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ORIGINAL ARTICLE

Exhaled nitric oxide in school children: Searching for the lost variability

P.W. Garcia-Marcos[a,*], M.J. Soriano-Pérez[b], V. Perez-Fernández[a], J. Valverde-Molina[c]

[a] Department of General Pediatrics, Arrixaca University Children's Hospital, University of Murcia, Murcia, Spain
[b] Emergency Department, Los Arcos del Mar Menor University Hospital, San Javier, Murcia, Spain
[c] Department of Pediatric Respiratory Medicine, Los Arcos del Mar Menor University Hospital, San Javier, Murcia, Spain

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Abstract
Objective: The factors – including asthma and rhinoconjunctivitis – which influence FeNO values in a general population of school children have been studied in order to know to what extent the variability of those values can be explained.
Methods: FeNO was measured in a population of 240 school children aged 6–12 years by means of a Niox-Mino™ device in a standardised way. Parents filled in an ISAAC-validated questionnaire of symptoms and environmental factors. Diagnoses were checked against clinical records. Height and weight were measured. A multivariate regression analysis including all variables in the questionnaire was performed, which was followed by two Xi stepwise tests in order to build a predictive model which included the main variables influencing FeNO values.
Results: Among the 240 children, 10 suffered from asthma, 16 from rhinoconjunctivitis and 15 from both conditions. FeNO values (GM ± GSD) in children with rhinoconjunctivitis (19.61 ± 1.20 ppb), with asthma (18.62 ± 1.32 ppb), and with both conditions (17.62 ± 1.19 ppb) tended to be significantly higher than control children (11.42 ± 1.04 ppb), $p = 0.0016$, $p = 0.08$ and $p = 0.01$, respectively. The different predictive models were able to explain only 20–27% of FeNO variability.
Conclusions: The proportion of FeNO inter-individual variability which can be explained by individual (including suffering from asthma or rhinoconjunctivitis), family, and environmental factors is very low (20–27%). This could have implications on the usefulness of FeNO as a diagnostic tool in asthma.

Introduction

Asthma consists of chronic hyper-responsiveness and variable inflammatory obstruction, affecting the airways. This chronic condition leads to airway wall remodelling,

* Corresponding author.
E-mail address: pat.garcia.marcos@gmail.com (P.W. Garcia-Marcos).

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which appears to be associated with persistent airway inflammation, initially without clinical evidence of airway obstruction. Abnormally thickened airways may be the mechanism underlying both bronchial hyper-responsiveness and fixed loss of respiratory function.[1]

Fractional exhaled Nitric Oxide (FeNO) has been reported as a non-invasive airway inflammation marker in asthma. In fact, FeNO, measured in the general population, has shown higher levels in children with symptoms of asthma and atopy.[2] However, the interpretation of FeNO levels should be taken with caution as their predictive value is unknown. Although higher FeNO values are associated to asthma, the presence of other atopic conditions such as allergic rhinoconjunctivitis or atopic dermatitis may confound this association. Furthermore, FeNO was found to be increased in asthmatic children and in children with atopic disorders, regardless of the presence of respiratory symptoms.[2,3] However, not only asthma or atopy, but also other factors such as age, gender, height, body mass index, tobacco smoking, parental asthma/allergy, and allergen sensitisation have been shown to exert an influence on FeNO values.[4–7]

The aim of the present study is to determine whether other still non-studied environmental circumstances might influence FeNO values in school children; and to know to what extent individual (including atopy defined by positive prick-test, asthma and/or rhinoconjunctivitis), family, and environmental factors could explain FeNO inter-individual variability.

Methods

Study population

In order to avoid variability in the study due to non-Caucasian ethnicity, all children aged 6–12 in a public primary school with the lowest rate of immigrants in the area (2%) were invited to participate ($n = 466$). The ISAAC validated questionnaire was distributed in the school to the children's parents, with an explanatory letter attached, which included information on how to fill in the questionnaire and about the FeNO measurement method. The completed questionnaire was brought back and given to the teacher in each class.

Ethics

An informed consent form was included with each questionnaire. The Ethics Committee o the ''Los Arcos del Mar Menor'' University hospital approved the study.

Selection of children

In order to build the definite dataset, the following criteria were used:

- *Inclusion criteria*: Boys and girls, aged 6–12 (both inclusive) with a correctly completed questionnaire, and fewer than seven attempts for a correct FeNO measurement.
- *Exclusion criteria*: Discordant diagnoses between questionnaire and clinical record, being currently on inhaled corticosteroids, incorrect/incomplete questionnaire, more than seven attempts for FeNO measure performance, non-Caucasian ethnicity.

Questionnaires and variable definitions

Data were collected using the ISAAC phase III questionnaire (core and environmental questionnaires) (http://isaac.auckland.ac.nz). The environmental questions include a food frequency (per week) questionnaire (never or occasionally, 1–2 times, 3 or more); parental history of asthma, rhinitis or atopic dermatitis (Yes/No); smoking habits of father and/or mother (Yes/No); number of people living in the family house; months of exclusive breastfeeding; preterm birth (Yes/No); presence of mould stains on the household walls (Yes/No); truck traffic in the street where the family house is located (never/seldom/frequently during the day/almost the full day); pet removal from home (Yes/No); skin prick test performed (Yes/No; if Yes, Positive/Negative) in the children and parents (which was checked against the clinical record when performed); regular acetaminophen intake for fever during the first year of life (Yes/No); and oil used for cooking. Symptoms of asthma were defined as a positive answer to the question: ''Has your child had wheezing or chest whistling in the chest in the past 12 months?'' Similarly, symptoms of rhinoconjunctivitis were defined as a positive answer to both questions: ''Has your child had itchy nose or sneezing, not related to a cold in the previous 12 months?'' and ''Have these nose problems come together with itchy or red eyes?'' Atopy eczema was defined as a positive response to: ''Has your child had an itchy rash located in the folds of the elbows/behind the knees/in front of the ankles/under the buttocks/around the neck, ears or eyes in the last 12 months?'' The Mediterranean diet score was calculated according to the method previously used.[8] All factors included in the study are shown in Table 1.

Height and weight measurements

Height was measured without shoes using a Seca™ stadiometer (graduated scale with mobile head support) with an error range of ± 1 cm. At least two measures were taken, relocating the child between each measure. Subsequently, weight was measured without shoes and wearing light clothes, using a Seca™ scale, calibrated daily, with an error range of ± 1 kg.

FeNo test

FeNO tests were performed at the school setting, using the portable Niox-Mino™ device (Aerocrine, Solna, Sweden) as follows: the patients made an initial expiration and then they made a deep inspiration to inhale NO-free air through the disposable filter up to total lung capacity. Immediately afterwards, they breathed the air out through the filter into the device at an exhalation rate of 50 ml/s, which was controlled by a light and acoustic sensor. NO environment was considered to be <5 ppb and measurements were always performed in the same room and at the same time of the day. Children have a lower lung capacity than adults, which