Objective of the study was to evaluate if sex-based differences exist in clinical and epidemiologic characteristics of bronchial asthma (BA) in children before and after puberty.

Material and methods. 120 school-age children with persistent BA (80 of whom – males and 49 – pre-puberty individuals), have been examined in observational study with cross-section design. Inclusion criteria: age from 6 to 18 years old; a diagnosis of BA for at least one year; informed consent of parents and children. Exclusion criteria: orphans; the presence of any other chronic lung disease. The first group included 49 patients before puberty, the second clinical group was formed of 71 patients after puberty onset. The clinical anamnestic, allergologic, spirometric and statistical methods of research were used.

Results. Early onset BA non significantly associated with male gender before puberty and late onset BA phenotype slightly predominated in post-pubertal females (RR=1,3; 95%CI:0,6-3,0). Regardless of gender non-severe BA predominated in pre-puberty period and post-puberty period associated with non significantly increased risk of severe BA phenotype (RR=1,6; 95%CI:0,5-5,1 and RR=1,4; 95%CI:0,8-2,5 in females and males respectively). Atopic BA predominated in males and non-atopic phenotype associated with female gender both in pre- and postpuberty. Phenotype of BA with exercise induced bronchoconstriction was equally distributed among both sexes regardless of puberty status. After puberty risk of hospitalization to emergency department due to BA exacerbation in males significantly decreased (RR=0,6; 95% CI:0,4-0,8), while in females such risk slightly increased (RR=1,4; 95% CI:0,7-2,7).

Conclusion. Male gender slightly associated with atopic phenotype, early onset BA before puberty and significantly reduced risk of hospitalization due to exacerbation after puberty. Female gender slightly associated with non-atopic BA phenotype and elevated risk of hospitalization due to BA exacerbation after puberty.
Оригінальні дослідження

полового созревання. Использовали клинически-анамнестические, аллергологические, спирометрические и статистические методы исследования.

Результаты. БА раннего начала несущественно ассоциировала с мужским полом до полового созревания, а поздний фенотип БА несколько преобладал у девочек после пубертата (ОР=1,3, 95% ДИ: 0,6-3,0). Нетяжелая БА преобладала в пренепубертатный период ассоциировал с незначительно повышенным риском тяжелого фенотипа БА (ОР=1,6, 95%ДИ: 0,5-5,1 и ОР=1,4; 95%ДИ: 0,8-2,5 у девочек и мальчиков соответственно). Атопическая БА преобладала у мальчиков, а неатопический фенотип чаще был связан с женским полом как в до-, так и в посперубертатном периоде. Фенотип БА с бронхоkonstruktiveй, индуцированной физической нагрузкой, был равномерно распространен среди обоих полов независимо от половой зрелости. После полового созревания риск госпитализации в отделение неотложной помощи из-за обострения БА у мальчиков значительно снизился (ОР=0,6, 95%ДИ: 0,4-0,8), а у девочек — несколько увеличился (ОР=1,4; 95%ДИ: 0,7-2,7).

Вывод. У мальчиков несколько чаще наблюдается атопический фенотип, раннее начало бронхиальной астмы до полового созревания и после пубертата значительно снижает риск госпитализации из-за обострения. У девочек несколько чаще диагностируется неатопический и поздний фенотип бронхиальной астмы, а после полового созревания повышается риск госпитализации из-за обострения бронхиальной астмы.

Ключові слова: фенотипи астми, діти, стать, статеве дозрівання.

Буковинський медичний вісник. Т.21, № 3 (83). С. 03-07

ГЕНДЕРНО-СПЕЦИФІЧНІ ВІДМІННОСТІ ФЕНОТИПІВ БРОНХІАЛЬНОЇ АСТМИ У ДІТЕЙ ЗАЛЕЖНО ВІД ПУБЕРТАТУ

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Мета дослідження полягала в оцінці відмінностей клінічних та епідеміологічних характеристик бронхиальної астми (БА) у дітей залежно від статі до і після статевого дозрівання.

Матеріал і методи. 120 дітей шкільного віку з персистуючою БА (80 з яких — хлопчики і 49 — пацієнти до початку пубертата) були обстежені в описовому дослідженні з поперечним дизайном. Критерії включення: вік від 6 до 18 років; діагноз БА не менше одного року; інформована згода батьків і дітей. Критерії виключення: сироти; наявність будь-якого іншого хронічного захворювання. Перша група включала 49 пацієнтів до початку статевого дозрівання, друга клінічна група була сформована із 71 пацієнта після початку статевого дозрівання. Використовували клінічно-анамнестичні, алергологічні, спірометричні і статистичні методи дослідження.

Результати. БА раннього початку несуттєво ассоціювалась з чоловічою статтю до статевого дозрівання, а пізній фенотип БА децю переважав у дівчаток після пубертата (BP=1,3, 95%ДИ: 0,6-3,0). Нетяжка БА переважала до початку пубертата незалежно від гендеру, а післяпубертатний період ассоціював з незначно підвищеним ризиком тяжкого фенотипу БА (BP=1,6, 95%ДИ: 0,5-5,1 і BP=1,4; 95%ДИ: 0,8-2,5 у дівчаток і хлопчиків відповідно). Атопична БА переважала у хлопчиків, а неатопичний фенотип частіше був пов’язаний із жіночою статтю як у до-, так і в
**Introduction.** The prevalence of bronchial asthma (BA) has increased and asthma currently affects approximately 1-18% of children worldwide [1]. BA has sex-specific differences in prevalence, in particular BA is far more common in boys than girls during early childhood, but the prevalence equalizes between the genders during adolescence and then switches to a female predominance in adulthood [2, 3]. BA comprised of highly heterogeneous clinical phenotypes resulting from complex interplay between genetic and environmental stimuli. The factors related to BA prevalence may differ depending on sex in preschool and school-aged children [4, 5]. The sex difference in the prevalence of BA is reflected in the sex difference in the hospitalization rate and BA severity [3]. While much focus has been placed on extrinsic environmental stimuli, intrinsic environment such as sex can interact with genes to influence BA risk [6, 7]. The impact of a BA may be different according to gender in terms of different BA clinical phenotypes manifestations in children and adolescents [8-10]. However, only few studies have examined sex-specific effects, especially in childhood [5, 6].

**Objective of the study** was to evaluate if sex-based differences exist in clinical and epidemiologic characteristics of BA in children before and after puberty.

**Material and methods.** The research assignments were to study the peculiarities of clinical phenotypes of BA in children depending on gender in and to investigate the detailed data of BA manifestations in males and females before and after puberty onset. 120 children of 6-18 years old of both sexes with at least one year duration of persistent BA were examined. The first (I) group included 49 patients with persistent BA before puberty, the second (II) clinical group was formed of 71 patients with diagnosis of persistent BA after puberty onset. No significant differences by sex, age, and place of residence have been shown due to correctly formed clinical groups of comparison. Methods: questionnaire answers (Alexithymia Questionnaire for Children; the Toronto Alexithymia Scale; The Spielberger State–Trait Anxiety Inventory), familial anamnesis, Tanner scale score, birth weight and body mass index (BMI), allergic skin tests results, total serum IgE, index of bronchial lability, PC20H (bronchial non specific hyperresponsiveness test to histamine inhalations which caused 20% fall of FEV1), the clinico-anamnestic, allergologic, spirometric and statistical methods of research were used.

**Results and their discussion.** In the examined cohort late onset BA phenotype (debut after 6 years old) predominated regardless of gender and puberty status, first of all in post-pubertal females as compared to pre-puberty period (RR=1.3; 95%CI:0.6-3.0). Such association may be explained by tendency of increasing BA prevalence in girls with aging as well as with BA under diagnosing (Yentl syndrome). Early onset BA (up to 3 years old) non significantly associated with male gender before puberty. Non-severe BA diagnosing predominated in pre-puberty period both in girls and boys, but post-puberty period regardless of sex associated with non significantly increased risk of severe BA phenotype as compared to alternative asthma variant (RR=1.6; 95%CI:0.5-5.1 and RR=1.4; 95%CI:0.8-2.5 respectively). Atopic (allergic) BA predominated in males regardless of puberty status, as well as non-atopic phenotype associated with female gender both in pre- and postpuberty. Exercise induced asthma (phenotype with exercise induced bronchoconstriction) was almost equally distributed among both sexes regardless of puberty status. Furthermore, such atopic manifestations as max skin papula to one of the epidermal allergens and genealogic index of positive allergic familial anamnesis significantly predominated in males as compared to females in pre – and postpuererty respectively. No any significant differences of the spirometric indices were revealed in groups of children depending on gender and puberty status (see table).

Females tended to have lower birth weight as compared to males regardless of puberty status and no differences of actual BMI in groups of comparison were revealed. Alexithymia significantly associ-
ated with pre-puberty period regardless of gender (p<0.04) and no any sex differences of state or trait anxiety levels were revealed in groups of comparison, but transition from pre- to post-puberty in females was accompanied by significant rise of state anxiety (34,0±13,6 versus 44,6±10,2 points, p<0.04).

After puberty risk of hospitalization to emergency department due to BA exacerbation significantly decreased as compared to pre-puberty period in males (RR=0,6; 95%CI:0,4-0,8) and such risk slightly increased in post-puberty in females (RR=1,4; 95%CI:0,7-2,7).

**Conclusions**

1. Late onset BA phenotype with debut after 6 years old non significantly predominated in children regardless of gender and puberty status, first of all in post-pubertal females, while early onset BA (up to 3 years old) associated with male gender before puberty.

2. Non-severe BA diagnosing predominated in pre-puberty period both in girls and boys, but post-puberty period associated with slightly increased risk of severe BA phenotype regardless of gender. After puberty risk of hospitalization to emergency department due to BA exacerbation in girls significantly decreased and in girls such risk slightly increased.

3. Non-atopic BA phenotype associated with female gender both in pre- and post-puberty, while atopic (allergic) BA predominated in males regardless of puberty status, as well as skin papula to the epidermal allergens and genealogic index of positive allergic familial anamnesis significantly predominated in males as compared to females in pre- and post-puberty respectively. Gender-stratified analyses identified associations with significantly lower birth weight in females as compared to males regardless of puberty status and no differences of actual BMI in groups of comparison were revealed.

**Prospects for further research.** Further investigations are needed to examine the effect of gender-specific differences in changes of asthma prevalence and phenotypes in pre- and post puberty taking into account Tanner stages.

**References**

1. Cho YM, Ryu SH, Choi MS, Tinyami ET, Seo S, Choung JT, et al. Asthma and allergic diseases in preschool children in Korea: findings from the pilot study of the Korean Surveillance System for Childhood Asthma. J. Asthma. 2014;51(4):373-9.

2. Mersha TB, Martin LJ, Biagini Myers JM, Kovacic MB, He H, Lindsey M, et al. Genomic architecture of asthma differs by sex. Genomics. 2015; 106(1):15-22.

3. Protudjer JL, Lundholm C, Bergström A, Kull I, Almqvist C. Puberty and asthma in a cohort of Swedish children. Ann. Allergy Asthma Immunol. 2014; 112(1):78-9.

4. Hong CC, Pajak A, Teitelbaum SL, Vangeepuram N, Galvez M, Pinney SM, et al. Younger pubertal age is associated with allergy and other atopic conditions in girls. Pediatric Allergy and Immunology. 2014; 25(8):773-80.

5. Lieberoth S, Gade E, Kyvik KO, Backer V, Thomsen SF. Early menarche is associated with increased risk of asthma: Prospective population-based study of twins. Respiratory medicine. 2015;109(5):565-71.

6. Jang Y, Shin A. Sex-Based Differences in Asthma among Preschool and School-Aged Children in Korea. Pediatr. Pulmonol. 2015; 50 (10):955-62.

7. Andersson M, Hedman L, Bjerg A, Forsberg B., Lundbäck B, Rönmark E. Remission and persistence of asthma

| Characteristic | Clinical groups | Males | Females | Pt   |
|---------------|----------------|-------|---------|------|
| Max skin papula to one of the epidermal allergens (mm) | I | 16,2±4,5 | 11,4±7,5 | <0,03 |
| | II | 15,1±8,3 | 12,8±6,6 | =0,34 |
| Total serum IgE (IU/ml) | I | 740,6±471,5 | 493,2±446,6 | =0,27 |
| | II | 783,9±476,0 | 619,9±494,0 | =0,33 |
| Positive allergic familial anamnesis per person (genealogic index) | I | 0,153±0,097 | 0,151±0,065 | =0,92 |
| | II | 0,164±0,090 | 0,177±0,060 | =0,03 |
| Bronchial lability index (FEV1, %) | I | 12,9±9,8 | 15,2±13,3 | =0,58 |
| | II | 17,9±13,9 | 18,6±13,9 | =0,12 |
| PC20H (mg/ml) (bronchial hyperresponsiveness to histamine) | I | 0,94±1,03 | 2,28±3,32 | =0,18 |
| | II | 2,48±4,00 | 0,75±0,80 | =0,24 |
| Birth weight (g) | I | 3604,7±546,4 | 3235,6±701,9 | =0,051 |
| | II | 3465,0±495,0 | 3150,0±578,0 | =0,03 |
| BMI actual, kg/m² | I | 19,5±6,8 | 18,9±3,1 | =0,32 |
| | II | 22,0±5,7 | 21,2±3,5 | =0,56 |
9. Chen YC, Dong GH, Lin KC, Lee YL. Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: a systematic review and meta-analysis. Obes. Rev. 2013;14(3):222–31.

10. Wang L, Wang K, Gao X, Paul TK, Cai J, Wang Y. Sex difference in the association between obesity and asthma in U.S. adults: Findings from a national study. Respir. Med. 2015; 109(8):955-62.