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ORIGINAL ARTICLE

Asthma diagnosis and severity monitoring in primary school children: Essential role of sequential testing of exhaled nitric oxide

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Abstract
Background: Chronic eosinophilic airway inflammation, airflow limitation, and airway hyperresponsiveness are the mainstays of asthma diagnosis. The increased levels of exhaled nitric oxide (FeNO) in asthma are closely related to the extent of airway inflammation. Sequential measurement of FeNO concentrations may accurately predict asthma severity and guide therapeutic decisions.
Methods: A total of 22,083 grade 1 students in Taipei city primary schools were screened for wheezing episodes using the International Study of Asthma and Allergies in Childhood questionnaire (ISAAC) questionnaires while their sero-atopic conditions were confirmed by Fluorescent Enzyme Immune Assay (FEIA). All students with allergies were tested by FeNO electrochemical test. 100 age-matched healthy students were used as control group (FeNO levels < 25 ppb).
Results: From the 2650 students (12%) initially included via the wheezing criteria, 2065 (78.0%) were confirmed to have allergy by FEIA (sensitisation to at least two common aero-allergens in Taiwan) and diagnosed by a paediatric allergologist. Among them, 1852 (89.6%) had elevated FeNO values (>25 ppb) and 266 (10%) had FeNO values < 25 ppb. Using the GINA guidelines, 140 mild-to-moderate asthma students who had received inhaled corticosteroids (ICS) with or without Singulair treatment completed serial FeNO testing every three months for one year. The FeNO levels decreased in 121 students (86.4%) and increased in 19 students (13.6%), which was compatible to changing childhood asthma control score and response to step-down treatment, respectively.
Conclusion: FeNO is an easy, used non-invasive tool for the diagnosis of allergic asthma. Sequential FeNO testing can accurately reflect asthma severity and provide for successful stepwise therapy for asthmatic children.

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Introduction

Airway eosinophilia is considered a critical event in the pathogenesis of asthma. Eotaxin and RANTES have been implicated in the allergic inflammation associated with asthma by promoting the migration and activation of inflammatory cells, including eosinophils. Concentrations of these cytokines in exhaled breath condensates (EBC) have been significantly correlated with exhaled nitric oxide (FeNO) concentrations and serum eosinophil cationic protein (ECP) levels in asthmatics, particularly in unstable and steroid-naive stable asthmatics.[1,2]

Guidelines for asthma management suggest a stepwise approach to pharmacotherapy based on assessments of severity and control. However, the assessment of asthma control currently relies on surrogate measures like the frequency of symptoms or the frequency of use of short-acting β2-adrenergic agonists (SABA).[3,4] Increased expression of inducible nitric oxide synthase and elevated FeNO levels are seen in asthmatic patients and have become increasingly recognised for their use in evaluating bronchial inflammation when monitoring anti-inflammatory treatment.[5] Moreover, atopic individuals have increased FeNO levels, suggesting that atopy may be a co-determinant in FeNO production, although multivariate analysis has shown that atopy is not a significant predictor of FeNO levels in asthmatic patients.[6]

Exhaled nitric oxide has proven to be a marker of airway inflammation and has become a substantial part of clinical management of asthmatic in children due to its potential to predict possible exacerbation and for adjusting the dose of inhaled corticosteroids (ICS).[7] Measuring FeNO enables an easy and rapid assessment of airway inflammation such that there is now an international consensus on this testing methodology.[8]

The aim of this study was to evaluate whether sequential FeNO testing could accurately reflect asthma severity and provide for successful stepwise therapy for asthmatic children.

Materials and methods

A total of 22,083 first grade school children aged 6–7 years were included in this study. With the aid of their parents, current wheezing (within the last 12 months) was assessed using the ISAAC questionnaire. Sero-atopy was defined as a measurable specific IgE (≥0.35 IU/ml) to any two of the common allergens tested in Taiwan: dust mites (der p, der f), *blomia tropicalis*, cat dander, dog dander, *alternaria*, and ragweed (Phadia ImmunoCAP system, Phadia AB, Sweden). Specific IgE tests were used for the students who met ISAAC wheezing criteria. The childhood asthma score was used to evaluate the pre-and post-treatment clinical features of the asthmatic children (cut off points: ≥21 controlled, =20 partly controlled, ≤19 uncontrolled, ≤12 very poor controlled). The Institutional Review Board (IRB) of Taipei City Hospital approved the study and all of the participants, their parents or guardians provided written informed consent.

A sequence of FeNO measurements (MINO device) once every three months for one year was made for children who were diagnosed by a paediatric allergologist as seroatopy positive. All of the study participants received maintenance ICS (Flixotide 50 μg; 2 puffs) with or without Singulair (5 mg orally per day) depending on their asthmatic condition.

A control group of 100 healthy students who met the exclusion criteria of no personal or family history of atopy, no history or symptoms of asthma and allergic rhinitis, never been diagnosed as asthmatic by a physician, and no corticosteroid or Singulair use in the last month also underwent FeNO measurements.

The above procedures used on patients and controls have been done after informed consent had been obtained.

Table 1 Characteristics of the study participants ($n = 140$).

Age, years, mean ± SD	6.0 ± 0.35
Male, n (%)	82 (56.6%)
Female, n (%)	58 (41.4%)
Comorbidity, n (%)	
Allergic rhinitis	79 (56.4%)
Atopic dermatitis	15 (10.7%)
Gastro-oesophageal reflux	0 (0%)
ISAAC wheezing criteria met	Positive
Childhood asthma control test, mean ± SD	18.13 ± 2.10
Inhaled allergen-specific IgE	
Dermatophagoides pteronyssinus	127 (91%)
Dermatophagoides farinae	116 (82.8%)
German cockroach	21 (15%)
Initial FeNO level	32.31 ± 13
Prescribed anti-asthmatic medication	
Inhaled corticosteroids (ICS), *n* (%)	85 (60.7%)
ICS plus antileukotriene, *n* (%)	55 (39.3%)

Results

A total of 22,083 grade 1 students were screened using the standardised ISAAC questionnaires to identify those who fulfilled the criteria for wheezing. Among the 279 students who met this criterion, 269 (96.4%) were sensitised to at least two common allergens in Taiwan and were diagnosed as asthmatic by a paediatric allergologist.

Among the 269 allergic asthmatic children, 241 (89.6%) had elevated FeNO levels (>20 ppb) and 28 (10%) had decreased levels (<20 ppb). A total of 140 students who received ICS with or without Singulair treatment completed the series of FeNO testing (Table 1). The FeNO levels decreased in 121 students (86.4%) and increased in 19 students (13.6%), which were correlated with the changing of C-CAT (≥20 ppb, ≤19 ppb).

The 100 healthy students in the control group showed normal FeNO concentrations (<13 ppb) (Fig. 1).

Discussion

Exhaled nitric oxide has been used as a surrogate measurement to determine the extent of airway inflammation in mild to moderate asthma. However, whether FeNo levels reflect disease activity in symptomatic asthmatics receiving low dose ICS with or without Singulair is uncertain. In the present study, the ability of sequential FeNO