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The association between fractional exhaled nitric oxide (FeNO) and cat dander in asthmatic children

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ABSTRACT

Background: The aim of our study was to assess risk factors of increased FeNO in asthmatic children with no cat at home.
Methods: It was a retrospective, cross-sectional study. We evaluated data from medical documentation of children with asthma: FeNO results, allergen sensitization, seasonal allergen exposure, FEV_1, allergic rhinitis (AR) diagnosis and cat presence at home. We assessed asthma severity using mean doses of inhaled glucocorticosteroids and a management approach based on control according to the newest guidelines of Global Initiative for Asthma (GINA) throughout the last three months before the measurement of FeNO and spirometry.
Results: 316 patients (age 6–18) completed the study. Sensitization to cat dander was associated with the highest median value of FeNO concentration compared to other allergens in our patients (28,4 ppb) and co-existing sensitization did not affect FeNO level. Median levels of FeNO increased linearly with patient's age. In asthmatics with AR, the levels of FeNO were increased significantly compared to asthmatics without AR (20.8 vs. 16.3, respectively). We showed that in patients without AR, sensitization to cat allergen was associated with more severe asthma in comparison to other perennial allergy (step 4 vs. other steps according to GINA treatment steps). The above relation was not observed in patients with AR. We did not observe correlation between allergy profile and FEV_1 among patients in neither subgroup nor in general population.
Conclusions: We revealed that sensitization to cat dander was associated with the highest increase of FeNO concentration compared to other allergens in patients not having any cat at home ever. We also observed that in patients without allergic rhinitis, sensitization to cat allergen, compared to other perennial allergy, was associated with more severe asthma.

Introduction

The current concept of asthma involves a chronic inflammatory process which causes the development of airflow limitation and increased responsiveness to allergens [1]. Fractional exhaled nitric oxide (FeNO) has proven to be a reliable noninvasive measure for airway inflammation. The synthesis of NO is mediated by NO synthases (NOS) and only the expression of inducible isoform (iNOS) correlates with the levels of exhaled NO [2–5]. FeNO also correlates with bronchial reactivity and decreases with anti-inflammatory asthma therapy, such as inhaled corticosteroids and antileukotrienes, in children [6,7]. However, it needs to be noted there are some studies indicating that FeNO does not correlate with the measures of airway hyperresponsiveness or pulmonary function values in children [8,9]. When assessing the relationship between NO and asthma, the role of atopy must be considered. Several studies have shown that children with atopic asthma demonstrate higher levels of FeNO than other patients with asthma [10–12]. Moreover, the pattern of allergen sensitization is likely to play an important role. Sensitization to certain groups of

Abbreviations: AR, allergic rhinitis; ERS/ATS, European Respiratory Society/American Thoracic Society; GINA, Global Initiative for Asthma; *Fel d* 1 protein, *Felis domesticus* protein 1; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; IFN-gamma, interferon-gamma; IL-5, interleukin 5; iNOS, inducible nitric oxide synthase; NOS, nitric oxide synthases; SPT, skin prick tests.

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indoor allergens, namely pet dander and house dust mites, has recently been shown to possess a much greater ability to increase FeNO levels in asthmatic children than other groups of allergens [13]. However, it is worth noting that the same may be true for other allergic diseases in children [14], probably due to specific features of the main proteins in both allergen groups [14,15].

The aim of our study was to assess risk factors of increased FeNO in asthmatic children with no animal at home. Therefore, we evaluated the relationship between FeNO, allergy profile, seasonal allergen exposure, forced expiratory volume in one second (FEV_1) and asthma severity in a sample of school children with allergist-diagnosed asthma.

Material and methods

Study design

It was a retrospective, cross-sectional study with a primary goal to evaluate the environmental predictors of exhaled nitric oxide in children with allergic and nonallergic asthma, with or without AR. We evaluated data from medical documentation of 316 children (age 6–18) who attended our Allergic Outpatient Clinic from January 2008 to March 2009. Three physicians (allergists) assessed the participants. The diagnosis of asthma and allergic rhinitis were universally established by the doctors according to standard definitions of both diseases in the latest guidelines [1,16,17]. Medical documentation of the patients was analyzed with special attention to an allergic rhinitis diagnosis, the results of FeNO, allergen sensitization, and animal presence at home. Asthma control was established according to the newest guidelines of Global Initiative for Asthma (GINA) [1]. We analyzed the mean doses of inhaled glucocorticosteroids and the management approach based on control [1], which were assessed throughout the period of three months preceding the measurements of FeNO and spirometry. GINA report underlines that the patient's current level of asthma control and current treatment determine the selection of pharmacologic treatment [1]. For instance, if asthma is not controlled on the current treatment regimen, the treatment should be stepped up until control is achieved [1]. Pharmacological treatment steps, according to GINA for children older than 5, adolescents and adults are as follows [1]:

Step 1: As-needed reliever medication.
Step 2: Reliever medication plus a single controller.
Step 3: Reliever medication plus one or two controllers.
Step 4: Reliever medication plus two or more controllers.
Step 5: Reliever medication plus additional controller options.

In our Allergic Outpatient Clinic, FeNO was measured prior to a forced flow-volume curve measurement on the same day (in the morning, between 9 a.m. and 11 a.m.) in all patients. The study was approved by the Medical Ethical Committee of the Medical University of Lodz. All parents or guardians of the patients gave their oral consent for the evaluation of data from medical documentation of their children.

Inclusion criteria

School children with allergic and nonallergic asthma, with or without allergic rhinitis, reporting not having kept a cat at home ever.

Exclusion criteria

Exclusion criteria included a diagnosis of a specific respiratory disease, such as cystic fibrosis, primary ciliary dyskinesia, interstitial lung disease, pneumonia; tuberculosis and/or current upper airway infection; other clinically significant pulmonary, hematological, hepatic, gastrointestinal, renal, endocrine, neurological, cardiovascular, and/or psychiatric diseases or malignancies that could influence the results of the study; obesity; inability to obtain an appropriate FeNO and spirometry measurement.

Allergen sensitization

In our outpatient clinic, using skin prick tests (SPT), we tested the subjects' reaction to the following most common inhalant and food allergens: *Dermatophagoides farinae, Dermatophagoides pteronyssinus*, *Alternaria*, *Cladosporium*, cat dander, dog dander, mixed grass pollen (Yorkshire fog, Cocksfoot, Rye-grass, Timothy, Blue grass (Kentucky), Meadow fescue), rye, birch, hazel, ribwort, alder, motherwort, feather. Positive (histamine chloride, 10 mg/mL) and negative (glycerol) controls (extracts from Nexter-Allergopharma, Reinbeg, Germany) were also used. A positive SPT reaction was defined as a mean wheal diameter of 3 mm in excess of the negative control. Atopy was defined as a positive skin test response to any of the 18 allergens tested.

Allergen exposure during the time of FeNO measurement

Seasonal allergen exposure from January 2008 to March 2009 during the time of FeNO measurement was assessed using pollen calendars from the internet service of Polish Bibliography of Clinical Palynology [18], valid for the period from January 2007 till July 2009 in Lodz region. Seasonal allergen exposure was defined as allergen exposure causing rapid and reproducible onset and offset of symptoms of allergic disease that appear only during certain times of the year. The exposure was based on the individual patients' allergy profiles and referred to as being "positive" when a patient had FeNO measured during the seasonal exposure to the allergens he/she was sensitized to, and described as being "negative" when a patient was out of the seasonal exposure time during FeNO measurement.

Nitric oxide measurement

The NO measurements were performed according to the European Respiratory Society/American Thoracic Society (ERS/ATS) recommendations [19] with a chemiluminescence analyzer (model 280i nitric oxide analyzer; Sievers, Boulder, CO, USA) and defined in parts per billion. The analyzer provides an on-line continuous measurement of NO in a single exhalation with a detection range of 0.1–500 ppb. Environmental NO was measured before and after each test and never exceeded 5 ppb. All subjects were studied in the sitting position, without wearing a nose clip. The subjects exhaled at a constant flow rate (50 mL/s) from total lung capacity to residual volume without breath holding. They maintained a constant mouth pressure (17 cm H_2O) by monitoring a visual display in order to eliminate contamination from nasal NO. Dead space and nasal NO (which are reflected by the NO concentration peak during exhalation) and NO from the lower respiratory tract (determined by the plateau value after the peak) were recorded automatically by using the manufacturer's software. Three FeNO measurements of the plateau phase were obtained, with less than 10% variation. The mean value of three successive, reproducible recordings was retained for statistical analysis.

Fev_1

Pulmonary function testing was performed with a Master Screen unit (Erich Jaeger Gmbh-Hochberg, Germany). Predicted values for all lung function variables were based on a previous