morata-Alba J et al. processed 323 children and concluded that premature-born children had a higher prevalence of bronchiolitis, recurrent wheezing, and asthma than term-born children [14]. Despite numerous studies supporting the abovementioned facts, we face many controversies nowadays. Garcia-Garcia ML et al. showed that the risk of developing asthma was equal in premature (32-36 weeks of gestation) and term-born children suffering from bronchiolitis in infancy [15].

In our study, premature-born children had poorly controlled asthma or uncontrolled asthma more frequently, and the lower the gestation week, the lower the degree of asthma control.

Using Fisher's test, we found a significant influence of gestation weeks at birth on asthma control in both groups of respondents: the test value was 11.281, p=0.019.

Furthermore, we wanted to examine the influence of gestational age (GA) in individual groups of respondents with GST polymorphisms on the degree of asthma control, and we found that in the group of subjects with a positive GSTT1 polymorphism, gestational age at birth significantly affected asthma control. Fisher's test was 10.109, p=0.030, while in the group of respondents with a positive TM1 polymorphism, gestational age at birth did not significantly influence the degree of asthma control. Fisher's test was 4.895, p=0.276. Keeping in mind the above stated, gestational age at birth significantly impacted the degree of asthma control in older age.

Nowadays, the pathophysiology of asthma is considered to be based on the oxidative stress process. Oxidative stress affects the complex control of the disease, reducing the reactivity to prescribed corticosteroids. It changes the expression and signaling of glucocorticoid receptors, which also explains the possible situation of refractoriness to corticosteroid therapy [16].

Glutathione S-transferase is a family of genes that affect glutathione protein synthesis, which is an essential factor in the detoxification of the RONS.

Some previous studies state that people with GSTM null and GSTT null genotypes of glutathione S-transferase

have more frequent respiratory problems. In a case study that followed hospitalized patients due to an asthma attack and healthy controls, a higher prevalence of GSTM null and GSTT1 null polymorphisms was detected in respondents with asthma [17].

In their prospective study, Dai X et al. followed 620 children, recording their exposure to harmful influences in the prenatal and infant period and determining lung function values at ages 12 and 18. They concluded that a significant interaction existed between early exposure to harmful influences, GSTM null mutations, and decreased FEV1 and FVC values [18].

In our research, we wanted to determine the influence of GST gene polymorphisms on the degree of asthma control.

Out of the total number of respondents, 150 children were found to have GSTT1 gene polymorphism. Poorly controlled and uncontrolled asthma was more prevalent in the group of asthmatic children with the GSTT1 gene polymorphism compared to the group of asthmatic children in whom we did not prove the presence of this gene polymorphism. The Fisher test showed that there was no significant influence of the GTT1 gene polymorphism on asthma control: the value of the test was 4.886, p=0.083.

Out of the 200 respondents, the GSTM1 polymorphism was confirmed in 98.

Poorly controlled and uncontrolled asthma was more prevalent in the group of asthmatic children with the GSTM1 gene polymorphism than in the group of asthmatic children without this gene polymorphism. However, the Chi-square test showed no significant effect of the GSTM1 gene polymorphism on asthma control: the test value was 2.738.

Although poorly controlled asthma and uncontrolled asthma were more prevalent in children with positive GSTT1 and GSTM1 gene polymorphisms, we could not demonstrate a statistically significant influence of the mentioned polymorphisms on the degree of asthma control. The stated fact can be explained by the complex pathophysiology of asthma, still utterly unknown to us, and by possible additional influences on asthma control and clinical expression of the disease.

As stated by Zang X et al. in their study, the impact of GSTT1 and GSTM1 polymorphisms will continue to be a challenge in the future, with the Aim of determining their role in the pathophysiology of asthma and their impact on the clinical expression of the disease [19].

Conclusion

In our work, we established a significant influence of gestational age at birth on the degree of asthma control in older age. Although poorly controlled asthma and uncontrolled asthma were more prevalent in children with positive GSTT1 and GSM1 gene polymorphisms, we could not demonstrate a statistically significant influence of the mentioned polymorphisms on the degree of asthma control.

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