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FeNO levels in children with asthma and other diseases of the lung

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Abstract. – BACKGROUND: Prolonged cough in children is one of the major complaints seen in hospitals. It is difficult to make a proper diagnosis and start the appropriate treatment. Fraction of exhaled nitric oxide (FeNO) measurement is a valuable non-invasive diagnostic tool in determining the cause of prolonged cough in children. Although there are several studies on asthma and COPD, there is a lack of them on other lung diseases such as tuberculosis, bronchiectasia, bronchiolitis obliterans (BO), and pneumonia.

PATIENTS AND METHODS: In this study, pre-treatment FeNO levels of patients with various lung diseases were measured and results from the sick patient groups were compared with the results from the control group.

RESULTS: Pre-treatment FeNO levels in BO, asthma, and tuberculosis patient groups were higher than in the control group ($p < 0.001$). There was no significant difference between the acute bacterial pneumonia and bronchiectasia groups, and the control group ($p > 0.05$).

CONCLUSIONS: FeNO measurement is a highly important guiding tool in diagnosis and treatment of various lung diseases.

Key Words:
Childhood, Asthma, Pulmonary disease, Exhaled nitric oxide.

Introduction

Pediatric clinics often admit patients complaining from prolonged cough and it is usually difficult to make an accurate diagnosis[1]. It can be quite difficult to determine the inflammation in the airway and then identify its type. The facilitation of differential diagnosis, determination of severity, and reaction to suitable treatment of various lung diseases is possible through constant observation of the inflammation. FeNO (Fraction of Exhaled Nitric Oxide) is a simple and effective, non-invasive tool for assessing the inflammation of airways[2]. This non-invasive way of determining biomarker levels in exhalation also enables re-sampling[3,4].

More studies now emphasize the potential of exhalation tests in clinically identifying and controlling lung diseases such as asthma, COPD (chronic obstructive pulmonary disease), and PCD (primary ciliary dyskinesia)[5]. The correlation between these biomarkers and diseases such as tuberculosis, BO (bronchiolitis obliterans), and acute bacterial pneumonia remains unclear.

The purpose of this article is to investigate the efficacy and potential use of FeNO on the assessment of pulmonary diseases with differential diagnosis in patients with prolonged cough.

Patients and Methods

Study Group

A total of 214 consecutive patients who consulted the Department of Pediatric Pulmonology at Dicle University Medical Faculty Hospital with prolonged cough or wheezing complaints for over four weeks were recruited to the study with an informed consent between September 2009 and October 2011. Children between the ages of 4 and 17 who were recently diagnosed with bronchial asthma, bronchiolitis obliterans, non-primary ciliary dyskinesia (Non-PCD) bronchiectasia, acute bacterial pneumonia, and active pulmonary tuberculosis were included in the study along with a healthy control group. Criteria for exclusion from study were: no underlying chronic diseases, no prior treatment with corticosteroids or bronchodilators, and being a current smoker.

19 consecutive patients with non-PCD bronchiectasia, who were going through a series of exams for diagnosing the level of their disease, were recruited to the study. Patients who were recently diagnosed, had no acute or subacute infections, and were not using any kind of inhalers or systemic steroids were also included in the study. An HRCT (High Resolution Computed Tomography) scan was performed in bronchiectasia patients to confirm the disease[6].

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BO diagnosis in patients with chronic cough complaints was made through detailed medical history, examination, and thorax HRCT findings. 18 BO patients who were enrolled in the study were recently diagnosed and not using inhalers, systemic steroids or bronchodilators, and were not treated with an antimicrobial agent within the last six weeks despite all the symptoms.

35 active pulmonary tuberculosis cases included patients, over the age of four, who had no anti-tuberculosis or antimicrobial therapy and no active non-pulmonary tuberculosis retention within the last six weeks. All patients were diagnosed through contact history, physical examination and radiological findings, history of BCG vaccination, and sputum culture for presence of acido-resistant bacilli.

The diagnosis of asthma was made by detailed medical history, physical examination, pulmonary function test, and when necessary, by a reversibility test. Bronchial asthma patients with atopic dermatitis, allergic rhinitis, and eczema were excluded. Skin prick and other allergy tests were unable to be performed on all of the patients due to lack of laboratory resources. A total of 42 asthma patients were enrolled.

50 patients with acute bacterial pneumonia who were recruited to the study were diagnosed by physical examination, acute phase reactants, peripheral blood smear findings, and positive blood culture results. Patients in the acute bacterial pulmonary exacerbation phase of chronic bronchitis or chronic pulmonary disease were excluded.

The healthy control group consisted of 50 subjects. All the subjects included in this group were children of the hospital employees and have never had any major pulmonary symptoms or chronic diseases.

This study was approved by the Ethics Committee of Dicle University.

FeNO Measurements

Test hours were between 08:00 and 17:00. Any information regarding ingested food or physical activity 60 minutes prior to the test was recorded. Subjects were asked to take a seat and relax for 5 minutes prior to the test. A single-breath online technique with NIOX (Monitoring System; Aerocrine, Sweden) was used, in accordance with the ATS (American Thoracic Society) guidelines, to measure FeNO levels[7]. Comfortably seated subjects, with no nose clips, inhaled the NO-free air completely filling their lungs over 2-3 seconds using the mouthpiece and then exhaled with a flow rate of 50 mL/s through a positive mouthpiece with a counter pressure of 10-20 cm H_2O forcing the soft palate to be closed in order to prevent any contamination from the nasal cavity. The duration of exhalation for children under the age of ten was 6 seconds and the FeNO measurement was made in the last 2 seconds. This duration was 10 seconds for children over 10 years old and FeNO measurement was made in the last 3 seconds. In order for the measurement to be valid, the mean flow had to be between 0.045-0.055 L/s, the instant flow had to be between 0.0375-0.0625 L/s, and the instantaneous mouth pressure had to be between 5-20 cm H_2O. There was also a maximum deviation limit of 2.5 ppb or 10% and test duration of 15 minutes for the test to be valid. There was at least a 30-second interval between each exhalation, and while the maximum number of exhalations was 6, the total number of exhalations to achieve three valid FeNO measurements was recorded. The average of three valid exhalations was taken to find the final FeNO value.

Statistical Analysis

SPSS (Statistical Package for Social Sciences Inc., Chicago, IL, USA) 16.0 was used to compare the FeNO levels of all groups. Descriptive statistics are expressed as mean (SD). Because the numerical values did not match normal distribution, Kruskal Wallis and Mann Whitney U tests were used to compare the groups. Statistical significance was determined as $p < 0.05$.

Table I. Comparison of BO, Asthma, Pulmonary Tuberculosis, Pneumonia, Bronchiectasia and control groups demographic parameters.

	Asthma (n = 42)	BO (n = 18)	Tuberculosis (n = 35)	Pneumonia (n = 50)	Bronchiectasia (n = 19)	Control (n = 50)
Age (Yrs.)	9.5 (6-14)	11.3 (6-16)	11.2 (6-15)	9.6 (4-14)	9.7 (5-13)	9.3 (5-16)
Gender (/F)	27 / 15	13 / 5	14 / 21	22 / 28	10 / 9	29 / 21

Data are expresses as geometric means and 95% CIs.
95% CIs: 95% confidence intervals; M: Male; F: Female; Yrs: Years; BO: Bronchiolitis Obliterans.

Table II. Comparison of FeNO levels between groups.

	N	Mean SD (ppb)	Median	Min	Max
Asthma	42	19.50 ± 15.8	16	3	91
Tuberculosis	35	12.06 ± 4.3	12	5	23
Pneumonia	50	10.22 ± 3.7	10	4	22
Bronchiectasia	19	8.00 ± 2.7	7	4	14
BO	18	35.83 ± 17.2	36	6	67
Control	50	7.74 ± 3.3	7	1	20

BO: Bronchiolitis Obliterans; Min: Minimum; Max: Maximum; ppb: Parts per billion

Results

The distributions of number, gender and age of patients in the asthma, BO, tuberculosis, bronchiectasia, pneumonia, and control groups are shown in Table I.

FeNO levels of patients in BO and asthma groups are significantly higher when compared with the rest of the groups ($p < 0.05$). The minimum, maximum, and average FeNO levels in all six groups are shown in Table II.

As expected, FeNO levels of patients in the asthma group are significantly higher when compared with all the others, except the BO group ($p < 0.05$). There also is a significant difference in FeNO levels of the BO group when compared with all the other groups, including the asthma group ($p < 0.001$). Diagram comparing the FeNO levels between the groups is shown in Figure 1.

Discussion

The measurement of NO levels in exhalation air has recently attracted more attention due to high demand for a simpler way to determine the etiology of patients with chronic cough and to use a reliable, non-invasive monitoring technique throughout the treatment. Even though FeNO measurement has recently been dubbed as an "allergic inflammometer", it also displays the tone of the smooth muscles in the airway[8].

Although the increase in FeNO levels mostly shows eosinophilic inflammation in the airway and is not a unique indicator of asthma, this increase can potentially be interpreted as a differential diagnosis of asthma for both children[9] and adults[10] with 90% certainty and 95% positive predictive value when a cut-off point of over 15 ppb NO is used[11,12]. In this study, the pre-treatment average FeNO levels of infants in the asthma group (19.50 ± 15.8 ppb) were significantly higher ($p < 0.05$) than those in the tuberculosis (12.06 ± 4.3 ppb), bronchiectasia (8.00 ± 2.7 ppb), acute bacterial pneumonia (10.22 ± 3.7 ppb), and control (7.74 ± 3.3 ppb) groups, but not the BO group (35.83 ± 17.2 ppb). Considering information on FeNO levels in children not being affected by asthma phenotyping but only being effective in adult patients, no phenotyping was

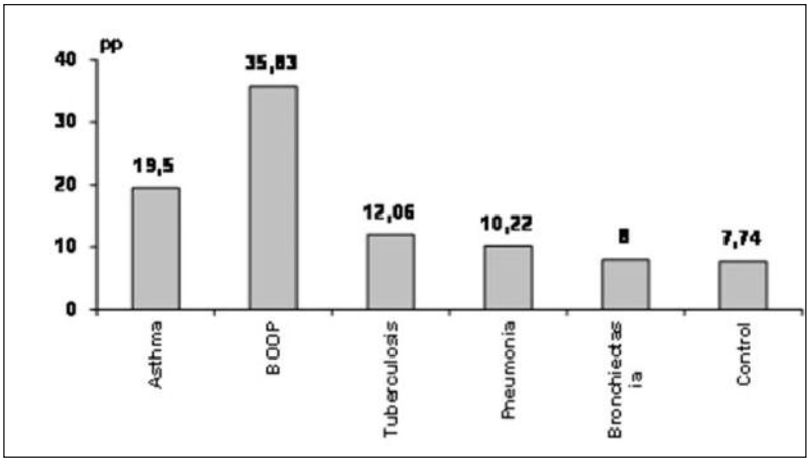

Figure 1. Comparison of FeNO levels between groups.

done for the asthma group[13,14]. Moreover, FeNO levels of 32.2 ± 25.9 ppb for patients with asthma and 16.3 ± 8.4 ppb for healthy subjects presented in literature[15] were higher than the FeNO levels measured in this study. This may be due to nutritional habits, different measurement techniques or other factors that are undefined or undistinguished which may have affected FeNO levels. Age, gender, and atopic symptoms were not always considered or analyzed.

Another prominent result was that FeNO levels of BO patients (35.83 ± 17.2 ppb) were higher than of asthma and all the other patient groups ($p < 0.001$). In a study by Brugiere et al[16], the exhaled NO levels were found to be higher in lung transplant recipients with BO, or even in potential BO patients, suggesting that FeNO measurements prior to immunosuppressive therapy could be used as an effective guide. FeNO measurement results of patients with BO mostly reflect the adult patient group. We believe that a reliable and non-invasive inflammatory marker like the FeNO measurement is a must-have in monitoring and treatment of children with this type of chronic pulmonary disease who often need a long term, high-dose systemic steroid therapy. We intend to present how the FeNO levels affect the treatment process in BO patients, who are being monitored with a systemic steroid therapy, in our next study.

There was no significant difference in FeNO levels of bronchiectasia patients with no pneumonia (8.00 ± 2.7 ppb) when compared with the pneumonia (10.22 ± 3.7 ppb), pulmonary tuberculosis (12.06 ± 4.3 ppb), and healthy control (7.74 ± 3.3 ppb) group subjects ($p > 0.05$). There are only a few reports on the measurement of NO in exhalation air as a marker of airway inflammation in bronchiectasia in children. Patients with bronchiectasia are more prone to bacterial infection due to an abnormal bronchial wall causing delayed nasal mucociliary clearance and airway dilatation. The literature shows that the severity of bacterial bronchiectasia is partially related to the inflammation marker measurements[17], and that the levels of NO exhaled by patients with pneumonia are significantly higher than those without[18]. Moreover, prolonged infection and chronic inflammatory response are more common in cases of severe bronchiectasia. These may also advance into causing damage to neighboring healthy pulmonary tissue. It is critical to monitor the inflammation in cases of bronchiectasia in order to stop the disease from progressing any further and improve patients' quality of life. In addition to the FeNO measurements, nasal NO levels can be used in diagnosing PCD in potential adult[19,20] and infant[21] patients within various clinical fields.

FeNO levels of patients in active pulmonary tuberculosis group (12.06 ± 4.3 ppb) were similar to those in pneumonia (10.22 ± 3.7 ppb) and bronchiectasia (8.00 ± 2.7 ppb) groups, but were significantly higher than those in the healthy control group (7.74 ± 3.3 ppb; $p < 0.05$). There are several works showing elevated NO levels in bronchial asthma and bronchiectasia patients[22]; however, a study on murine infection of *M. tuberculosis* shows that NO plays a significant role against *M. tuberculosis* infections[23]. In this paper, the NO levels of patients with active pulmonary tuberculosis were measured. Considering the difficulty of diagnosing pulmonary tuberculosis in children and the fact that non-invasive methods are still not fully utilized, we believe that the measurement of FeNO levels can help differentiate children with active pulmonary tuberculosis from the healthy ones.

Diagnosis of acute bacterial pneumonia in both children and adults can be easily made. However, the NO levels are elevated within the initial stages of the common cold[24,25] mostly causing exacerbation in COPD. While considering the symptoms, parents can use portable analyzers for the measurement of NO for an earlier diagnosis and treatment options to help reduce exacerbation.

Conclusions

Evaluation of FeNO levels has an important role in the management of patients with chronic cough. Determining the cut-offs for FeNO levels in children with bronchial asthma or in healthy children, as well as in cases such as pulmonary tuberculosis, bronchiectasia (PCD or Non-PCD), BO and in the acute pulmonary exacerbation stages of chronic diseases will provide great convenience for pediatricians in determining the etiology of chronic cough.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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