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Evaluation of fractional exhaled nitric oxide in school-age children with asthma and sensitization to cat allergens

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Abstract: *bronchial asthma is a chronic condition that is considerably prevalent among children. According to scientific evidence, cat allergens are most frequently responsible for the onset of asthma manifestations in children. Children are more likely to develop atopic asthma with eosinophilic inflammation. Under these circumstances, specific biomarkers are used as indicators of this inflammation. Fractional exhaled nitric oxide has been identified as a marker of eosinophilic airway inflammation in asthma. The aim of the research was to determine the fractional exhaled nitric oxide concentrations in school-age children with bronchial asthma and sensitization to cat allergens in order to predict asthma control status and assess therapeutic response. A total of 430 children aged between 6 and 17 years with asthma and sensitization to cat allergens participated in the study. The sensitization profile was investigated using a multicomponent molecular allergy diagnostic test (ALEX², Austria). The fractional exhaled nitric oxide levels were evaluated (NIOX VERO, Sweden). A total of 302 patients were enrolled in a retrospective study to find out how likely they were to gain bronchial asthma control over the course of therapy. As a result, a one-factor logistic regression analysis was conducted. A total of 128 children were included in the 12-month prospective research. All patients had a rise in fractional exhaled nitric oxide of > 20 ppb, with children with severe asthma having levels of 35 ppb or higher. The study discovered that changes in the fractional exhaled nitric oxide concentrations at the end of a three-month therapy could be linked to the maintenance of bronchial asthma control after a 12-month treatment period ($r = 0.619$; $p < 0.001$). After a year of therapy, increasing baseline fractional exhaled nitric oxide levels reduced the probability of establishing bronchial asthma control in children (OR <1; $p < 0.001$). The dynamics of fractional exhaled nitric oxide reduction increased the probability of achieving bronchial asthma control after completion of a three-month therapy (OR> 1; $p < 0.001$). The effect of allergen-specific immunotherapy on the specified indicator of eosinophilic inflammation was demonstrated by a statistically significant difference in the mean values of fractional exhaled nitric oxide after a 12-month treatment period in the group of patients who received allergen-specific immunotherapy in combination with controller therapy versus the group of patients who received only controller therapy ($p = 0.012$). Thus, among school-age children with asthma and sensitization to cat allergens, the levels of fractional exhaled nitric oxide increased, especially in severe asthma. Not only the baseline fractional exhaled nitric oxide levels but also their dynamics after a three-month therapy should be considered when predicting the probability*

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of establishing asthma control in these children. The inclusion of allergen-specific immunotherapy in the complex treatment of bronchial asthma in school-age children with sensitization to cat allergens has been shown to have a favourable therapeutic effect on the fractional exhaled nitric oxide levels.

Keywords: allergens, asthma, children, nitric oxide, therapy.

Introduction

Bronchial asthma is a chronic condition with a rising incidence and prevalence among children (Ramratnam SK, et al., 2017; Global Initiative for Asthma, 2022). There is considerable evidence that cat allergens are triggers of childhood asthma, and cat allergen sensitivity is common, especially among children with respiratory allergies (Dávila I, et al., 2018; Dharmage SC, et al., 2019; Sparkes AH., 2022).

In general, children are more likely to develop atopic asthma with eosinophilic inflammation. Under these circumstances, specific biomarkers are used as indicators of this inflammation. These include the count of eosinophils in blood and sputum, fractional exhaled nitric oxide (FeNO) and the study of T2 cytokine gene expression (Arnold RJ, et al., 2018; Peters MC and Wenzel SE., 2020). Nitric oxide (NO) is known to be a signalling molecule synthesized from L-arginine in response to inflammatory cytokines in airway epithelial cells and is present in exhaled breath (Rao DR, et al., 2016).

FeNO is well-known as a marker of eosinophilic airway inflammation, and its application as a diagnostic tool for asthma treatment is being debated (Arnold R.J.G., et al., 2018; Laura Chen, et al., 2022). The measurement of FeNO and forced expiratory flow (FEF 25-75%) has been found to increase asthma diagnosis accuracy in children aged 8-16 years (Eom SY, et al., 2020).

FeNO should be used not only for asthma diagnosis but also for inhaled corticosteroid administration and therapeutic response assessment (Wang K, et al., 2020; Rupani H and Kent BD., 2022). The focus is on dynamic monitoring of FeNO values, which has been found to be beneficial in therapy management and treatment failure reduction (Wang X, et al., 2019). This problem is being investigated in terms of different age groups, particularly schoolchildren, and the impact of various individual characteristics on FeNO levels (Czubaj-Kowal M, et al., 2022).

Aim

The aim of the research was to determine the fractional exhaled nitric oxide concentrations in school-age children with asthma and sensitization to cat allergens in order to predict asthma control status and assess therapeutic response.

Materials and methods

430 patients were selected to participate in the study. The presence of bronchial asthma, children of both sexes, age 6-17 years, sensitization to at least one of the cat allergens (Fel d 1, Fel d 2, Fel d 4, Fel d 7) and availability of informed consent were determined as the inclusion criteria. Severe asthma criteria were met by 26 (6.05%) patients; intermittent asthma was observed in 124 (28.84%) patients; mild persistent – 192 (44.65%) patients; moderate persistent - 88 (20.47%) patients.

The patients underwent clinical examination, a skin-prick test, spirometry (BTL-08 SPIRO, UK), and total IgE testing. The sensitization profile was studied using the ALEX² test (Austria). The FeNO concentration was measured in ppb (parts per billion) (NIOX VERO, Sweden).

187 boys (61.92%) and 115 girls (38.08%) were enrolled in a retrospective study to determine the probability of achieving bronchial asthma control. A one-factor logistic regression analysis was conducted.

The 12-month prospective study included 128 children - 69 boys (53.91%) and 59 girls (46.09%). The patients were divided into 3 groups. A total of 96 children were assigned to Group No1, which received only basic therapy without allergen-specific immunotherapy (AIT). Group No2 consisted of 32 children who were prescribed both basic therapy and AIT, while Group No3 consisted of 40 children who got only basic therapy without AIT and were clinically comparable to Group No2. 13 children received AIT using Alxoid (polymerized allergen extract) (Inmunotek, S.L., Spain) as a suspension for subcutaneous administration (2000 TO/mL and 10,000 TO/mL), which contains cat hair allergenic extract. 19 children

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received AIT using Oraltek (monoallergen) (Inmunotek, S.L., Spain) in the form of a sublingual spray (30,000 TO/mL), which contains cat hair allergenic extract.

The IBM SPSS Statistics Base (version 22) was used to conduct the statistical analysis. Statistical significance was defined as a value of $p<0.05$. The geometric mean and the 95% confidence interval (CI) were reported for each group. The Commission on Bioethical Expertise and Scientific Research Ethics of Bogomolets National Medical University approved the design of this research.

Results

All patients had a rise in fractional exhaled nitric oxide of > 20 ppb, with children with severe asthma having levels of 35 ppb or higher. FeNO values were 30.47 (95% CI 30.10 - 30.84) ppb in patients with intermittent and mild persistent asthma, 33.67 (95% CI 32.32 - 35.02) ppb in patients with moderate asthma, and 39.65 (95% CI 37.21 - 42.10) ppb in patients with severe asthma. There was a statistically significant difference in FeNO values for severe and moderate asthma ($p = 0.009$), for severe and intermittent or mild persistent asthma ($p <0.001$), for moderate and intermittent or mild persistent asthma ($p = 0.007$).

After a 12-month treatment period, the findings demonstrated a correlation between bronchial asthma control and baseline FeNO ($r = - 0.172$; $p <0.001$), as well as a correlation between bronchial asthma control and FeNO dynamics after a three-month therapy ($r = 0.619$; $p <0.001$). The study revealed a correlation between FeNO dynamics and sensitization to three or more cat allergens ($r = -0.384$; $p <0.001$), as well as a correlation between FeNO dynamics and the elimination of exposure to cats - $r = -0.333$; $p <0.001$.

One-factor logistic regression analysis was carried out to predict bronchial asthma control status in these children after a 12-month treatment period. The findings are described in Table 1. Baseline FeNO and FeNO dynamics were among the identified factor characteristics. The clinical observations of 302 patients who met the criteria for inclusion were assessed. The ultimate result was identified as the establishment of bronchial asthma control in school-age children with sensitization to cat allergens after a 12- month treatment period, with Y = 0 if bronchial asthma control was not established, and Y = 1 if bronchial asthma control was established. Among 302 patients, clinical asthma control status was improved in 185 (61.3%) children, while it was not better in 117 (38.7%) patients after a 12-month treatment period.

Increasing baseline FeNO levels reduced the probability of establishing bronchial asthma control in these children after a year of therapy (OR <1; $p <0.001$). The dynamics of FeNO reduction increased the probability of achieving bronchial asthma control after a three-month therapy (OR> 1; $p <0.001$).

In a prospective study with a 12-month dynamic follow-up, therapeutic parameters were evaluated in 128 patients who met the inclusion criteria. In general, the study revealed a statistically significant difference between baseline FeNO values and FeNO dynamics after a 12-month treatment period ($p <0.001$), with the dynamics

Table 1. One-factor logistic regression analysis for predicting bronchial asthma control status in school-age children with sensitization to cat allergens after a 12-month treatment period

Factor	The value of the model coefficient, b±mb	Significance level of the difference between the correlation coefficient and 0, p	Area under the ROC curve model, AUC (95% CI)	Odds ratio, OR (95% CI)	Significance level of the difference between OR and 0, p
Baseline FeNO, ppb	-0,12±0,03	<0,001	0,61 (0,54–0,67)	0,89 (0,84–0,94)	<0,001
FeNO dynamics after a three-month therapy, %	0,26±0,03	<0,001	0,90 (0,86–0,94)	1,30 (1,24–1,37)	<0,001

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Group	Before treatment	After a 12-month treatment period	p
No1, n=96	32,59 ± 4,95	26,59 ± 4,27	p < 0,001
No2, n=32	30,50 ± 2,92	22,97 ± 1,56	p < 0,001
No3, n=40	31,18 ± 4,36 p = 0,703 *	24,80 ± 3,72 p = 0,012 *	p < 0,001

** p between groups No2 and No3*

Table 2. FeNO value dynamics in school-age children with bronchial asthma and sensitization to cat allergens after treatment

of FeNO reduction. However, after a year of therapy, FeNO values of > 20 ppb were observed in 127 children (99.22%), while in one patient, the FeNO level was 20 ppb.

Group No2, which received AIT in combination with controller therapy, and the comparison Group No3, which received only controller therapy without AIT, had no statistically significant difference (p = 0.703) in baseline FeNO values, with 30.50 (95 % CI 29.45 - 31.55) ppb and 31.18 (95% CI 29.78 - 32.57) ppb, respectively. A 12-month dynamic observation showed a decrease in FeNO values to 22.97 (95% CI 22.41 - 23.53) ppb and 24.80 (95% CI 23.61 - 25.99) ppb, respectively (p <0.001 for both groups compared to the baseline FeNO measurement). After a 12-month treatment period, mean FeNO values in Group No1 were 26.59 (95% CI 25.73 - 27.46)% compared to 32.59 (95% CI 31.59 - 33.60)% p <0.001) at baseline. At the 12-month visit, the difference between mean FeNO values in groups No2 and No3 was statistically significant (p = 0.012) (Table 2).

Discussion

Increased baseline FeNO values are a marker of eosinophilic airway inflammation in children and are consistent with data from other studies (Loewenthal L and Menzies-Gow A., 2022). The dynamics of FeNO values, not just baseline FeNO values, have been demonstrated to be crucial for improving asthma control after a 12-month treatment period. FeNO should not be considered a diagnostic criterion for asthma, but it is useful for monitoring and tracking the progression of atopic diseases, particularly the response to therapy in asthma patients.

Using the method of construction and analysis of one-factor logistic regression models, we found a correlation (p <0.05) between the probability of establishing bronchial asthma control in school-age children with sensitization to cat allergens after a year of therapy and the values of both baseline FeNO and FeNO dynamics after a three-month therapy. This is important for predicting the clinical course of asthma in children and improving asthma control. FeNO dynamics should be continuously monitored because they indicate a decrease in the severity of eosinophilic airway inflammation, which is associated with the therapeutic response. Anti-inflammatory therapy is primarily prescribed.

However, a personalized approach to the treatment of children with asthma should evaluate the potential impact on causative allergens as well as elimination methods. Allergen-specific immunotherapy provides beneficial effects because it influences the course of allergic disease by inducing immune tolerance (Lee S, et al., 2022). The effect of AIT on FeNO values is demonstrated by a statistically significant difference in mean FeNO values after a 12-month treatment period in the group of patients receiving AIT in combination with controller therapy versus the group of patients receiving only controller therapy (p = 0.012). This effect of allergen-specific immunotherapy on fractional exhaled nitric oxide values in asthmatic children is consistent with the results of other studies (Ai T, et al., 2020), but they specify them for the age group of 6-17 years and existing sensitization to cat allergens.

Conclusions

1. In school-age children with asthma and sensitization to cat allergens, fractional exhaled nitric oxide levels are elevated, particularly in severe asthma, as a reflection of existing eosinophilic airway inflammation.
2. Increasing baseline FeNO values reduce the probability of establishing bronchial asthma control in these children after a 12-month treatment period.

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3. Following a three-month therapy, a more significant decrease in FeNO values increases the probability of achieving bronchial asthma control in these patients.
4. The inclusion of allergen-specific immunotherapy in the complex treatment of asthma in school-age children with sensitization to cat allergens has been shown to have a favourable therapeutic effect on the fractional exhaled nitric oxide levels.

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Conflicts of interest

The author declares no conflicts of interest.

Consent to publication

The author approved the final version of the manuscript and agreed to have it published.

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A – Research concept and design,
B – Collection and/or assembly of data,
C – Data analysis and interpretation,
D – Writing the article,
E – Critical revision of the article,
F – Final approval of article.

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Дослідження фракційного оксиду азоту в повітрі, що видихається у дітей шкільного віку з бронхіальною астмою та сенсибілізацією до алергенів котів

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Анотація: бронхіальна астма є одним із найпоширеніших хронічних захворювань в дитячому віці. Доведено, що алергени, котрі продукуються котами, є тригерами астми у дітей. Для дітей більш притаманна атопічна бронхіальна астма з еозинофільним запаленням, при цьому вивчаються біомаркери зазначеного запалення. Фракційний оксид азоту в повітрі, що видихається відомий як показник еозинофільного запалення дихальних шляхів. Мета дослідження – вивчення значення фракційного оксиду азоту в повітрі, що видихається у дітей шкільного віку з бронхіальною астмою та сенсибілізацією до алергенів котів для прогнозування досягнення контролю астми та оцінки терапії, що проводиться. До дослідження було включено 430 дітей віком 6-17 років з бронхіальною астмою та сенсибілізацією до алергенів котів. Вивчався профіль сенсибілізації за допомогою багатокомпонентної молекулярної алергодіагностики (ALEX², Австрія). Аналізували рівень фракційного оксиду азоту в повітрі, що видихається (NIOX VERO, Швеція). Для аналізу ймовірності досягнення контролю астми було ретроспективно проаналізовано 302 пацієнта та використано метод побудови та аналізу однофакторних логістичних моделей регресії. До проспективного дослідження тривалістю 12 місяців було включено 128 дітей. Спостерігалося підвищення фракційного оксиду азоту в повітрі, що видихається > 20 ppb у всіх пацієнтів, причому діти з важкою астмою мали рівень 35 ppb та вище. Показаний кореляційний зв'язок між досягненням контролю астми через 12 місяців лікування та динамікою через 3 місяця рівня фракційного оксиду азоту в повітрі, що видихається ($r = 0,619$; $p < 0,001$). Спостерігається зниження ймовірності досягнення контролю астми у дітей шкільного віку з сенсибілізацією до алергенів кота через 12 місяців при зростанні початкового рівня фракційного оксиду азоту в повітрі, що видихається (ВШ < 1; $p < 0,001$). Також має місце збільшення ймовірності досягнення цього контролю при зростанні показника динаміки через 3 місяця фракційного оксиду азоту в повітрі, що видихається у бік зменшення його рівня (ВШ > 1; $p < 0,001$). Статистично значуща різниця між середнім значенням показнику фракційного оксиду азоту в повітрі, що видихається через 12 місяців в групі пацієнтів, котрі отримували алерген-специфічну імунотерапію на тлі базисної терапії та в групі дітей, котрі отримували

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лише базисну терапію (p = 0,012) демонструє вплив алерген-специфічної імунотерапії на зазначений показник еозинофільного запалення. Таким чином, рівень фракційного оксиду азоту в повітрі, що видихається у дітей шкільного віку з бронхіальною астмою та сенсибілізацією до алергенів котів підвищений, особливо при важкій астмі. Для прогнозування ймовірності досягнення контролю астми у цих дітей слід враховувати не лише початковий рівень фракційного оксиду азоту в повітрі, що видихається, але й його динаміку через 3 місяця лікування. Доведений позитивний терапевтичний вплив включення алерген-специфічної імунотерапії до комплексного лікування астми у дітей шкільного віку з сенсибілізацією до алергенів котів на рівень фракційного оксиду азоту в повітрі, що видихається.

Ключові слова: алергени, астма, діти, оксид азоту, терапія.