UDC: 616.248-053.2-07

L. O. Bezrukov, M. N. Garas
SI «Bukovinian State Medical University»

Nonspecific bronchial hyperreactivity in schoolchildren with atopic and nonatopic phenotypes of bronchial asthma

Key words: *bronchial asthma, children, atopic phenotype, bronchial hyperreactivity.*

Bronchial asthma (BA) and recurrent bronchitis occupy the leading place among chronic and recurrent respiratory diseases in children age. Special importance of problem of these diseases gets in view of the provisions that recurrent respiratory diseases in children is the debut of chronic bronchopulmonary pathology of adult period of life [1, 16]. One of the important aspects of inadequate asthma control is determined by its phenotypic heterogeneity [15, 18]. The question of differentiation asthma phenotypes of childhood-determining the particular aspects of the disease and individual approaches to treatment is a major controversial problems in allergology [5]. Clinical phenotypes of asthma are heterogeneous; their formation depends on the genetic and environmental influences and is determined mostly by the interaction of cellular elements of the respiratory tract and immune system [19]. Currently phenotyping of disease occurs in the two areas: clinical, pathophysiological, molecular markers [12] and variants of response to therapy [21]. Since the asthma classification provides for atopic and nonatopic forms [7, 10, 14], it was expedient considered to analyze the indices, that reflect characteristic phenomenon of disease as bronchial hyperreactivity in these phenotypes, due to evidence-based medicine.

The aim of the study was to evaluate the indicies of bronchial hyperresponsiveness and lability in school-age children with atopic and nonatopic asthma phenotypes.

Materials and methods

In pulmonary department of Regional Pediatric Clinical Hospital (Chernivtsi) under the principles of bioethics were examined 64 children, suffering from bronchial asthma. To identify the degree of atopy anamnestic atopic status and skin allergic tests were used. According to a survey 38 children with atopic asthma phenotype formed first clinical group (I), and the remaining 26 patients with nonatopic asthma joined the second (II) clinical group. For the main clinical features comparison group did not differ significantly. So, boys in I clinical group accounted for 28 (73,7 %), in the comparison group were 14 persons (53,9 %, $p\phi > 0,05$), the rural population accounted for 60,5 % among children with atopic asthma phenotype and in the second clinical group were 73,1 % (19 patients, $p\phi > 0,05$). The average age of representatives in I clinical group was ($11,6 \pm 0,55$), in the comparison group of children was ($12,0 \pm 0,68$) years ($p > 0,05$).

Bronchial lability was determined according to recommendations [6, 8, 20] by assessing their response to dosed physical load (DFL) and short-acting β_2-agonists inhalation (salbutamol 200 mcg) followed by calculating the index of bronchial lability as the sum of the components, such as index of bronchospasm (IBS) and bronchodilation (IBD). A positive bronchodilation answer was considered with indicators IDB more than 12 % [6].

Research of bronchial hyperresponsiveness was performed using standardized spirometric inhaled histamine test [17] considering of recommendations for standardization of study [9]. Indices of provocative concentration of histamine to cause 20 % fall in FEV (PC20H) and provocative dose of histamine (PD20H) used to determine the airway hypersensitivity. In the study considered that the lower indices mean the higher histamine hypersensitivity [4]. During bronhoprovocation test with dosed physical load in a patient of II clinical group airway wheezing symptoms were recorded, and the patient was eliminated from further study.

Statistical analysis received data was performed with biostatistics position [13]. To assess the diagnostic value of tests was determined the sensitivity, specificity, positive and negative predictive value with defined confidence intervals (95 % CI) and likelihood ratio of test results. Risk assessment implementation of events was held considering of probability values relative risk, odds ratio and posttest probability, as well as their confidence intervals [2].

Results

Table 1 shows the performance of bronchial lability in children comparing groups in response to dosed physical load and inhalation of salbutamol (IBD) and the average value of the integral bronchial lability index (BLI).

A tendency to more severe lability was observed in children with atopic asthma phenotype, mainly due to significant dilatation in response to inhalation of short-acting β_2-agonists. Thus, a positive test with short-acting β_2-agonists was observed in 42,1 % children of the I clinical group and only in 28 % children in the comparison group ($p\phi > 0,05$).

Expressive airways dilated reaction (BLI > 20 %) inherent in every fifth patient with atopic asthma (21,1 %) and for only 4 % of children with nonatopic asthma phenotype ($p\phi < 0,05$). Thus, the IBD with values over 20 % pointed to the relative risk of atopic phenotype of 1,9 (95 % CI 0,2–13,9) at 17,4 odds ratio (95 % CI 2,1–142,1). Posttest probability of atopic asthma verification due to these values of IBD increased on 41 %.

Low indexes (IBS and IDB) mainly were inherent in representatives of II clinical group. In particular, the increase in forced expiratory volume in 1 second less than 12 % after salbutamol inhalation was observed in 2/3 of children with nonatopic asthma phenotype and only in 52,1 % of the I clinical group ($p\phi > 0,05$). Minimum bronchospasmodic reaction in response to dosed physical load (IBS less than 10 %) was recorded significantly more often in patients with atopic asthma phenotype (60,5 %) relative to the comparison group (36 %; $P\phi < 0,05$). Paradoxically dilated response to dosed physical load was observed in 10,5 % children of I clinical group. Thus, IBS with values above 10 % testified relative risk of atopic phenotype of 1,4 (95 % CI 0,7–2,5) with 2,2 odds ratio (95 % CI 0,7–6,5). Posttest probability of atopic phenotype detection with IBS above 10 % increased only on 10 %.

Since the bronchial lability index is an integral index and displays the total bronchial response to dosed physical load and inhalation of salbutamol, its expressive value proved to in children with atopic asthma phenotype. In particular, high lability of the bronchi (BLI > 20 %) was observed more than half of the representatives of I clinical group (52, 6 %) and only in 40 % of children with nonatopic asthma ($p\phi > 0,05$). Expressive bronchial lability (BLI > 30 %) also recorded more frequently among patients with atopic disease phenotype, particularly in every fourth person (26,3 %), compared with representatives of II clinical group (16 %; $p\phi > 0,05$). In accordance expressive bronchial lability pointed to relative risk of atopic asthma 1,2 (95 % CI 0,4–3,5) with 1,8 odds ratio (95 % CI 0,5–6,8). Posttest probability of atopic asthma verification in these values of lability index increased less than 12 %.

During analysis of bronchial hyperresponsiveness the tendency to expressive of this phenomenon was established in children with atopic asthma phenotype. In particular, PC20H was (1,3 ± 0,3) mg/ml in patients of I group versus (2,2 ± 0,8) mg/ml representatives of comparison group ($p > 0,05$).

Expressive bronchial hyperresponsiveness (PC20H < 0,6 mg/mL) was observed in almost 2/3 of patients of I clinical group (60,5 %) and only in 28 % of children of the comparison group ($p\phi > 0,05$), and pointed to the relative risk of atopic asthma 1,6 (95 % CI 0,8–3,3) with 3,9 odds ratio (95 % CI 1,3–11,7). Posttest probability of atopic asthma phenotypes detection with expressive hyperresponsiveness increased only on 18 %.

Informativeness of bronchial lability and hyperresponsiveness indices in the confirmation of atopic disease phenotype relative nonatopic asthma is shown in Table 2.

Bronchial lability and hyperresponsiveness indices in confirming atopic asthma relatively nonatopic phenotype of the disease proved to enough specific with a significant proportion of false negative results.

Table 1

Indices of bronchial lability in clinical groups of schoolchildren (M ± m)

Clinical groups		Numbers of schoolchildren	Index of bronchospasm, %	Index of bronchodilation, %	Bronchial lability index, %
I	Children with atopic asthma	38	11,4 ± 1,7	11,8 ± 1,9	23,2 ± 2,7
II	Children with nonatopic asthma	25	10,5 ± 1,7	7,6 ± 1,9	18,1 ± 2,8
p			> 0,05	> 0,05	> 0,05

Note: p – probability criterion of Student

Table 2

Diagnostic value indices of nonspecific bronchial hyperreactivity in confirming atopic asthma

Bronchial lability and hyperresponsiveness indices	Diagnostic value, %				Likelihood ratio	
			predictive value			
	sensitivity	specificity	positive	negative	of positive results	of negative results
IBD > 20 %	42	96	94	52	10,5	0,6
IBS > 10 %	55	64	67	51	1,5	0,6
BLI > 30 %	26	84	71	42	1,6	0,8
PC20H < 0,6 mg/mL	60	72	76	54	2,1	0,5

Conclusions

1. Children with atopic asthma characterized by tendency to expressive bronchial lability mostly due to bronhodilation response to short-acting β_2-agonists and expressive airway hyperresponsiveness to histamine.

2. In selected distribution points bronchial lability indices, including integral index and bronchodilation index, characterized by sufficient specificity (84 % and 96 %, respectively) for the verification of atopic asthma phenotype in children.

3. Use markers of nonspecific bronchial hyperreactivity to confirmation atopic asthma phenotype relative nonatopic makes sense only in combination with other clinical, laboratory and intsrumental indices that reflect the main characteristics of the disease.

Prospects for future research consist in identifying in children with atopic and nonatopic asthma phenotypes markers of activity of airway inflammation and evaluation of diagnostic and prognostic value of these markers.

References

1. *Антипкин, Ю. Г.* Рецидивирующий бронхит у детей: дискуссионные вопросы [Текст] / Ю. Г. Антипкин, В. Ф. Лапшин, Т. Р. Уманец // Здоров'я України. – 2008. – № 18/1. – С. 19–21.

2. Біостатистика [Текст] / За ред. В. Ф. Москаленка. – К. : Книга плюс, 2009. – 184 с.

3. *Іванова, Л. А.* Показники гіперсприйнятливості бронхів при різних фенотипах бронхіальної астми в дітей [Текст] / Л. А. Іванова // Буковинський мед. вісник. – 2010. – Т. 14, № 4. – С. 35–37.

4. *Куличенко, Т. В.* Бронхопровокационное тестирование в педиатрической практике / Т. В. Куличенко, О. Ф. Лукина [Текст] // Вопросы современной педиатрии. – 2005. – Т. 4, № 4. – С. 38–42.

5. *Недельська, С. М.* Фенотипові особливості бронхіальної астми у дітей міста Запоріжжя [Текст] / С. М. Недельська, Л. І. Кляцька, Н. М. Марчук // Актуальні питання педіатрії, акушерства та гінекології. – 2013. – № 2. – С. 57–60.

6. *Новик, Г. А.* Спирометрия и пикфлоуметрия при бронхиальной астме у детей (практика оценки и мониторинга) [Текст] / Г. А. Новик, А. В. Боричев. – СПб. : ГПМА, 2007. – 68 с.

7. Про затвердження та впровадження медико-технологічних документів зі стандартизації медичної допомоги при бронхіальній астмі [Електронний ресурс]: Наказ МОЗ України від 08.10.2013 № 868. – Режим доступу : www. document.ua.

8. *Сидельников, В. М.* Практическая аллергология детского возраста [Текст] / В. М. Сидельников, Л. А. Безруков, В. Г. Мигаль. – К. : Здоров'я, 1985. – С. 22–23.

9. Стандартизация легочных функциональных тестов. Доклад рабочей группы «Стандартизация тестов исследования легочной функции». Официальный отчет Европейского респираторного общества [Текст] // Пульмонология. – 1993. – Приложение. – 96 с.

10. Сучасна класифікація бронхіальної астми у дітей [Текст] / Ю. Г. Антипкін, В. Ф. Лапшин, Т. Р. Уманець [та ін.] // Перинатологія та педіатрія. – 2011. – № 1. – С. 8–10.

11. *Уманець, Т. Р.* Клініко-анамнестичні особливості фенотипів бронхіальної астми у дітей [Текст] / Т. Р. Уманець // Перинатологія та педіатрія. – 2011. – № 2. – С. 69–71.

12. *Carolan, B. J.* Clinical phenotypes of chronic obstructive pulmonary disease and asthma: recent advances [Text] / B. J.Carolan, E. R.Sutherland // The Journal of Allergy and Clinical Immunology. – 2013. – Vol. 131, № 3. – P. 627–634.

13. Fundamentally of biostatistics [Text] / B. Rosner. – Belmont : Duxbury Press, 2003. – 682 p.

14. *Global* strategy for asthma management and prevention, Revised 2014 [Електронний ресурс] / J. M. FitzGerald, E. D. Bateman, J. Bousquet [et al.]. – Режим доступу : www.ginasthma.org.

15. *Green, R. H.* Stability of inflammatory phenotypes in asthma [Text] / R. H. Green, I. Pavord // Thorax. – 2012. – № 2. – P. 46–57.

16. *Hedlin, G.* An update on paediatric asthma [Text] / G. Hedlin, J. Konradsen, A. Bush // Eur. Respir. Rev. – 2012. – Vol. 21 (125). – P. 175–185.

17. *Juniper, E. F.* Histamine and Methacholine inhalation tests [Text] / E. F. Juniper, D. W. Cockcroft, F. E. Hargreave. – Lund, Sweden, 1994. – 51 p.

18. *Kiley, J.* Asthma phenotypes [Text] / J. Kiley, R. Smith, P. Noel // Curr. Opin. Pulm. Med. – 2007. – Vol. 13, № 1. – P. 19–23.

19. *Lloyd, C. M.* T-cells in asthma: influences of genetics, environment, and T-cell plasticity / C. M. Lloyd, S. Saglani [Text] // The Journal of Allergy and Clinical Immunology. – 2013. – Vol. 131, № 5. – P. 1267–1274.

20. *Silverman, M.* Standardization of exercise tests in asthmatic children / M. Silverman, S. D. Anderson [Text] // Arch. Dis. Child. – 1972. – Vol. 47. – P. 882–889.

21. *Weiss, S. T.* New approaches to personalized medicine for asthma: Where are we? [Text] / S. T. Weiss // The Journal of Allergy and Clinical Immunology. – 2012. –Vol. 129, № 2. – P. 327–334.

НЕСПЕЦИФИЧЕСКАЯ ГИПЕРРЕАКТИВНОСТЬ БРОНХОВ У ШКОЛЬНИКОВ С АТОПИЧЕСКИМ И НЕАТОПИЧЕСКИМ ФЕНОТИПАМИ БРОНХИАЛЬНОЙ АСТМЫ

Л. А. Безруков, Н. Н. Гарас

Резюме

Одним из актуальных аспектов недостаточного контроля бронхиальной астмы (БА) определяется ее фенотипическая неоднородность. Вопрос дифференциации астма-фенотипов детского возраста, определяющие особенности течения заболевания и индивидуальные подходы к лечению является одной из основных дискуссионных проблем в детской аллергологии.

Целью исследования *было оценить показатели гипервосприимчивости и лабильности бронхов у детей школьного возраста, больных БА, с атопическим и неатопическим фенотипами заболевания.*

Материалы и методы исследования. *В статье представлены результаты анализа показателей неспецифической гиперреактивности бронхов у 64 детей с фенотипами атопической (38 пациентов) и неатопической (26 школьников) БА. Для выявления степени атопии использовали исследования анамнестического атопического статуса и показатели кожных реакций немедленного типа со стандартными небактериальными аэроаллергенами. Лабильность бронхов определяли путем оценки их реакции на дозированную физическую нагрузку и ингаляцию β_2-адреномиметика короткого действия. Гипервосприимчивость бронхов исследовали с помощью стандартизированного ингаляционного спирометрического теста с гистамином. По основным клиническим признакам группы сравнения достоверно не отличались.*

Результаты и их обсуждение. *Установлено, что для детей с атопической БА характерна тенденция к выраженной лабильности бронхов (23,2 ± 2,7) % против (18,1 ± 2,8) %, $p<0,05$, в основном, за счет бронходилатационной реакции на β_2-адреномиметик короткого действия (11,8 ± 1,9) % против (7,6 ± 1,9) %, $p<0,05$, а также выраженная гипервосприимчивость дыхательных путей к гистамину (1,3 ± 0,3) мг/мл у пациентов первой группы против (2,2 ± 0,8) мг/мл у представителей группы сравнения, $p<0,05$. В то же время, в верификации атопического фенотипа БА у детей показатель лабильности бронхов (>20 %) и индекс бронходилатации (>30 %) оказались специфическими (84 % и 96 % соответственно), однако низкочувствительными (26 % и 42 % соответственно).*

Ключевые слова: *бронхиальная астма, дети, атопический фенотип, гиперреактивность бронхов.*

Научно-практический журнал «Астма и аллергия», 2015, №1

Л. А. Безруков,
д-р мед. наук, профессор,
ГУ «Буковинский государственный медицинский университет»,
58023, Украина, г. Черновцы, ул. Русская, 207а
тел.: +38(037)257-56-60
e-mail: leobezrukov@yandex.ru

NONSPECIFIC BRONCHIAL HYPERREACTIVITY IN SCHOOLCHILDREN WITH ATOPIC AND NONATOPIC PHENOTYPES OF BRONCHIAL ASTHMA

L. O. Bezrukov, M. N. Garas

Summary

One of the important aspects of inadequate asthma control is determined by its phenotypic heterogeneity. Question of asthma phenotypes differentiation in childhood, defining features of the disease course and individual treatment approaches, is a major controversial problem in pediatric allergology.

The aim *of the study was to evaluate the indicies of bronchial hyperresponsiveness and lability in school-age children with atopic and nonatopic asthma phenotypes.*

Materials and methods. *In article has been presented the results of analysis of nonspecific bronchial hyperreactivity indices in 64 children with atopic (38 patients) and nonatopic (26 schoolchildren) phenotypes of bronchial asthma. To identify the degree of atopy has been used anamnestic atopic status and skin allergic tests. Bronchial lability was determined according to recommendations by assessing their response to dosed physical load and short-acting β_2-agonists inhalation. Investigation of bronchial hyperresponsiveness was performed using standardized spirometric inhalation histamine test. For the main clinical features comparison groups did not differ significantly.*

Results and conclusions. *It was found that children with atopic asthma is characterized by a tendency to expressive bronchial lability (23,2 ± 2,7) % versus (18,1 ± 2,8) %, $p<0,05$, mostly due to dilation response to short acting β_2-agonists (11,8 ± 1,9) % versus (7,6 ± 1,9) %, $p<0,05$, and expressive airway hyperresponsiveness to histamine (1,3 ± 0,3) mg/ml in patients of the first group versus (2,2 ± 0,8) mg/ml of the representatives of the comparison group, $p<0,05$). However, in the verification of atopic asthma phenotype in children, bronchial lability index (> 20 %) and the bronchodilation index (>30 %) were specific (84 % and 96 %, respectively) with low sensitivity (26 % и 42 % respectively).*

Key words: *bronchial asthma, children, atopic phenotype, bronchial hyperreactivity.*

Theoretical and practical J. «Asthma and Allergy», 2015, 1

L. A. Bezrukov,
MD, Professor,
GU «Bukovinian State Medical University»
58023, Ukraine, Chernivtsi, Ruska str., 207a
tel.: +38(037)257-56-60
e-mail: leobezrukov@yandex.ru