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Association between allergic sensitization and exhaled nitric oxide in children in the School Inner-City Asthma Study

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Fractional exhaled nitric oxide (FeNO) is increased in children with asthma and is thought to reflect eosinophilic lung inflammation.^{1, 2} It is not known whether sensitization to one particular allergen is more strongly associated with worsened lung inflammation over any other particular allergen. Our aim was to determine whether children with asthma and allergic sensitization have higher levels of lung inflammation as measured by FeNO compared to children without allergic sensitization, and whether sensitization to one specific allergen was most predictive of elevated FeNO in a school-based setting.

We studied 128 children consecutively enrolled in the School Inner-City Asthma Study (SICAS) from 2008–2012 for whom we obtained skin prick testing for indoor allergens, outdoor allergens and FeNO (NIOX TM System, Aerocrine, Sweden). Further details regarding SICAS methods have been previously reported³. The FeNO was obtained at the same time as the skin prick testing utilizing standard methods³, and a wheal size of >3 mm compared with a saline control was used to define a positive sensitization test. FeNO was collected according to standard ATS procedures.⁴ The primary outcome was FeNO, and the logarithmic value of FeNO was used to obtain an approximately normal distribution. We performed an independent t-test of the mean FeNO (log transformed) between sensitized and unsensitized children, and the Mann-Whitney U test was used to compare untransformed FeNO levels in sensitized vs. unsensitized children. Univariate regression was utilized to determine the relationship between sensitization to allergens and FeNO (log transformed). In the multiple regression model, we adjusted for age, gender, inhaled corticosteroid use and multiple sensitizations, all variables that were significantly associated with model outcome. Analyses were conducted using SPSS version 19 (SPSS, Chicago, IL) and SAS v9.2 (Cary, NC: SAS Institute Inc, 2011).

The mean FeNO level was 24.75 ppb, and the median was 15 ppb (range, 5–143) for the 128 children studied (eTable 1). Only 6% of children were white, while 40.6% and 28.1% of children were black and Hispanic respectively. The mean age at the time of FeNO measurement was 8.8 years. Over 70% of SICAS children were sensitized to more than one allergen, and over 60% were sensitized to more than two allergens. The most common allergens to which children were sensitized were cat (40.6%), dust mite (35%), tree pollen (32%), mouse (37.5%), cockroach (24.2%), grass (25%), rat (25.8%) and ragweed (20.3%).

We found that log-transformed FeNO significantly increased as the number of positive skin prick tests per child increased. Mean FeNO levels (ppb) were significantly different between those children with no sensitization and those children with 1–3, 4–5 and 6 positive skin prick tests. In comparing FeNO levels between children with and without sensitization to specific indoor allergens, we found that for cat, mouse, dust mite, rat and cockroach, the FeNO levels were significantly higher in children who were sensitized to that specific allergen compared to those who were not.

Sensitization to cat, rat, mouse, tree pollen, dust mite, and cockroach were significant predictors of increased FeNO in the univariate model (Table 1). When adjusted for age, gender, inhaled corticosteroid use, asthma control and multiple sensitizations (more than one positive skin prick test), sensitization to cat and rat allergen were significant predictors of increased FeNO with p values of <0.01 and 0.016 respectively.

Our study focused on the relationship between allergic sensitization and FeNO levels, an objective measure of lung inflammation in children with asthma. The children enrolled in SICAS were highly allergic, with over 70% being sensitized to more than one allergen. This high degree of allergic sensitization translated to higher FeNO levels in comparison to unsensitized children. The mean FeNO for our cohort was above 20 ppb (24.75 ppb), indicating that significant eosinophilic airway inflammation is likely present.⁵ In attempting to identify which allergens contribute most to elevated FeNO levels, we found sensitization to cat and rat, and also multiple sensitizations to be significant independent predictors of increased FeNO after adjusting for age, gender and ICS use. To our knowledge, no other studies have shown sensitization to rat allergen to be a significant independent predictor of increased FeNO levels, adjusting for other factors. There may be unique characteristics of this allergen that correlate with allergic airway inflammation.

In our multiple regression model, sensitization to six or more allergens carried the strongest beta-coefficient of 0.608. This is in contrast to some studies that have demonstrated that sensitization to specific allergens such as dust mite are major determinants of increased FeNO in children.⁶ Our study highlights the importance of rat allergen sensitization as well and the dose-response relationship of polysensitization and airway inflammation.

Other studies have demonstrated that sensitization to multiple specific allergens is associated with elevated FeNO levels⁷⁻⁹, and our study adds to this body of literature by confirming this relationship in a population that is more diverse compared to other communities that have been studied. Our results are therefore generalizable to other diverse, urban populations with a high proportion of non-white ethnicities.

The clinical implications of our results are important. A study from the National Cooperative Inner City Asthma Study showed that children with asthma who were both exposed and sensitized to rat allergen had higher rates of hospitalization and unscheduled doctor visits.¹⁰ Our study adds to these findings by showing that sensitization to rat allergy also predicts airway inflammation. Finding that rat and multiple sensitization predicts high FeNO levels is important as FeNO levels have been shown to be predictive of asthma exacerbations.¹¹

We acknowledge that we are limited by sample size in that limited resources allowed us to obtain FeNO in a subset of children.

We found that in our school-based cohort of ethnically diverse, highly allergic children, that FeNO levels were predicted by cat and rat sensitization, and most strongly by having multiple sensitizations. Future studies should be aimed at reducing cat and rat allergen exposure and assessing the effect on asthma morbidity as well as markers of airway inflammation

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

FeNO	Fractional Exhaled Nitric Oxide
SICAS	School Inner-City Asthma Study

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Table 1

Predictors of FeNO, Multivariate regression; Outcome is the natural log of FeNO

Allergic Sensitization	Univariate Regression			Multiple Regression		
	B coefficient	Standard Error	P value	B coefficient	Standard Error	P value
Intercept						
Cat	0.785	0.122	<0.0001	0.401	0.153	0.01
Rat	0.738	0.143	<0.0001	0.440	0.183	0.016
Mouse	0.641	0.130	<0.0001	-0.105	0.178	0.557
Multiple sensitizations ^a	0.370 ^b	0.052	<0.0001			
1-3				0.402	0.147	0.006
4-5				0.357	0.216	0.099
6				0.608	0.226	0.007

Adjusted for age, gender, inhaled corticosteroid use, and asthma control

^a # sensitizations binned into the following categories for # positive skin tests: 0, 1-3, 4-5, 6

^b sensitizations used as single predictor in univariate analysis