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IMPACT OF RISK FACTORS IN DEVELOPING ASTHMA COMBINED WITH GASTROESOPHAGEAL REFLUX DISEASE IN CHILDREN

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Abstract. Impact of risk factors in developing bronchial asthma combined with gastroesophageal reflux disease in children. Umanets T.R., Buratynska A.A., Tolkach S.I., Stepanova L.S., Matveeva S.Yu., Kondratenkova T.V., Smirnova O.A., Garaschenko T.A., Lapshyn V.F., Antipkin Yu.G. *The purpose of the study was to determine the risk factors affecting the development of asthma combined with gastroesophageal reflux disease (GERD). Seventy children aged 5-17 years with asthma were examined. They were divided to two groups: group 1 (50 children with asthma and GERD), and group 2 (20 children with isolated asthma). Medical history data were collected through*

specially designed questionnaire for parents. It was determined that the perinatal risk factors that likely contributed to developing co-morbid asthma and GERD were a threatened miscarriage (OR=6.65; 95% CI, 1.7-25.6, p=0.003), acute respiratory illnesses during pregnancy (OR=6.52; 95% CI, 1.4-31.2, p=0.008), polyhydramnios (p=0.039) and uterine inertia (p=0.0003). Food hypersensitivity in the first year of life, the severity of asthma in examined children played role in increasing the risk of developing asthma combined with GERD (OR=4.83; 95% CI, 1.3-18.6, p=0.013 and OR=4.45; 95% CI, 1.2-17.1, p=0.019 respectively).

Реферат. Вплив факторів ризику на формування бронхіальної астми, поєднаної з гастроезофагеальною рефлюксною хворобою, у дітей. Уманець Т.Р., Буратинська А.А., Толкач С.І., Степанова Л.С., Матвєєва С.Ю., Кондратенкова Т.В., Смірнова О.А., Гаращенко Т.А., Лапшин В.Ф., Антипкін Ю.Г. *Метою роботи було вивчення факторів ризику, що впливають на розвиток бронхіальної астми (БА), поєднаної з гастроезофагеальною рефлюксною хворобою (ГЕРХ). Обстежено 70 дітей віком 6-17 років з БА, які методом рандомізації були розподілені на дві групи: 1 група – 50 дітей з БА і з ГЕРХ, і 2 група – 20 дітей з ізольованою БА. Анамнестичні дані було зібрано шляхом анкетування батьків з використанням розробленого опитувальника. Установлено, що серед перинатальних факторів ризику, що вірогідно впливали на формування коморбідної БА з ГЕРХ, були: загроза переривання вагітності (OR=6,65; 95% CI, 1,7-25,6, p=0,003), гострі респіраторні захворювання під час вагітності (OR=6,52; 95% CI, 1,4-31,2, p=0,008), багатоводдя (p=0,039) та слабкість пологової діяльності (p=0,0003). Наявність в анамнезі реакцій гіперчутливості на їжу на першому році життя, тяжкість перебігу БА в обстежених дітей підвищувало ризик формування БА, поєднаної з ГЕРХ (OR=4,83; 95% CI, 1,3-18,6, p=0,013 та OR=4,45; 95% CI, 1,2-17,1, p=0,019 відповідно).*

According to the published studies, 37-78.2% of children with asthma suffer from combined pathology of the digestive system [1]. One of the most common co-morbid conditions in children with asthma is gastroesophageal reflux disease (GERD), which is registered in 32% to 80% of patients [6].

Asthma is developed in a combination of genetic and environmental factors [8]. All known risk factors for asthma in children are divided into two groups: endogenous (genetic, including genetic predisposition to atopy and bronchial hypersensitivity, sex, obesity) and exogenous (allergens, respiratory infections, nutrition, tobacco exposure, pollutants) [8].

A number of perinatal factors can contribute to asthma developing. Thyroid dysfunction and high blood pressure in the mother during pregnancy; premature birth; parental smoking [11]; caesarean section and other instrumental interventions in delivery [13] are among the risk factors contributing to development of asthma and other allergic diseases in children. The birth weight in newborn less than 2500 g [12] and more than 4000 g [11] are considered risk factors for asthma.

It is recognized that breastfeeding reduces the risk of allergic diseases, including asthma [10].

Risk factors for GERD include caesarean section, premature birth, low birth weight [7], male gender, adolescence, concomitant pathology of the upper digestive tract, hereditary predisposition to diseases of the digestive tract, early introduction of solid baby food, early mixed or formula-feeding, lack of exercise, lack of sleep, irregular and irrational feeding, bad eating habits [3].

It is known that the symptoms of asthma can provoke the development of GERD, which in turn can lead to worsening of asthma course [6].

Despite the large number of scientific studies today, the full array of risk factors that contribute to the development of combined pathology of asthma and GERD remain unclear.

Therefore the purpose of this study was to determine the risk factors contributing to development of asthma combined with gastroesophageal reflux disease.

MATERIALS AND METHODS OF RESEARCH

Seventy children aged 5-17 years with asthma of varying severity and level of controlling it were examined. They were divided into two groups: group 1 (50 children with asthma and GERD), and group 2 (20 children with isolated asthma).

Both groups of children were identical in age and gender. Asthma was diagnosed, and the degree of its severity was established according to the approved criteria (MH Order No. 868 and GINA International Recommendations, 2020) [8]. Taking into account the new diagnostic criteria developed by experts from different countries, the diagnoses of GERD was confirmed [9]. Medical history data were collected through specially developed questionnaire for parents. Statistical processing of the obtained results was performed using the program STATISTICA 13.0 (StatSoftInc., series No. ZZS9990000099100363DEMO-L) and software Microsoft Excel (Microsoft Office 2013 Professional Plus, license agreement (EULAID:O15_RTM_VL.1_RTM_RU). Pearson's chi-squared test was used to compare frequency data, and Fisher's exact test was used for a small number of observations in groups of 5 or less. For all calculated statistical estimates, the statistical significance was checked at the level of not less than 95% ($p<0,05$). Student's t-test, odds ratio (OR) and

their confidence intervals (95% CI) were computed for data analyses.

Informed consent for conducting study was obtained from all parents of the patients. The study was conducted according to main rules and regulations of the ICH GCP and Helsinki declarations on ethics in medical research conducted on human subjects, and subsequent follow-ups (Seoul, 2008), the Convention Council of Europe on Human Rights and Biomedicine (2007), and also recommendations of the Bioethics Committee at Presidium of the National Academy of Medical Sciences of Ukraine (2002) and the rules of the Ethics Committee of the Institute of Pediatrics, Obstetrics and Gynecology named after academician O. Lukyanova, National Academy of Medical Sciences of Ukraine [2, 4, 5].

RESULTS AND DISCUSSION

The demographic characteristics of children in the groups are shown in Table 1. In both observation groups, the majority of the examined children were boys (respectively 80.0% and 85.0%, p=0.627). The average age of children in group 1 was 11.88 (±3,51), and in group 2 – 11.5(±4,27), (p=0.702). No significant differences in gender and age were found between groups of children.

Uncontrolled asthma was registered only in children of group 1 (p=0.083), and intermittent – only in children of group 2 (p=0.0003). The formation of GERD in children with asthma was likely influenced by the severity and persistence of asthma (OR=4.45; 95% CI, 1.2-17.1, p=0.019) (table 1).

Table 1

Demographic characteristics of children (n) in groups 1,2, abs. n. (%)

Indicator	Number of children (n) in groups 1,2		χ^2	p	OR (95%, CI)
	1, n = 50	2, n = 20			
Children 5-11 years	23 (46.0)	12 (60.0)	1.12	0.29	0.57 (0.2-1.6)
Children 12-17 years	27 (54.0)	8 (40.0)	1.12	0.29	1.76 (0.6-5.0)
Girls	10 (20.0)	3 (15.0)	-	0.455	1.42 (0.3-5.8)
Boys	40 (80.0)	17 (85.0)	0.24	0.627	0.71 (0.1-2.9)
Clinical characteristics of asthma:					
Controlled	14 (28.0)	10 (50.0)	3.07	0.079	0.39 (0.1-1.1)
Partially controlled	29 (58.0)	10 (50.0)	0.37	0.542	1.38 (0.5-3.9)
Uncontrolled	7 (14.0)	0	-	0.083	-
Intermittent	0	6 (30.0)	-	0.0003*	-
Mild Persistent	7 (14.0)	4 (20.0)	-	0.385	0.65 (0.2-2.5)
Moderate Persistent	21 (42.0)	7 (35.0)	0.29	0.589	1.35 (0.5-3.9)
Severe Persistence	22 (44.0)	3 (15.0)	-	0.019*	4.45 (1.2-17.1)

Note. * – statistically significant difference at p<0.05 between groups 1, 2, between the corresponding indicators by the Pearson's chi-squared test.

It is known that researches consider caesarean section [7] and other instrumental intervention in delivery [13] as perinatal risk factors for isolated asthma and isolated GERD in children. Analysing the medical history of the examined children, it was found (Table 2) that the mothers of group 1 were significantly more likely to have threatened miscarriage (OR=6.65; 95% CI, 1.729-25.597, p=0.0003), acute respiratory diseases during pregnancy (OR=6,52; 95% CI, 1,363-31,174, p=0.008) (table 2). Polyhydramnios (p=0.039) and uterine inertia (p=0.0003) are reported only in mothers of children of group 1.

There are debated results of studies on the influence of birth weight [11, 12] in the development of isolated asthma or isolated GERD. According to the results of the study, the average birth weight in children of group 1 was 3447.73 (±456.87), in children of group 2 – 3428.0 (±772.75), p=0.905. Low birth weight (less than 2500 g) was found in 1 child

(2.0%) of group 1, and in 1 child (5.0%) of group 2 (OR=0.39; 95% CI, 0.023-6.518, p=0.493). High birth weight (4000 or more than 4000) was in 6 children (12.0%) of group 1 and 4 children (20.0%) of group 2 (OR=0.54; 95% CI, 0.133-2.163, p=0.303). More children of groups 1 and 2 had normal birth weight (43 (86.0%) and 15 (75.0%), respectively) (OR=2.05; 95% CI, 0.564-7.434, p=0.270, $\chi 2$=1.22). Thus, birth weight in children did not affect the development of asthma associated with GERD (Table 2).

Table 2

Perinatal risk factors in children (n) in groups 1,2, abs. n. (%)

Indicator	The number of women examined (n) in the groups 1,2 according to the detected pathology		χ^2	p	OR (95%, CI)
	1, n = 50	2, n = 20			
Bad habits (smoking)	21 (42.0)	8 (40.0)	0.02	0.878	1.09 (0.4-3.1)
Chemical hazards	3 (6.0)	2 (10.0)	-	0.444	0.57 (0.1-3.7)
Preeclampsia in first half of pregnancy	12 (24.0)	5 (25.0)	-	0.578	0.95 (0.3-3.2)
Preeclampsia in second half of pregnancy	7 (14.0)	1 (5.0)	-	0.269	3.09 (0.4-26.9)
Threatened miscarriage	27 (54.0)	3 (15.0)	-	0.003*	6.65 (1.7-25.6)
Nephropathy	17 (34.0)	3 (15.0)	-	0.095	2.92 (0.8-11.4)
Acute respiratory diseases	21 (42.0)	2 (10.0)	-	0.008*	6.52 (1.4-31.2)
Polyhydramnios	9 (18.0)	0	-	0.039*	-
Fetal hypotrophia	1 (2.0)	0	-	0.714	-
Chronic fetal hypoxia	7 (14.0)	0	-	0.083	-
Asphyxia	14 (28.0)	2 (10.0)	-	0.092	3.5 (0.7-17.1)
Caesarean section	11 (22.0)	3 (15.0)	-	0.381	1.6 (0.4-6.5)
Premature birth	6 (12.0)	2 (10.0)	-	0.588	1.23 (0.2-6.7)
Preterm rupture of membranes	7 (14.0)	1 (5.0)	-	0.269	3.09 (0.4-26.9)
Nuchal cord	7 (14.0)	4 (20.0)	-	0.385	0.65 (0.2-2.5)
Uterine inertia	20 (40.0)	0	-	0.0003*	-
Rapid labor	5 (10.0)	2 (10.0)	-	0.684	1.0 (0.2-5.6)
Birth weight less than 2500 g	1 (2.0)	1 (5.0)	-	0.493	0.39 (0.023-6.518)
Normal birth weight	43 (86.0)	15 (75.0)	1.22	0.270	2.05 (0.564-7.434)
Birth weight more than 4000 g	6 (12.0)	4 (20.0)	-	0.303	0.54 (0.133-2.163)
Jaundice	17 (34.0)	6 (30.0)	0.10	0.748	1.2 (0.4-3.7)
Breastfeeding	46 (92.0)	18 (90.0)	0.07	0.787	1.2 (0.2-7.6)
Formula-feeding	4 (8.0)	2 (10.0)	-	0.556	0.78 (0.1-4.7)

Note. * – statistically significant difference at p<0.05 between groups 1, 2, between the corresponding indicators by the Pearson's chi-squared test.

According to the published research data, development of asthma and pathology of the digestive system depends on the type of feeding at an early age [11]. According to the findings in the surveyed

children, the positive benefit of breastfeeding was established; an average duration of breastfeeding in children of group 1 was 12.5 (±10.12) months and in children of group 2 – 16.5 (±12.58) months (p=0.188), which indicated the adequate duration of breastfeeding and therefore it was not associated with risk of asthma developing and asthma-associated GERD.

Table 3 presents the allergy history of children in the observation groups.

Table 3

Data of allergic history in children (n) in groups 1,2, abs. n. (%)

Indicator	Number of diseases in families of children and in children (n)		χ^2	p	OR (95%, CI)
	1, n = 50	2, n = 20			
Burdened heredity of atopy:					
a) mother;	4 (8.0)	3 (15.0)	-	0.316	0.49 (0.1-2.4)
b) father;	5 (10.0)	1 (5.0)	-	0.444	2.11 (0.2-19.3)
c) both parents.	1 (2.0)	1 (5.0)	-	0.493	0.39 (0.02-6.5)
Food hypersensitivity:					
a) mother;	7 (14.0)	3 (15.0)	-	0.591	0.92 (0.2-4.0)
b) father;	4 (8.0)	1 (5.0)	-	0.556	1.65 (0.2-15.8)
c) sibling.	2 (4.0)	0	-	0.507	-
The presence of asthma:					
a) mother;	10 (20.0)	3 (15.0)	-	0.455	1.42 (0.3-5.8)
b) father;	7 (14.0)	3 (15.0)	-	0.591	0.92 (0.2-4.0)
c) both parents;	2 (4.0)	0	-	0.507	-
d) sibling.	1 (2.0)	0	-	0.710	-
None of parents suffers from allergic reactions.	11 (22.0)	6 (33.0)	0.50	0.480	0.66 (0.2-2.1)
Allergic diseases (except asthma):					
a) mother;	15 (30.0)	5 (25.0)	-	0.457	1.29 (0.4-4.2)
b) father;	7 (14.0)	3 (15.0)	-	0.590	0.92 (0.2-4.0)
c) both parents;	2 (4.0)	0	-	0.507	-
d) sibling.	1 (2.0)	0	-	0.710	-
Food hypersensitivity in a child at the time of observation	34 (68.0)	9 (45.0)	3.19	0.074	2.60 (0.9-7.5)
Food hypersensitivity in a child in the first year of life	23 (46.0)	3 (15.0)	-	0.013*	4.83 (1.3-18.6)

Note. * – statistically significant difference at p<0.05 between groups 1, 2, between the corresponding indicators by the Pearson's chi-squared test.

The presence of sensitization to food allergens in children is a risk factor for the development of pathology of the upper digestive tract in children with asthma [1]. In our study, a reliable risk factor for the formation of GERD in children with asthma was food hypersensitivity (cow's milk, chicken egg)

in the first year of life (OR=4.83; 95% CI, 1.254-18.574, p=0.013) (table 3). Other allergy history data were not likely to be associated with co-morbid asthma with GERD in the children examined.

Our research concludes that in determining the risk factors playing role in developing asthma combined with GERD, it is important to take into account the perinatal and allergy history factors, and the severity of asthma – the factors that affect the development of this co-morbid pathology in children.

CONCLUSIONS

1. It was found that the perinatal risk factors play role in developing asthma combined with GERD. There are threatened miscarriage, acute respiratory diseases, polyhydramnios, uterine inertia.
2. Presence of food hypersensitivity in the first year of life in medical history, and severe asthma increase the risk of developing asthma associated with GERD.

Conflict of interests. The authors declare no conflict of interest.

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