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Predictive value of fractional nitric oxide in asthma diagnosis-subgroup analyses

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ABSTRACT

Background: There are no studies investigating the benefit of using FeNO measurements in correlation with sensitization to perennial and seasonal allergens in children with asthma.
Objective: To define the group of children with respiratory symptoms in whose FeNO measurement has predictive value for asthma. We assessed the effect of age, allergy profile, atopy, lung function and the presence of allergic rhinitis on interpretation of FeNO levels for clinical applications.
Methods: It was a retrospective, cross-sectional study. We evaluated data from medical documentation of 1767 children with symptoms of allergic diseases such as asthma and/or allergic rhinitis. We included in the analyses subjects who had the following tests done during diagnostic procedures (single measurement): FeNO, spirometry, specific IgE results. All subjects had undergone a minimum 3-years prospective clinical observation after the first FeNO measurement until the later assignment (or not) of an asthma/allergic rhinitis diagnosis.
Results: We included 1767 children into the analysis; asthma diagnosis was confirm in 1054 (59.6%) children. We showed that only atopy (OR: 1.9; 95%CI: 1.5–2.4) and presence of allergic rhinitis (OR: 1.6; 95%CI: 1.4–1.9) were independently associated with increased FeNO level. Only among patients with atopy and allergic rhinitis FeNO level (above 23 ppb) was associated with asthma diagnosis. Sensitivity, specificity, positive predictive value and negative predictive value of FeNO >23 ppb for asthma diagnosis were as follows: 0.9(95%CI: 0.68–0.98), 0.52(95%CI: 0.42–0.61), 0.25(95%CI: 0.16–0.37), 0.97(95%CI: 0.88–0.99).
Conclusion: We showed that in children with atopy and with allergic rhinitis a negative predictive value for asthma diagnosis was very high with the optimal cut-off point of FeNO 23 ppb. Therefore we showed the utility of FeNO measurements to exclude asthma in the subgroup of patients with atopy and allergic rhinitis.

1. Introduction

The measure of the fractional concentration of exhaled nitric oxide (FeNO) may be considered a surrogate marker for airway inflammation. FeNO levels correlate with serum eosinophil cationic protein (ECP), eosinophilic counts in sputum, peripheral eosinophilia, total IgE and the number of positive skin prick tests [1–3]. FeNO is elevated in patients with untreated asthma, atopic dermatitis and allergic rhinitis while it is decreased as a consequence of corticosteroid therapy [4,5]. High FeNO levels can suggest a subclinical inflammation of the airways, even in the absence of symptoms and impairment of lung function [5]. In

Abbreviations: ATS/ERS, American Thoracic Society/European Respiratory Society; BHR, bronchial hyperresponsiveness; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; FEV1%VC, forced expiratory volume in one second expressed as a percentage of the vital capacity; ECP, eosinophil cationic protein; ICS, inhaled corticosteroids; IgE, immunoglobuline E; KU/L, kilo unit per liter; NO, nitric oxide; OR, odds ratio; CI, confidence interval; NPV, negative predictive value; AR, allergic rhinitis; ROC curve, Receiver Operating Characteristic curve; SRtot, total standardised residuals.

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earlier study in our clinic, we found that among all studied lung function parameters only higher FeNO and Rint (airway resistance by interrupter technique), and FEV1/FVC <80% were significantly associated with asthma [6]; we observed a significant association between FeNO and Rint in the prediction of asthma diagnosis. Allergic rhinitis and asthma are closely associated and inflammation is a common pathological characteristic shared by both disorders. There are no studies investigating the benefit of using FeNO measurements in correlation with sensitization to perennial and seasonal allergens in children with asthma with or without allergic rhinitis, thus no clear conclusion can be given. The aim of our study was to define the group of children with respiratory symptoms in whose FeNO measurement has predictive value for asthma. Specifically, we assessed the effect of allergic sensitization and the presence of allergic rhinitis on interpretation of FeNO levels for clinical applications.

2. Materials and methods

2.1. Study design

This is a cross-sectional, retrospective, study of prospectively collected data. We evaluated data from medical documentation of 1767 children (aged 6–18) with symptoms of allergic diseases such as asthma and/or allergic rhinitis who had attended our Allergic Outpatient Clinic from January 2005 to December 2012. In the analyses we included those subjects who had the following tests done during diagnostic procedures (single measurement routinely taken at our clinic at the beginning of diagnostic procedures): FeNO, spirometry (to exclude bronchoconstriction), specific IgE results. Medical documentation of the patients who were completely naïve to therapy at that time, was analyzed by allergist doctors who paid special attention to the initial obtained results of: FeNO, spirometry, an asthma diagnosis, an allergic rhinitis diagnosis as well as allergen sensitization (specific IgE results).

All subjects had undergone a minimum 3-years prospective clinical observation after the first FeNO measurement until the later assignment (or not) of an asthma/allergic rhinitis diagnosis (confirmation of asthma diagnosis, made in the retrospective analysis, refers to the chart in real time). The diagnosis of asthma, allergic rhinitis in real time were universally established by the allergist doctors (different allergist than in retrospective time was seeing the patients in real time and was assessing the asthma diagnoses in the charts) according to standard definitions of diseases in the latest guidelines [7,8] or their respective previous versions (due to the fact that patients had been admitted since January 2005). Diagnosis of asthma was universally established by symptoms of asthma, the findings on physical examination of the respiratory system, and improvement in the pre-bronchodilator $FEV_1 \geqslant 12\%$ after administration of salbutamol (200 μg) in all the patients [7]. All lung function testing was done only on clinically stable outpatients, who were able to perform reproducible measurements of FeNO and spirometry. None of the patient was chronically treated with inhaled corticosteroids and/or leukotriene inhibitors, which could "mask asthma"; only short time treatment was applied. The same data extractors assess both chart diagnosis of asthma and the related test data.

The study was approved by the Medical Ethics Committee of the Medical University of Lodz. All parents or guardians of the patients gave their oral and written consent for the evaluation of data from medical documentation of their children. The study was registered on: www.ClinicalTrials.gov, with ClinicalTrials.gov ID: NCT01805635.

2.2. Allergen sensitization

Allergen sensitization was defined as specific IgE of $\geqslant 0.35$ KU/L for at least one of tested allergens (chemiluminescence method (CLIA), Immulite 2000, XPI, Siemens, Germany). For purpose of the study we defined perennial allergy as presence of serum IgE of $\geqslant 0.35$ KU/L specific for perennial allergens: i.e. dust mites, molds, cat and dog dander; seasonal allergy as presence of serum IgE of $\geqslant 0.35$ KU/L specific for seasonal allergens: i.e. grasses, wild grasses, and trees pollens.

2.3. Nitric oxide measurement

The NO measurements were performed according to the European Respiratory Society/American Thoracic Society (ERS/ATS) recommendations [9,10], 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 it never exceeded 5 ppb. All subjects were tested in a 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 3 successive, reproducible recordings was retained for statistical analysis.

2.4. Pulmonary function tests

Pulmonary function testing was done with a Master Screen unit (Erich Jaeger Gmbh-Hochberg, Germany). Flow and volume were measured with a pressure-screen-type pneumotachograph, calibrated daily. All measurements were performed by trained investigator. Measurements were carried out in a familiar and quiet room. Standing height and weight were assessed: subjects were measured without shoes, wearing light summer clothing. During measurements, children were instructed to sit upright, and a nose clip and a non-compressible mouthpiece were used. When needed, an adult accompanied the subject during testing. Predicted values for all lung function variables were based on a previous study of healthy controls, provided by the lung function test equipment manufacturer. All pulmonary function tests were performed according to the American Thoracic Society/European Respiratory Society standards [11–14]. The highest of 3 successful measurements was taken and analyzed. The results were expressed as the percentage of a predicted value.

2.5. Statistical methods

Associations between asthma diagnosis, defined as a dependent variable, and all studied parameters as independent variables were assessed by logistic regression analysis in a univariate and multivariate model, which allows to point out the best predictor of a dependent variable. To estimate the cut-off level of FeNO for prediction of asthma diagnosis ROC curve analysis was implemented. For all significant predictors of asthma sensitivity, specificity, positive and negative predictive values were estimated. All statistical analyzes were performed using STATISTICA ver8.0. $P < 0.05$ was used as a definition of statistical significance.